The Neural Correlates of Dual-Task Walking in People with Neurological Disorders

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ABSTRACT

Background

Individuals with Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), and stroke experience various cognitive and motor impairments, which can negatively affect their ability to complete daily activities such as walking and talking. Walking and talking or dual-task walking often leads to a decline in performance in one or both tasks, which is called dual-task cost. This dual-task cost seems to be more pronounced in individuals with neurological conditions compared to age-matched healthy individuals, possibly due to disease-associated impairments. While the results of neuroimaging studies are inconsistent, several studies have found structural or functional brain changes that might contribute to a decrease in dual-task walking performance in people with neurological disorders.

Research question/objective

The objective of this study was to systematically review peer-reviewed articles that examined the neural correlates of cognitive-motor dual-task interference in people with neurological conditions. The primary aim was to identify brain areas or measures that might underlie dual-task walking performance of people with MS, stroke, AD, and PD. The secondary aim was to compare their dual-task performance with other groups such as healthy individuals.

Methods

A systematic review of the literature was conducted, following PRISMA guidelines, on Medline, Embase, and Scopus databases. Studies were included if they examined dual-task walking performance and associated structural or functional brain changes in adults with stroke, MS, PD, and AD. Studies were first screened using a title and abstract and then full-text review was performed. The quality of each study was assessed using the Joanna Briggs Institute (JBI) critical

appraisal checklist and then the data regarding cognitive and motor performance during dual- versus single task conditions and brain imaging were extracted. The findings were grouped according to neurological condition and then by imaging technique.

Results

After screening, 23 studies were selected to be included in this review. The majority (90%) showed a decline in dual-task walking performance compared to single-walking in people with neurological conditions and this decline was greater than healthy individuals. Most structural imaging studies (75%) reported a significant positive correlation between lower brain structural integrity and poorer dual-task walking performance. Specifically, the striatum regions including pedunculopontine nucleus and hippocampus in PD demonstrated this positive correlation. In MS, the supplementary motor area showed a positive correlation. In terms of functional brain changes, 60% observed an increase in prefrontal cortex activity during dual tasking in people with PD and stroke, which was associated with decreased performance in most cases (n = 3) while some found an association with maintained performance (n = 2). Further, people with MS and stroke both showed a significant relationship between a higher supplementary motor area activity and poor dual-task walking performance.

Conclusions

This systematic review identified several structural and functional neural correlates of dual-task walking in people with PD, MS, and stroke and has facilitated a better understanding of neural basis of dual-task interference in people with neurological conditions. However, the relationship between the brain and behavioural outcomes is complicated and various factors may influence neural correlates, such as individuals' characteristics (e.g., neural reserve, age), the nature of cognitive task used, and presentation modality (e.g., visual).

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
CRUNCH	Compensation-related utilization of neural circuits hypothesis
DT	Dual task
DTC	Dual-task cost
EDSS	Expanded disability status scale
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
FoG	Freezing of gait
HbO_2	Oxygenated hemoglobin
Hbb	Deoxygenated hemoglobin
PD	Parkinson's disease
PFC	Prefrontal cortex
PPN	Pedunculopontine nucleus
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
SMA	Supplementary motor area
SNc	Substantia nigra pars compacta
ST	Single task
UPDRS	Unified Parkinson's disease rating scale

1. INTRODUCTION

1.1 Background

Parkinson's disease, multiple sclerosis, stroke, and Alzheimer's disease are among the most common neurological conditions (Miller, 2014), which cause various changes to the nervous system (e.g., brain atrophy) (Brodtmann et al., 2020; Deture & Dickson, 2019; Huang et al., 2017; Zhai et al., 2017). Parkinson's disease (Elbaz et al., 2016), multiple sclerosis (Huang et al., 2017), and Alzheimer's disease (Deture & Dickson, 2019) are progressive and cannot be cured and thus individuals experience worsening of symptoms over time. Although many strokes are treatable, stroke survivors frequently have chronic disability and there is a risk of reoccurrence (Donkor, 2018). Neuronal changes involved in these neurological conditions reduce cognitive and motor ability of these populations (Caligiore et al., 2016; Peterson & Fling, 2018; Handelzalts et al., 2019; Deture & Dickson, 2019). For example, degeneration of basal ganglia in people with Parkinson's disease seem to negatively affect gait performance and executive functions (Moustafa et al., 2016). Similarly, cognitive and motor disturbances have been associated with white and grey matter lesions in various areas of the brain in people with multiple sclerosis (e.g., basal ganglia) (Peterson & Fling, 2018), stroke (e.g., frontal lobe, motor cortex) (Handelzalts et al., 2019; Nagaratnam et al., 2003), and Alzheimer's disease (e.g., hippocampus) (Deture & Dickson, 2019). Commonly observed gait deficits include slower gait speed and increased gait variability (e.g., stride length, step length) (Beyaert et al., 2015; Comber et al., 2016; Hausdorff, 2009). Dysfunctions in various cognitive areas also have been reported (e.g., executive functions, visuospatial functions, memory) (Al-Qazzaz et al., 2014; Deture & Dickson, 2019; Storandt et al., 2008; Sumowski et al., 2018; Watson & Leverenz, 2011).

Dual-task walking (e.g., walking and talking) abilities of people with neurological disorders is reduced compared to healthy individuals possibly due to disease-related cognitive and gait changes (McIsaac et al., 2018). Specifically, these changes can make walking less automatic and thus dual-task walking (e.g., walking and talking) can be challenging for people with neurological conditions (Fritz et al., 2016). Further, dual-task walking requires optimal executive functioning (Strobach et al., 2018), which includes higher cognitive processes such as working memory and cognitive inhibition (Diamond, 2014). Among them, divided attention seems to be particularly important since it allows individuals to process two or more tasks at the same time (Yogev-Seligmann et al., 2008). Consequently, dual-task studies have consistently reported a decrease in gait speed and an increase in gait variability during dual tasking in people with neurological disorders compared to healthy individuals (Kelly et al., 2012; Hamilton et al., 2009; Deblock-Bellamy et al., 2020).

Several attempts have been made to understand the neural basis (structural or functional) of declines in dual-task walking performance in people with neurological disorders (Chaparro et al., 2017; Coghe et al., 2018; Pedulla et al., 2019). Some structural imaging (e.g., magnetic resonance imaging) studies have found an association between lower structural integrity (e.g., grey matter) and worse dual-task walking performance (Coghe et al., 2018) while others found no significant associations (Herman et al., 2013; Liparoti et al., 2019). In terms of functional brain changes, several studies reported a greater brain activity during dual-task walking in people with neurological disorders compared to healthy people (Chaparro et al., 2017; Hernandez et al., 2016). This upregulation of brain activity has been interpreted as a compensatory strategy for disease-associated cognitive and motor impairments according to the compensation-related utilisation of neural circuits hypothesis (CRUNCH) that have been applied to older adults versus young adults

(Chaparro et al., 2017). However, it has been shown that an increase in brain activity does not always translate to better performance (Gertel et al., 2020; Cassady et al., 2021), which reveals a complex relationship between the brain and dual-task walking performance in people with neurological disorders.

1.2 Purpose

The goal of this systematic review was to collect and analyze neuroimaging studies that examined the relationship between brain imaging and dual-task walking performance of people with Parkinson's disease, multiple sclerosis, stroke, and Alzheimer's disease. As previously mentioned, some studies have identified brain areas or measures that might be involved in dual-task walking in people with neurological disorders (Coghe et al., 2018; Hernandez et al., 2016; Nieuwhof et al., 2016) and the CRUNCH model might be utilized to explain the findings (Festini et al., 2018). However, several brain areas seem to be involved and the effect of brain changes on dual-task performance seems complex (Leone et al., 2017; Watanabe & Funahashi, 2018). To date, no comprehensive review has been conducted on the neural basis of cognitive-motor dual-task cost in people with neurological conditions. Thus, the main purpose of this review was to identify the neural correlates (structural or functional changes in brain areas/measures) of dual-task walking in people with Parkinson's disease, multiple sclerosis, stroke, and Alzheimer's disease. Additionally, if there were comparison groups (e.g., healthy people), cognitive and motor performance of people with neurological disorders were examined and compared with those groups.

2. LITERATURE REVIEW

2.1 Neurological disorders and associated impairments

Neurological disorders are conditions that affect the central and peripheral nervous system (World Health Organization, 2016), which leads to various physical, psychological (e.g., depression) and cognitive symptoms (Butler & Zeman, 2005). Symptoms can vary widely depending on the location of affected nerve fibers (Levin, 2021). Common symptoms include muscle weakness, loss of sensation, headache, gait difficulties, decreased coordination, speech issues, and various cognitive changes (e.g., poor memory and attention) (Levin, 2021). Among various neurological disorders, Miller et al. (2014) identified Parkinson's disease, multiple sclerosis, stroke, and Alzheimer's disease as among the most common neurological conditions that are particularly prevalent in older adults. In the paragraphs that follow, each of these neurological conditions are described and specific brain areas and functions that are typically affected by these conditions are presented.

Parkinson's disease: Parkinson's disease (PD) is a progressive neurodegenerative disease and thus, people with PD experience a worsening of symptoms over time (Elbaz et al., 2016). PD can be divided into five stages: (a) stage one (mild symptoms); (b) stage two (symptoms get worse but still mild); (c) stage three (mild to moderate symptoms); (d) stage four (advanced stage) and (e) stage five (most advanced) (Parkinson's foundation, n.d). The Hoehn and Yahr scale and Unified Parkinson's Disease Rating Scale (UPDRS) are commonly used to monitor the progression of motor symptoms and influence of the disease on daily activities of people with PD (Parkinson's foundation, n.d; Perlmutter, 2009). The manifestation of PD involves degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) (Kouli et al., 2018), which plays an important role in regulating motor movements (Sonne et al., 2020). The incidence rate is

about 10-50/100,000 person-years and its prevalence rate is about 100-300/100,000 people (Elbaz et al., 2016). The incidence and prevalence increase dramatically with age (Elbaz et al., 2016). Currently, there is no cure for PD (Elbaz et al., 2016) and the management includes alleviation of motor and non-motor symptoms through medication or surgery (Armstrong & Okun, 2020).

PD induces neurodegeneration in various regions of the brain (Zhai et al., 2017). In particular, striatum regions and the basal ganglia seem to be most affected as they are highly connected with SNc through dopaminergic nerves (Zhai et al., 2017). The basal ganglia are typically divided into four compartments: (1) the neostriatum including caudate nucleus and putamen; (2) the pallidal segments (internal and external); (3) the subthalamic nucleus and (4) the substantia nigra pars reticulata and compacta (Galvan et al., 2015). Basal ganglia are responsible for executing voluntary movements precisely (Prakash et al., 2016) and work closely with the prefrontal cortex (PFC) and frontal region in general and thus damages to basal ganglia are likely to impair executive functions (e.g., planning, coordinating, shifting) (Leisman et al., 2014). The PFC is highly innervated with dopaminergic neurons (Drag et al., 2009) and abnormalities in prefrontal networks seem to be associated with decreased performance on cognitive tasks in people with PD (Parker et al., 2013). Another structure that closely interacts with the basal ganglia is the pedunculopontine nucleus (PPN) that is often affected by PD (Tykocki et al., 2011). PPN regulates human behaviours including locomotion (Molina et al., 2020; French & Muthusamy, 2018) and plays a role in cognitive functioning (e.g., attention) (Yarnall et al., 2011).

There are several motor difficulties commonly experienced by people with PD, which include “bradykinesia (e.g., slowed movement), hypokinesia (e.g., small amplitude movements), resting tremor, rigidity, and postural instability” (Hausdorff, 2009, p. 19). Freezing of gait (FoG) is also commonly reported, which is described as a sudden break while walking and it is

experienced by 60% of individuals with advanced PD (Chen et al., 2013). FoG seems to be associated with striatal and frontal lobe lesions (Chen et al., 2013). Other gait changes exhibited by people with PD include reduced gait speed, and stride length, and increased double support time and stride variability (Hausdorff, 2009; Kelly et al., 2012). Additionally, people with PD tend to show reduced arm swing, left-right coordination, and postural control, and increased gait asymmetry (Hausdorff, 2009). Impairments in visuospatial and executive functions (e.g., working memory, attention) are also frequently reported (Cosgrove & Alty, 2017).

Multiple Sclerosis: According to the most recent data, around 97,300 Canadians have been diagnosed with multiple sclerosis (MS) with most cases occurring in people aged between 20 to 49 (Gilmour et al., 2018). Similar to PD, MS is a chronic neurodegenerative disease that affects the central nervous system including the spinal cord and brain (Huang et al., 2017). Specifically, it affects the protective layers of neurons called myelin and other cells in the central nervous system (e.g., oligodendrocytes) (Huang et al., 2017). This results in neuronal damages and lesions that disturb nerve transmissions (Ghasemi et al., 2017). There are three clinical phenotypes: relapsing-remitting MS (symptoms come and go), secondary-progressive MS (symptoms get worse with some/no relapses) and primary progressive MS (symptoms get worse from the onset) (Nazish et al., 2018). The majority of people start with the relapsing-remitting MS type (Huang et al., 2017). Later, people enter the secondary progressive stage in which they experience worsening of symptoms with time (Huang et al., 2017). The Expanded Disability Status Scale (EDSS) and magnetic resonance imaging (e.g., lesion volume) are used to determine the disease progression and phenotype of MS (Lublin et al., 2013).

MS is characterized by a widespread white and grey matter atrophy, which leads to various cognitive and motor difficulties (Cameron & Nilsagard, 2018). Typically, white matter lesions are

found in corpus callosum, periventricular areas, pons, and cerebellum (Filippi et al., 2019). Lesions are also commonly found in parietooccipital regions, which are associated with changes in cognition and even personality (Gonzalez et al., 1994). Further, grey matter atrophy occurs across various areas such as cerebral cortex (e.g., frontal, temporal, parietal lobes), cerebellum, brain stem, and subcortical structures (e.g., basal ganglia) (Peterson & Fling, 2018). These neuropathological changes lead to executive dysfunctions and poor motor performance (Peterson & Fling, 2018). Specifically, the structural integrity of motor areas (e.g., supplementary motor area) has been associated with EDSS (Du et al., 2019). In addition, atrophy in the cerebellum influences the execution of motor movements and some non-motor functions (e.g., cognition, mood) (Peterson & Fling, 2018; Weier et al., 2014).

Approximately, 93% of people with MS encounter gait difficulties ten years after their diagnosis (Van der Feen et al., 2019). Specifically, Filli et al. (2018) found that compared to healthy individuals, people with MS tend to reduce step length and knee and ankle range of motion. Furthermore, a meta-analysis demonstrated that numerous studies observed a decrease in walking speed, cadence, stride and step length, and swing phase time, and increased double support time, step width, and stride time in people with MS compared to healthy individuals (Comber et al., 2017). Additionally, impairments in cognitive functions (e.g., executive functions, working memory, information processing speed) in people with MS (Jonsdottir et al., 2018; Van der Feen et al., 2020) also negatively influence the mobility of individuals with MS.

Stroke: Stroke is a cerebrovascular disease and is the second most common cause of death in which around 5.5 million people die every year due to stroke worldwide (Donkor, 2018). Around 50% of stroke survivors experience chronic disability and consequently, people with stroke often report reduced quality of physical, psychological, and social aspects of life (Donkor, 2018). Stroke

can be largely divided into two types: ischaemic and haemorrhagic stroke. Ischaemic stroke occurs when the blood supply to a region of the brain is interrupted while haemorrhagic stroke is caused by any abnormalities or breakage of blood vessels, which in both cases lead to tissue/cell injury and death due to disrupted blood supply (Donkor, 2018).

A rapid decline in brain volume has been observed in people with stroke during the first three months since diagnosis, which continue to decrease thereafter but at a slower rate (Brodtmann et al., 2020). In addition, lesions tend to spread across the brain after stroke for many years (Seghier et al., 2014). Depending on the locations of damage or obstruction, various brain regions can be affected by stroke (Hui et al., 2021). Shi et al. (2017) found a significant decrease in grey matter in the PFC, limbic system, and motor cortex. Lesions in the frontal lobe including prefrontal cortex can lead to various cognitive impairments and mood disorders (Nagaratnam et al., 2003) such as depression (Shi et al., 2014). The hippocampal and thalamic volume also decrease notably in people with stroke compared to healthy individuals (Brodtmann et al., 2020). Further, lesions in the areas related to gait such as motor cortex and basal ganglia were associated with poor gait performance (Handelzalts et al., 2019) and often hinder gait recovery of people with stroke (Handelzalts et al., 2019; Lee et al., 2017).

Gait and balance deficits are common among people with stroke (VanGilder et al., 2020). More than 80% of stroke survivors experience an immediate gait impairment that can be usually rehabilitated to a certain extent in the first two months post-stroke (Cirstea, 2020). However, only 27% can perform the skills that are deemed to be essential for community ambulation: ability to use stairs, walk inclined surface, walk with a speed of 0.8m/s or higher, and walk 367 meters or longer than 6 minutes with no help of others (Deblock-Bellamy et al., 2020). Heshmatollah et al. (2020) found that people with stroke reduce their gait speed, and step length, and increase double

support time compared to healthy controls (2020). In general, decreased gait speed and steps, and increased gait variability are commonly found in people with stroke (VanGilder et al., 2020). Along with gait difficulties, people with stroke often show various cognitive impairments (e.g., memory, language, attention, orientation) while attention and executive functions seem to be mainly affected (Al-Qazzaz et al., 2014). Individuals who have had a stroke tend to experience a more rapid decline in executive functions compared to healthy people (Levine et al., 2015).

Alzheimer's disease: Alzheimer's disease (AD) is a progressive neurodegenerative disease in which accumulation of amyloid plaques and neurofibrillary tangles lead to neural death (Deture & Dickson, 2019). Worldwide, there are 25 million people with dementia mostly with the AD type (Qiu et al., 2009). AD seems to be associated with age as its prevalence increases dramatically from 3% in people aged 65-74 years old to 50% in 85 years or older (Sosa-Ortiz et al., 2012). The incidence rate is particularly higher in North America and Europe compared to other areas such as Latin America (Sosa-Ortiz et al., 2012). Similar to the other neurological disorders described, AD is progressive, and thus cognitive and motor functions decline over time, and changes in behavior and mood also occur, which can eventually lead a loss of independence and quality of life (Kahle-Wrobleski et al., 2016).

The damage in AD is usually widespread but it typically starts in the brain areas that are associated with memory such as the hippocampus and entorhinal cortex (Huang et al., 2011; National Institute on Aging, 2017). As the disease progresses, it spreads to other regions (e.g., temporal areas, orbitofrontal cortex, association cortex) (Huang et al., 2011). AD primarily affects gray matter but can also lead to white matter loss (Kao et al., 2019), which both are associated with cognitive dysfunctions (Serra et al., 2010). A gray matter loss can be found across the brain (e.g., frontal, temporal, parietal) and limbic areas while medial and lateral temporal regions are

most affected (Serra et al., 2010). It has been shown that decreased grey matter volume in limbic and temporal lobes are associated with gait deficits (e.g., decreased gait speed) in people with mild cognitive impairment compared to healthy individuals (Cosentino et al., 2020). In addition, grey matter changes can occur in parieto-temporal regions and precuneus (Serra et al., 2010). Similarly, white matter in the frontal, parietal, occipital, and temporal lobe is commonly affected (Kao et al., 2019). This white matter loss has been associated with decreased motor performance (e.g., walking speed) including fine motor functions (Kao et al., 2019).

Initially, people with AD experience memory deficits as memory-related brain areas are affected first and later they experience other cognitive dysfunctions that affect visuospatial and motor functions (Deture & Dickson, 2019). Specifically, executive dysfunction is frequently reported even in people with AD at an early stage (Storandt et al., 2008). In terms of motor performance, a study showed around 50% of people with AD experience gait difficulties three years after receiving a diagnosis and 33% of those with gait difficulties are considered as non-ambulatory (Della Sala et al., 2004). Gras et al. observed decreased gait speed and step length, and increased stance time in people with AD compared to healthy individuals (2016). A longitudinal study that followed people with AD over 18 months also found decreased gait speed, which correlated with poorer baseline cognitive functions (Dyer et al., 2020).

Taken together, neurological disorders induce various pathological changes to the nervous system consequently leading to numerous cognitive and motor impairments (Levin, 2021) that can be rehabilitated to a certain extent but are often progressive changes that are irreversible (Elbaz et al., 2016; Deture & Dickson, 2019; Donkor, 2018; Huang et al., 2017). These pathological changes and disease-related chronic impairments can decrease functional mobility, independence, and quality of life of people with neurological disorders, negatively affecting their physical, social, and

cognitive aspects of daily living (Cella et al., 2012; Hariz et al., 2011; Kim et al., 2014; Marshall et al., 2013; Pike et al., 2012).

2.2 Dual-task paradigm: role of executive functions and attention

Dual-tasking simply refers to performing two tasks simultaneously (Strobach et al., 2018). In dual-task research, there are different combinations of dual-task (DT) such as cognitive-cognitive (completing two cognitive tasks), motor-motor (completing two motor tasks), and motor-cognitive (completing a motor and a cognitive task) (Strobach, 2020). Dual-tasking requires allocation of available resources to complete each task and executive functions are thought to be involved in this process (Stroabach et al., 2018). Executive functions allow individuals to plan and execute actions with flexibility and update and adjust behaviour as the context changes (Rabinovici et al., 2015). The literature suggests that there are three main parts to executive functions: working memory, cognitive flexibility, and inhibitory control (Diamond, 2013; Ferguson et al., 2021). Working memory refers to one's ability to hold information and process mentally (Diamond, 2013). Cognitive flexibility is related to changing perspectives and thoughts, which facilitates behavioural adaptations in response to changing environment (Diamond, 2013). Lastly, inhibitory control allows individuals to use attention, behaviour, and thoughts to control impulsive or automatic responses (Diamond, 2013).

Attention is an important part of executive functioning (Yogev-Seligmann et al., 2008). There is no one agreed definition of attention, however, it is related to how an individual become aware of and process certain stimuli (Yogev-Seligmann et al., 2008). There are two types of attention, selective and divided attention (Hahn et al., 2009). Selective attention allows individuals to focus on a particular stimulus while divided attention allows people to process more than one task simultaneously by splitting or shifting attention as necessary (Hahn et al., 2009) and thus it is

particularly relevant for dual-tasking (Yogev-Seligmann et al., 2008). In lab-based studies, individuals' dual-tasking ability has been used to quantify and assess executive functioning (Sebastián & Mediavilla, 2017). Executive functions have been associated with the frontal regions of the brain specifically prefrontal cortex (PFC) while other areas of the brain such as the parietal lobe, subcortical structures, and limbic regions seem to also contribute to executive functioning (Yogev-Seligmann et al., 2008).

2.3 Dual-task walking

Evidence from the recent studies suggest that walking is not entirely automatic and involves a higher cognitive input such as executive functions and attention that are also involved in dual-tasking (Woollacott & Shumway-Cook, 2002; Yogev-Seligmann et al., 2008). Therefore, executive functions (e.g., divided attention) are essential for successful performance of DT walking (e.g., walking and talking) (Fraser & Bherer, 2013; Plummer & Eskes, 2015). During DT walking, when comparing one's single task (ST) performance (e.g., performing the cognitive task alone or walking alone) to DT performance, several outcomes are possible: no dual task interference, cognitive facilitation, motor-related cognitive interference, motor facilitation, mutual facilitation, motor-priority trade-off, cognitive-related motor interference, cognitive priority trade-off, and mutual interference (Plummer et al., 2013).

Table 1 Possible behavioural outcomes of cognitive-motor dual task

	Cognitive performance		
Motor performance	No change	Improved	Worsened
No change	No dual-task interference	Cognitive facilitation	Motor-related cognitive interference

Improved	Motor facilitation	Mutual facilitation	Motor priority trade-off
Worsened	Cognitive-related motor interference	Cognitive priority trade-off	Mutual interference

Note. Adapted from "Cognitive-Motor Interference during Functional Mobility after Stroke: State of the Science and Implications for Future Research" by P. Plummer et al., 2013, Arch Phys Med Rehabil, 94(12). Copyright 2013 by PMC.

Due to the challenging nature of dual-tasking, it is common to observe a decrease in performance in one (e.g., motor-related cognitive interference, cognitive-related motor interference) or both tasks (e.g., mutual interference). This decrease in DT performance compared to single task (e.g., cognitive or motor or both) conditions can be quantified using the following equation, which is called a dual-task cost (DTC) (Plummer & Eskes, 2015). For example, a slower gait speed during dual-tasking would give a positive value of DTC, which represents a decrease in performance (lower dual-task capacity) (Coghe et al., 2018). If an increase in number represents worse performance (e.g., double support time), a negative sign is added or the numerator is inverted to obtain a positive value (e.g., dual-task – single task) (Plummer & Eskes, 2015). In this way, whenever dual-task costs are described based on this formula, a positive value represents a cost to performance (declines in performance) when dual-tasking compared to single task and a negative value would represent improved performance (facilitation) during dual tasking compared to single task.

$$\text{DTC}\ (\%) = \frac{(\text{single task} - \text{dual task})}{\text{single task}} \times 100\%$$

A recent meta-analysis, which mainly focused on gait, found that healthy older adults mostly experience a decrease in motor performance (e.g., gait speed, cadence) during dual tasking (Smith

et al., 2017). Further, a systematic review on people with stroke showed that this population mostly exhibit mutual interference in which performance of both tasks decrease under DT conditions (Deblock-Bellamy et al., 2020). In general, people with neurological disorders such as PD (Salazar et al., 2018) and MS (Hamilton et al., 2009) experience greater DTCs (e.g., slower gait speed) during dual-task walking compared to healthy individuals, which will be discussed in more detail in section 2.4.

Dual-task theories: Several theories have been proposed to explain why people experience DTCs. The most influential ones include the bottleneck theory and capacity sharing theory (Pashler, 1994; Hommel, 2020). According to the bottleneck theory, people can only process one task at a time, which causes a delay in processing another task (Fraser & Bherer, 2013; Sigman & Dehaene, 2006). On the other hand, the capacity sharing theory argues that two tasks can be processed together but limited resources and capacity may lead to a decrease in performance of one or both tasks (Fraser & Bherer, 2013; Kahneman, 1973). However, up to date, there is no agreement on which theory best predicts when, how, and why people experience DTC (Hommel, 2020).

2.4 Dual-task walking performance of people with neurological disorders

Dual-task cost is experienced by a wide range of populations including healthy young individuals (Bayot et al., 2018; Papegaaij et al., 2017; Woollacott & Shumway-Cook, 2002). For instance, younger adults have demonstrated poorer cognitive performance under a DT condition (e.g., walking and talking) compared to single task conditions (Brustio et al., 2017). However, DTC seems to be more pronounced in people with neurological disorders possibly due to disease-related physical and/or cognitive impairments (McIsaac et al., 2018). Dual-tasking requires optimal motor and cognitive functioning (Li et al., 2018). Specifically, as previously mentioned,

executive functions and PFC are essential for dual-tasking (Beste et al., 2018). However, executive dysfunctions and damages to the PFC are commonly found among people with neurological disorders (Rabinovici et al., 2015). In addition, walking becomes less automatic in these populations and requires more attention or cognitive resources, creating more interference with a cognitive task, leading to poorer DT performance compared to healthy individuals as briefly discussed above (Plummer & Eskes, 2015).

For example, Kelly et al. (2012) observed reductions in gait speed and stride length, left-right coordination, and increased stride variability in people with PD. Moreover, there is evidence that people with PD make more errors on cognitive tasks while dual tasking compared to healthy individuals (Nieuwhof et al., 2017). Similarly, in comparison to healthy people, people with MS tend to perform worse under DT conditions, demonstrating a slower walking speed and increased gait variability (e.g., swing time) (Hamilton et al., 2009; Learmonth et al., 2015; McIsaac et al., 2018). In addition, there is some evidence that people with MS are less accurate on cognitive tasks under DT conditions especially when the task difficulty increases (Beste et al., 2018). People with stroke tend to reduce their velocity, step and stride length under the DT walking condition compared to walking alone particularly when walking is combined with a counting backward task (e.g., serial-subtraction task) (Shin et al., 2017). Further, a systematic review demonstrated that under DT conditions, cognitive or motor performance or both decreased to a greater extent in people with stroke compared to healthy individuals (Deblock-Bellamy et al., 2020). Lastly, people with AD also tend to show a greater decline in motor (e.g., decreased speed) and/or cognitive (e.g., task accuracy) performance under DT conditions (Hunter et al., 2020). Significant changes in DT walking in people with cognitive decline has resulted in the use of DT walking assessments to identify individuals at risk of dementia (Montero-Odasso et al., 2017).

Experiencing greater DT interference can limit mobility of people with neurological disorders, which in turn can increase their fall risk (Brustio et al., 2017). A fall incidence is typically 2-4 times higher in people with neurological conditions compared to age-matched healthy individuals and 46% of the population fall at least once a year (Ehrhardt et al., 2020). Falls often lead to injuries and/or disability, which can negatively affect their quality of life and daily activities of living, putting burdens on individuals with neurological conditions and their caregivers (Stolze et al., 2003).

2.5 The use of neuroimaging techniques in dual-task studies

Primarily, DTC has been investigated by measuring behavioural performance (e.g., walking speed) of participants (Beurkens et al., 2016). Recently, structural and functional imaging techniques have been incorporated to understand the neural basis of DT interference (Beurkens et al., 2016). One of the most commonly used techniques to measure DT interference during DT walking is functional near-infrared spectroscopy (fNIRS). fNIRS imaging devices are non-invasive, very portable, and have a high tolerance for motions and thus are widely being used to measure real-time brain (e.g., PFC) activity changes during movement or mobility tasks (Pinti et al., 2018). fNIRS is capable of monitoring oxygenated (HbO_2) and deoxygenated hemoglobin (HHb) concentrations during dual tasking (Nieuwhof et al, 2016). Functional magnetic resonance imaging (fMRI) is also commonly used to detect local cerebral blood flow and changes in oxygenation concentration, but fMRI requires participants to lie supine in a scanner with limited movement and therefore cannot measure brain activity during mobility or gross motor tasks (Wang et al., 2018). Both fNIRS and fMRI techniques utilize the hemodynamic response to infer activity in different regions of the brain during DT performance (Mirelman et al., 2014; Wang et al., 2018). fNIRS research with younger adults performing a dual-task walking experiment has revealed that

when different brain regions are activated by certain stimuli, the energy demand increases and would lead to a higher blood flow to those areas that are activated (Mirelman et al, 2014), which is called the hemodynamic response (Wang et., 2018). Therefore, examining the hemodynamic response will allow one to infer and analyze changes in the brain activity by investigating changes in oxygenation level (Wang et al, 2018). On the other hand, structural imaging techniques are used to examine the anatomy and pathology of the brain (Hirsch et al., 2015). These techniques are useful for detecting brain damage and abnormalities (e.g., lesions in stroke) (Hirsch et al., 2015). Magnetic resonance imaging (MRI) is commonly used to measure the whole brain volume, the volume of specific brain areas, and grey and white matter volume (Hirsch et al., 2015).

2.6 Neural correlates of dual-task walking

The advancement of neuroimaging techniques has allowed studies to investigate the relationship between structural and/or functional brain changes and DT walking performance (Pizzamiglio et al., 2017). Structural brain findings have shown a link between lower structural integrity and poorer DT performance in people with structural brain changes (e.g., older adults, people with neurological disorders) (Li et al., 2018). For example, lower entorhinal cortex volume correlated with poorer DT performance among older adults with mild cognitive impairment (Sakurai et al., 2019). Interestingly, Urban et al. (2017) found a significant correlation between reduced cortical thickness in the PFC and parietal regions and poorer DT performance in young adults with traumatic brain injury (Urban et al., 2017). This demonstrates that regardless of age, people with structural brain changes could perform poorer under DT conditions compared to those without such brain changes. Regarding people with neurological disorders, Coghe et al. (2018) found a significant correlation between lower brain volume and poorer DT performance (e.g.,

decreased gait velocity) while others have found no significant brain-performance correlations (Liparoti et al., 2019; Herman et al., 2013).

In terms of functional brain changes, a recent review identified a few regions that are up-regulated during DT versus single task conditions (Liebherr et al., 2016). These areas include frontal regions (e.g., PFC), premotor cortex, parietal cortex, precuneus, cerebellum, and subcortical structures, suggesting that these areas might be closely related to DT performance in general (Liebherr et al., 2016). People with neurological disorders tend to show altered brain activity in motor and non-motor regions of the brain under DT conditions compared to healthy individuals (Chaparro et al., 2017; Vervoort et al., 2016). For example, fNIRS studies on people with MS have shown that this population tend to increase the PFC activity during dual tasking compared to healthy people (Chaparro et al., 2017; Hernandez et al., 2016; Pedulla et al., 2019). This upregulation of PFC activity was also observed in people with stroke (Chatterjee et al., 2019). Nieuwhof et al. found a similar result in which increased activity in putamen (subcortical structure) was detected in people with PD compared to healthy individuals under a DT condition using fMRI (2017).

2.7 Theoretical perspectives on brain activation changes

An increase in brain activity in people with neurological disorders can be interpreted as a strategy to compensate for disease-related cognitive and motor impairments (Chaparro et al., 2017; Nieuwhof et al., 2017). This notion of compensation is well established in older adults (Festini et al., 2018). According to the compensation-related utilisation of neural circuits hypothesis (CRUNCH) model, older adults will try to maintain performance by increasing their brain activity as the task difficulty increases, compensating for age-related impairments (Festini et al., 2018). It is plausible that people with neurological conditions employ a similar strategy to compensate for

disease-related impairments (Nieuwhof et al., 2017). For example, Hernandez et al. (2016) found an increase in brain activity in people with MS under the DT condition compared to healthy individuals while there was no significant difference in DT performance. This result fits with the CRUNCH model in which people with MS were able to maintain their performance by increasing the brain activity. However, as the task difficulty increases, individuals will reach a "crunch point" where the brain activity can no longer increase, which can potentially lead to poor performance (Festini et al., 2018). The crunch point can be affected by several factors such as individual differences (e.g., neural reserve) and difficulty of tasks used (Festini et al., 2018). People with neurological conditions might show a compensatory recruitment at an early stage of disease when neurodegeneration is not severe, however, as the disease progresses, they are likely to lose this ability (Cassady et al., 2021).

Interestingly, an overactivation of the brain doesn't seem to be always compensatory as a decrease in DT performance has been observed in people with neurological conditions even when there is an increase in brain activity (Liu et al., 2018). This phenomenon can be explained by the neural dedifferentiation hypothesis. As the nervous system matures, different brain regions become specialized for a specific class of stimuli (neural differentiation) (Koen et al., 2019). The reverse process, the loss of neural specificity, is termed neural dedifferentiation and is often observed in older adults due to age-related functional and structural changes to the brain (Koen et al., 2019). For example, older adults have shown decreased neural specificity of visual regions to different categories of visual stimulus (e.g., houses, chairs, faces) compared to young adults (Papegaaij et al., 2017). Neural dedifferentiation typically results in a more widespread activation of the brain, which is associated with poor performance (Papegaaij et al., 2017) or has no impact on performance (Gertel et al., 2020). For example, a significant correlation was found between

increased activity of ipsilateral motor areas and decreased motor performance in older adults (Papegaaij et al., 2017). Therefore, increased brain activity due to neural dedifferentiation is not considered as compensatory and will lead to a decrease (Li et al., 2018) or no changes in task performance (Gertel et al., 2020). Since disease-related brain changes also occur in people with neurological disorders, it is reasonable to predict that this population might also experience neural dedifferentiation (Cassady et al., 2021), leading to poor DT performance even when the brain activity increases (Cassady et al., 2021; Gertel et al., 2020).

2.8 Summary

Walking is an essential everyday activity that is often combined with another task (Plummer et al., 2013). This DT walking requires optimal motor and cognitive functioning (e.g., executive functions) (Woollacott & Shumway-Cook, 2002; Yogev-Seligmann et al., 2008). Therefore, people with neurological disorders, who experience a wide range of physical and cognitive impairments due to pathological changes to the nervous system, tend to show poorer DT walking performance compared to healthy individuals (McIsaac et al., 2018). Studies have been reported gait changes (e.g., slower speed, increased gait variability) and decreased cognitive task performance during DT walking compared to single tasking (e.g., cognitive or motor) in people with neurological conditions versus healthy controls (Kelly et al., 2012; McIsaac et al., 2018; Shin et al., 2017)

In order investigate the neural basis of DT walking performance in people with neurological disorders, various neuroimaging studies have been conducted (Coghe et al., 2018; Hernandez et al., 2016; Liparoti et al., 2019). These studies have identified a relationship between specific structural (Coghe et al., 2018; Li et al., 2018) or functional brain changes (e.g., PFC) (Chaparro et al., 2017; Hernandez et al., 2016; Pedulla et al., 2019) and DT walking performance

in people with neurological disorders while other studies found no significant associations (Liparoti et al., 2019; Stuart et al., 2020). While several brain regions seem to interplay, it remains unclear what are the common or distinct neural correlates of DT walking performance in people with stroke, PD, MS, and AD. Even within the studies that identified neural correlates of DT walking, the direction of changes in brain activity and DT performance seem to vary, which could be potentially explained by the CRUNCH model and neural dedifferentiation hypothesis that have been applied to older adults in comparison to young adults.

3. MANUSCRIPT

Neural correlates of dual-task walking in people with neurological disorders: a systematic review

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Abstract

Background People with neurological disorders experience difficulties with dual-task walking due to disease-related impairments. The objective of this review was to provide a comprehensive examination of the neural correlates (structural/functional brain changes) of dual-task walking in people with Parkinson's disease (PD), multiple sclerosis (MS), stroke, and Alzheimer's disease (AD).

Methods A systematic review of the literature was conducted, following PRISMA guidelines, on Medline, Embase, and Scopus. Included studies examined the relationship between structural and functional brain imaging and dual-task walking performance in people with PD, MS, stroke, and AD. Articles that met the inclusion criteria had baseline characteristics, study design, and behavioural and brain outcomes extracted. Twenty-three studies were included in this review.

Results Most structural imaging studies (75%) found an association between lower brain integrity and poor dual-task performance. Specific brain regions that showed this association include the striatum regions and hippocampus in PD and supplementary motor area in MS. Functional imaging studies reported an association between increased prefrontal cortex activity and maintained (compensatory recruitment) or decreased performance in PD and stroke. A subset (n = 2) of the stroke papers found no significant correlations. Increased supplementary motor area activity was associated with decreased performance in MS and stroke.

Conclusion In people with PD, MS, and stroke, several neural correlates of dual-task walking have been identified, however, the direction of the association between neural and performance outcomes varied across the studies. The type of cognitive task used and presentation modality (e.g., visual) may have contributed to these mixed findings.

Keywords cognitive-motor interference, functional and structural imaging, Parkinson's disease, Multiple Sclerosis, Stroke

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Declarations

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Code availability: not applicable

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Consent for publication: not applicable

Introduction

Parkinson's disease (PD), multiple sclerosis (MS), stroke, and Alzheimer's disease (AD) are among the most common neurological disorders [1]. People with neurological disorders experience various disease-related cognitive and motor impairments [2]. For example, executive (e.g., planning, coordinating, inhibiting) and visuospatial dysfunctions, and memory impairment are commonly reported [3-7]. In addition, this population frequently experience gait difficulties (e.g., slower gait speed) [8-11]. Numerous studies have shown the associations between pathological changes to the nervous system and gait and/or cognitive deficits in people with neurological disorders [6, 12-14]. For example, degeneration of basal ganglia was associated with gait deficits and executive dysfunctions in people with PD [15]. People with AD also frequently report cognitive impairments (e.g., memory) that have been associated with frontotemporal lobe degeneration [6]. White and grey matter loss in cortical (e.g., frontal lobe) and subcortical areas (e.g., basal ganglia) in people with MS have been correlated with poor outcomes on clinical assessments such as 25-foot walk test and expanded disability status scale [13]. Similarly, lesions of frontal area were associated with decreased cognitive processing speed and attention [14] and damages to motor areas and corticospinal tracts were related with poor walking performance [16] in people with stroke.

Walking can become more challenging when it is performed with another task (e.g., talking), which is called dual-task (DT) walking [17]. DT walking involves allocation of available attentional resources to each task, which requires executive functions that are mediated by the prefrontal cortex (PFC) [18]. When tasks demands exceed one's attentional capacity, one can observe a decrease in performance (e.g., slower gait speed) in one or both tasks, which is known as a DT cost (DTC) [19]. People with neurological disorders are more likely to experience DTC

[2] possibly due to frequently affected executive functions [20] and PFC [21] along with other disease-related cognitive and motor deficits [22]. Walking becomes less automatic with these changes and will demand executive resources when performed with a cognitive task, creating more interference between the tasks, which results in poorer DT performance compared to healthy individuals [22]. As such, people with PD [23] and MS [24] tend to show decreased DT-gait speed and cognitive performance, and increased gait variability compared to healthy individuals. People with stroke [25] and AD [26] also exhibit a similar DT-related decrease in gait speed and cognitive task accuracy.

A link between brain changes and DT walking performance in people with neurological disorders has been suggested by several neuroimaging studies [27, 28]. For example, Coghe et al. (2018) found a significant correlation between lower grey matter volume and poor DT walking performance (e.g., increased DTC of cadence) [27]. Regarding functional changes, increased brain activity (e.g., PFC) has been observed in people with neurological disorders during dual-task walking compared to healthy individuals [28-31]. According to the compensation-related utilisation of neural circuits hypothesis (CRUNCH), older adults increase their brain activity to maintain performance, minimizing the effects of age-related brain changes [32]. Likewise, increased brain activity in people with neurological disorders can be considered as a strategy to compensate for disease-related impairments [33]. When demand exceeds capacity however, there could be a decline in task performance and/or brain activity, which is called a "crunch point" [32]. The CRUNCH model fits well with Kahneman's classic capacity sharing theory [34], which is used to explain why people experience DTC, as both explains how limited resources (e.g., cognitive or neural) can affect our ability to increase brain activity and/or perform given tasks.

Taken together, while the results are inconsistent [35], some studies suggest that specific structural or functional brain changes might be associated with DTC in people with neurological disorders and certain findings may fit with the CRUNCH model that has been applied to older adults [32]. To date, no comprehensive review has been conducted on the neural basis of cognitive-motor DTC in people with neurological conditions. The primary goal of this review was to examine neural correlates of DT walking in people with PD, MS, AD, and stroke. Also, we sought to report on the DT walking performance of people with neurological conditions in comparison to other groups (e.g., healthy matched controls). This systematic review will allow for a better understanding of the neural basis of DTC-walking in people with PD, MS, AD, stroke. This could help identify shared or distinct neural correlates (e.g., specific brain regions) that are associated with DT walking performance in people with neurological disorders and inform on rehabilitation strategies that improve mobility and decrease the risk of falls.

Methods

Literature search and search strategy

Medline, Embase, and Scopus were searched using MeSH terms and keywords. The search terms were developed for population, intervention, and outcomes using the PICO model as a guideline. The search terms include: (a) condition related terms (stroke, MS, AD, or PD); (b) DT related terms such as DT performance, dual-tasking, DTC, and cognitive-motor interference and (c) gait related terms such as walking, gait, locomotion, and kinematics (see appendix).

Study selection and inclusion/exclusion criteria

The following criteria were used to determine the eligibility of papers: (a) Language: English; (b) Publication year: unlimited; (c) Type of study: peer-reviewed primary research articles and no reviews (e.g., systematic review), conference proceedings or research posters; (d) Included

adults over 18 years old with stroke, MS, AD or PD, excluding related conditions (e.g., dementia); (e) used cognitive-motor DT where the motor task was straight line overground walking with no added challenges (e.g., treadmill, obstacles); (f) used a neuroimaging technique to examine structural or functional brain changes; (g) reported behavioural (motor) performance under the DT and single task (ST) conditions; (h) reported functional or structural brain outcomes; (i) reported data regarding the relationship between behavioural performance and brain outcomes (e.g., correlations, regression analysis). Studies that didn't meet the last criterion were still included if they met the other criteria. Using these criteria, two reviewers (HK & SF) independently screened the titles and abstracts, and then included studies underwent full-text screening to determine the final included studies. Cohen's kappa coefficient was used to measure inter-rater reliability during this process.

Study quality assessment and data extraction

The Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional studies was used to determine risk of bias of included papers [36]. The checklist has eight items that assess risk of bias (Table 1) associated with inclusion/exclusion criteria (item #1), study subject and setting (item #2), exposure (item #3), measurement of health conditions (item #4), confounding factors (item #5 and #6), outcome measures (item #7), and lastly statistical analysis (item #8). Reviewers have the following options to choose; yes, no, unclear, and not applicable. Two raters (HK & SF) evaluated each paper independently and conflicts were resolved by discussion.

The following data were extracted from the included studies: (1) authors and year of publication; (2) study design; (3) participant characteristics (e.g., sample size, and age); (4) baseline demographic and clinical measures including neuropsychological assessments; (7) type

of cognitive and motor task used; (8) type of imaging technique used; (9) behavioural outcomes (e.g., gait under ST and DT conditions) and (10) brain outcomes (e.g., structural or functional including neural correlates). One author extracted, and the other author confirmed the extracted data. Conflicts were resolved by consensus.

This systematic review protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) ID: CRD42021227362.

Data analysis and synthesis

Studies were organized by neurological condition examined (PD, MS, stroke, AD) and then by neuroimaging technique used. For each study, behavioural and brain outcomes were discussed and if the data were available, the neural correlates between brain and behaviour were also reported. Specifically, following data were compared: (a) walking and cognitive performance under DT and single task (cognitive or motor) conditions; (b) Functional brain changes from single task to DT condition in people with neurological disorders and healthy individuals if there was a control group; (c) structural brain measures between people with neurological disorders and healthy individuals and (d) correlations between DT walking performance and brain imaging results.

Results

Selection of articles

The literature search retrieved 2588 articles. These articles were imported to Covidence [37] and 1232 duplicates were removed. The remaining 1356 articles were screened based on title and abstract and 1284 articles were excluded. 72 articles were eligible for full-text screening and 45 of them were excluded for one of the following reasons: (a) they represented conference proceedings/posters (17 articles); (b) only an abstract was available (11 articles); (c) wrong

outcomes (7 articles) (e.g., Dual task findings only reported with respect to pre- and post-intervention values (e.g., PRE dual-task cost vs POST dual-task cost) and no reporting of single vs dual-task values); (d) letter to the editor (5 articles); (e) wrong study design (3 articles); (f) study protocol (1 article) and (g) wrong patient population (1 article). This left 27 papers for the data extraction. During the data extraction process, four additional articles were excluded due to a lack of analysis on brain and/or behaviour outcomes under the ST and DT conditions, which resulted in 23 articles to be included for the data synthesis (Fig. 1). Out of 23 included articles, 11 articles were on PD, 6 on MS, 6 on stroke, and 0 on AD.

Fig. 1 Prisma diagram for the screening and inclusion of articles

Methodological quality

Out of 23 studies, 78% scored low risk of bias for all eight items on the JBI checklist. 13% had unclear risk of bias for one of the items (item #7, 6, 7 respectively). One study [38] scored high risk of bias for item #3 and unclear risk of bias for item #4. Lastly, a study by Hermand et al. (2019) [39] had unclear risk of bias for item #4 and 6 (Table 1).

Table 1 JBI quality assessment results for included studies

Participants' characteristics of included studies

Table 2 shows the summary of participants' characteristics including baseline measures of motor and neuropsychological performance. A total of 803 people with neurological conditions were included with the age range of 34.9 – 75 years. The disease duration ranged from 0.12 – 13.3 years. 14 studies included 384 healthy people, as controls, who were aged between 22.4 – 77.2 years old. More specifically, there were 547 people with PD aged between 59.5 – 75 years old with disease duration of 2.2 – 12.08 years and 249 healthy individuals aged between 57 – 77 years old. MS papers included 130 people with MS aged between 34.9 – 57 years old with disease

duration of 9.05 – 13.3 years and 97 healthy individuals aged between 39.4 – 61 years old. Lastly, stroke papers included 126 people with stroke aged between 51.5 – 71.4 years old (0.12 – 3.46 years post stroke) and 38 healthy people aged between 22.4 – 77.2 years old.

Table 2 Participants' characteristics including baseline clinical measures of included studies

Dual-task performance

Table 3 shows the summary of types of dual-tasks used, behavioural outcomes, and brain findings including neural correlates. The included studies reported behavioural measures for single and DT conditions and provided a comparison between these two conditions while a few studies only reported DTC scores (percent change from single- to dual-task). The neural correlates of dual-task walking for each neurological condition were reported while overall findings were reported for dual-task performance and other brain findings. Details on each neurological condition can be found in Table 3.

Cognitive performance

The serial-subtraction task was most used (56%) [40-52]. Other tasks utilized include n-back task [38, 39], auditory task [53, 54], AX-Continuous Performance Test [55, 56], letter recitation [29, 48], word list generation [47, 57], digit vigilance task [58], and Stroop color and word test [27]. All studies measured the number of correct responses and/or errors made. Out of 23 studies, only eight reported DT-cognitive performance versus ST. 37% reported a decrease in performance under DT versus ST conditions [46, 50, 53]. Sartor et al. (2017) reported better performance under DT condition in PD [44]. 50% reported no difference between the conditions [39, 38, 56, 58]. However, Hermand et al. (2020) found poorer DT cognitive performance in individuals with stroke with slight dependency by conducting subgroup analysis [38]. Out of six studies that compared cognitive performance of people with neurological disorders with healthy

controls, 67% observed increased DT-cognitive accuracy in healthy individuals compared to people with neurological disorders [41, 46, 47, 52]. The remaining reported no difference between the groups [29, 44].

Motor performance

Self-paced walking was most common (91%) while two studies instructed participants to walk fast [42, 47]. Four studies were not considered as there was no comparison between DT and ST conditions [27, 43, 52, 54]. Regardless of neurological conditions examined, the majority (90%) reported a decrease in DT performance compared to single task walking [29, 39-42, 44-46, 48-51, 53, 55-58]. Two reported no difference between the single task and DT conditions [47, 38]. Gait speed (m/s) and stride length (m) were most commonly measured. During DT versus single walking, 68% reported slower gait speed [29, 39-41, 44-46, 48, 50, 51, 55-57] and 42% reported shorter stride length [41, 42, 45, 50, 51, 53, 55, 56]. 69% reported better DT gait performance (e.g., increased gait speed) in healthy people compared to people with neurological disorders [41, 42, 44, 45, 47, 49, 52, 57, 58]. The rest found no difference between the groups [29, 43, 46, 54].

Structural and functional brain outcomes

Thirteen out of 23 studies used fNIRS, nine used MRI, and one used fMRI. 54% of fNIRS studies reported a significant increase in brain activity during DT versus ST conditions (cognitive or motor) [29, 40, 46, 50, 51, 57, 58]. The rest reported no significant difference between the task conditions [38, 39, 41, 52, 55, 56]. However, Hermand et al. (2020) found a DT-related increase in brain activity in people with MS with moderate dependency when subgroup analysis was performed [38]. The PFC was most (92%) commonly examined [29, 38, 39, 40, 41, 50, 51, 52, 55, 56, 57, 58]. Other brain areas investigated include premotor cortex (PMC) and supplementary motor area [46, 51]. 50% of fNIRS studies with healthy controls reported no difference in brain

activity between healthy individuals and people with neurological disorders [41, 57, 58]. 33% reported greater brain activation in healthy people compared to people with neurological conditions [46, 52]. One found higher brain activity in people with MS versus healthy individuals [29].

44% of MRI studies reported a significant decrease in brain volume/integrity in people with neurological disorders or high disability group versus healthy people or low disability group [27, 43, 49, 53]. Brain measures/areas examined are brain volume including white and/or grey matter [27, 49], striatum regions and related structures such as pedunculopontine nucleus (PPN) [43, 53]. One reported no difference in white matter changes between PD and healthy controls [44]. Argento et al. (2020) found an increase in cerebellar volume in people with MS compared to healthy people [47]. 33% only reported MRI measures (e.g., white matter lesions) with no comparisons with healthy individuals or there was no control group [42, 45, 48]. For stroke, there were no structural imaging studies.

One fMRI study reported the following results for people with PD versus healthy people: (a) hypo or hyper-connectivity within motor regions; (b) hypoconnectivity within striatum and between striatum and parietal areas and (c) hyperconnectivity between motor and parietal/striatum [54].

Correlations between behavioural and brain outcomes

Eighteen out of 23 studies reported the correlations (9 fNIRS, 8 MRI, and 1 fMRI): nine for PD (3 fNIRS; 5 MRI; 1 fMRI), four for MS (1 fNIRS; 3 MRI), and five for stroke (5 fNIRS). 44% of fNIRS studies reported a significant correlation between increased brain activity and poorer DT performance [41, 46, 50, 51]. 22% found a significant correlation between increased brain activity and better DT-walking [52, 56] while 33% found no significant results [39, 55, 57].

75% of MRI studies found a significant positive association between lower brain volume/integrity and poorer DT performance [27, 42, 43, 45, 48, 53]. The brain areas/measures that showed the positive association include striatum regions [42], PPN [53], hippocampus [43], periventricular white matter changes [45], whole brain volume [27], and motor areas (e.g., SMA) [48]. One study found lower brain volume combined with better DT performance in older adults with PD [44]. The remaining study found no significant correlations [49]. Lastly, one fMRI study found hypo or hyperconnectivity of the brain combined with poorer DT performance [54].

Parkinson's disease

Results from fNIRS studies were mixed. One found a correlation between increased PFC activity and slower DT gait speed while this correlated with increased speed in healthy people [41]. Vitorio et al. found a significant association between increased PFC activity and better DT performance (decreased gait variability) in PD with freezing of gait (FoG) only [56]. Stuart et al. reported no significant correlations between the PFC and DT walking [55]. 80% of MRI studies found a significant relationship between lower brain integrity and poorer DT performance (e.g., slower gait speed) [42, 43, 45, 53]. Specifically, brain measures/areas that demonstrated this relationship include striatum [42], PPN [53], hippocampus [43], and periventricular white matter lesions [45]. One study found a significant correlation between greater white matter lesions and better DT performance (e.g., increased gait speed) in older adults with PD but not in healthy individuals [44]. One fMRI study found a significant correlation between poorer DT gait performance and decreased connectivity between left caudate and superior temporal lobe and increased connectivity between left dorsal putamen and right precuneus in PD with FoG [54].

Multiple sclerosis

The fNIRS study reported a significant negative correlation between increased SMA activity and DT gait speed only in MS and not in healthy individuals [46]. Two (67%) MRI studies found a significant association between lower brain volume/integrity and poorer DT cadence and gait variability respectively [27, 48]. The brain measures/areas that correlated with poorer DT performance include whole brain and grey matter volume [27] and SMA white matter integrity [48]. Coghe et al. (2018), however, also found an association between lower brain volume and decreased DTC-walking (e.g., double support time) [27]. These correlations were only found in people with MS and not in healthy people [27]. The remaining study found no significant results in both people with MS and healthy individuals [49].

Stroke

40% of fNIRS studies found a significant relationship between increased brain activity and decreased DT motor (e.g., slower gait speed) [51] or cognitive (e.g., decreased accuracy) [50] performance. Brain areas that correlated with poorer DT performance are PFC [50, 51] and motor areas (e.g., PMC, SMA) [51]. 40% found no significant results [39, 57]. The last study found a significant correlation between elevated PFC activity and better DT-gait performance (decreased DTC on acceleration magnitude) in people with stroke but not in healthy individuals [52]. Instead, healthy individuals showed a significant correlation with better DT-cognitive performance [52].

Table 3 Behavioural and brain imaging results of included studies

Discussion

This systematic review reported findings of 23 studies on DT walking performance and neural correlates of people with stroke, MS, and PD. Most studies (n = 17) reported DTC of walking and half reported cognitive DTC. In addition, healthy people in general showed better DT performance than people with neurological conditions. In general, studies observed an association

between poorer DT performance and increased brain activity (e.g., PFC) or lower structural integrity (e.g., hippocampus) in people with neurological disorders while no such correlations were found in healthy individuals. A detailed discussion of cognitive-motor performance measures, structural and functional imaging findings as well as neural correlates will follow.

Behavioural findings

Walking performance

In line with the literature, people with neurological disorders demonstrated DTC-walking (e.g., slower gait speed) [2, 23, 24]. This is consistent with capacity sharing theory [17, 34] and demonstrates that a decline in performance was inevitable as demand exceeded capacity under DT conditions [59]. In addition, the DTC was greater than healthy people, which shows that dual-tasking ability of people with neurological conditions may be reduced because of underlying neural changes [2; 60]. According to the findings of this review, this could be possibly due to increased PFC activity [41] or hippocampal atrophy [43], for example in PD. Most studies observed a DT-related decline in speed and stride length. To a lesser extent, gait variability was examined, which increased while dual-tasking versus single-walking. While gait speed has been a common outcome measure of dual-tasks, there is some evidence that gait variability might better predict a fall risk than gait speed [61]. Further, studies exploring falls have argued that increased gait variability is a marker for falls in the populations included in this review [62-65]. Therefore, studies that aim to reduce fall risks should examine various features of gait including gait variability to better characterize fall risks and gait patterns of people with neurological conditions.

Cognitive performance

Less than half of the included studies observed cognitive-DTC. Others found improvements or no differences but still observed poorer DT-walk performance, which suggests

that in certain studies, people may have prioritized the cognitive task over walking [66]. This contradicts the posture first principle, which states that healthy people tend to prioritize balance over other tasks [67]. However, Yogev-Seligmann et al. (2012) proposed that a task prioritization during walking is dynamic and can be affected by various factors (e.g., physical capacity, hazards) [66]. An inappropriate assessment of these factors can occur in people with neurological disorders [59] and they may focus on cognitive task versus walking even though this might increase falls risk [66]. The mixed findings on cognitive performance may be due to the heterogeneity of cognitive tasks used, which assess different cognitive functions and have various levels of difficulty. For example, working memory tasks like n-back tasks have been known to affect DT cognitive performance more than simple reaction time tasks [68]. Since the findings from the included studies are mixed and less than half of the studies (n = 8) reported DT cognitive performance, we can only speculate on the prioritization of people with neurological disorders or assume they will show cognitive-DTC. Further, it is difficult to conclude about the overall DT performance when only gait data is presented as there could be a trade-off between cognitive and motor performance [69]. In future studies, it will be important to measure and report both cognitive and motor performance under the DT and ST conditions and within and between populations where possible. This will reduce ambiguity and will allow better understanding of shifts in cognitive and motor performances and DT ability of people with neurological conditions.

Brain findings

Compared to behavioural outcomes, brain findings including neural correlates were much more variable, which is in line with dual-task neuroimaging literature [35, 70].

Functional imaging

There was either a DT-related increase in brain activity or no difference. The former was associated with poorer DT performance in about half of the studies while others reported its association with better DT performance or no correlations. Most studies examined the PFC activity possibly to focus on executive functions involved in dual-tasking [35]. Since executive functions [20] and the PFC [21] are commonly affected in people with neurological disorders, it can be speculated that PFC damage might be closely related to DT performance of this population. However, based on the results, the relationship between the PFC and dual-tasking is not straightforward.

In both people with PD and stroke, the PFC activity increased or remained stable during dual-tasking. An increase in PFC activity correlated with better or poorer DT performance in PD while in stroke, most reported no correlations, but it was also associated with poorer or better DT performance. Other brain areas examined include PMC and SMA. People with MS and stroke both increased activity of these areas under DT versus ST conditions (motor or cognitive). Saleh et al. (2018) and in Liu et al. (2018) showed a negative correlation between SMA and DT performance in both populations [46, 51]. The SMA plays an important role in planning and executing voluntary movements and works closely with the PFC, suggesting its role in executive functioning [71] and dual-tasking [46].

One fMRI study found decreased DT performance combined with hyperconnectivity within striatum regions (putamen and nucleus) or hypoconnectivity between caudate nucleus and temporal lobe in PD with FoG. The striatum regions are predominately affected in PD [72], which are important for carrying out motor movements (e.g., gait) and executive functioning [15; 73] and thus has been implicated in cognitive-motor dual-tasking [33]. The reduced connection between

caudate and temporal lobe might be associated with the cognitive task performed (auditory Stroop task) as these structures interact to process auditory information during DT [74].

Overall, the results show no clear trend between DT performance and brain activity within or between people with neurological disorders. Even if some associations exist (e.g., SMA and DT), it is difficult to draw a conclusion as these results are based on a small number of studies. Findings suggest specific brain areas such as PFC and SMA may have the association with DT performance. However, the direction of brain activity changes and its effect on DT performance remain unclear. These mixed findings could be explained by the CRUNCH model [32] and neural dedifferentiation hypothesis [75]. As previously mentioned, the CRUNCH model predicts that older adults will increase their brain activity more than young adults to compensate for age-related brain changes until the crunch point is reach [32]. In line with this model, people with neurological disorders might have upregulated the brain activity to compensate for disease-related brain changes. However, when there is no control group, it is uncertain whether this increase in brain activity is the result of compensation or natural response to increasing tasks demands under DT [76]. While some participants were able to increase their brain activity, others might have reached or were close to their limit of neural reserve (crunch point) under the ST conditions and struggled to upregulate the brain activity as the task difficulty increases under the DT condition. Indeed, this is how Hermand et al. (2019) explained their unexpected findings of no PFC oxygenation changes and decreased DT walking performance in people with stroke [39]. In the included studies, there was evidence that the DT was demanding, as people slowed their gait speed from single to DT, but this was not accompanied by higher brain activity [39, 55]. Thus, the CRUNCH model could explain the variability in the direction of brain activity changes reported by the included studies.

The CRUNCH model also addresses the association between brain activity changes and performance. It predicts an increase in brain activity and performance (compensatory) and a decrease in brain activity and/or performance once the CRUNCH point is reached [32]. Therefore, the association between poor DT performance and decreased connectivity between the caudate and superior temporal lobe observed by the fMRI study supports the CRUNCH model. Also, the reported correlation between increased PFC activity and better DT performance in people with PD and stroke could be explained by CRUNCH. However, increased brain activity could also be due to neural dedifferentiation but unlike the CRUNCH model, it is associated with poor performance [75]. It has been suggested that neural dedifferentiation occurs due to age-related brain changes in older adults [75]. Neural dedifferentiation leads to a more diffused brain activity due to a loss of neural specificity [77]. In this case, elevated brain activity is not adaptive and reflects reduced ability of the brain to selectively respond to given tasks and thus it leads to poor performance [75, 78] or has no effect on performance [79]. Therefore, the reported relationship between increased brain activity (e.g., PFC, SMA) and decreased DT performance or no correlations indicate neural dedifferentiation. Taken together, increased functional activation could be associated with better (compensatory) [75] or poorer performance or may not related to performance (dedifferentiation) [79], which could be influenced by multiple factors such as individual differences (e.g., older age, neural reserve) and types of tasks used (e.g., working memory vs simple reaction time task) [80].

In healthy people, there was a significant correlation between increased brain activity (e.g., PFC) and better DT performance (compensatory) or no correlations (e.g., SMA). A lack of correlations could be due to small changes in brain activity and/or performance [81]. Further, in general, healthy people performed better than people with neurological conditions. This shows that healthy individuals were able to better manage DT conditions. A decrease in DT performance was

still observed but the degree of decline was much less than people with neurological conditions. It is important to note that most healthy individuals were older adults. Thus, it is possible that they are experiencing age-related cognitive and motor decline, which can contribute to decreased DT performance [82] even without neurological conditions.

Structural imaging

Most MRI studies found lower structural integrity in people with neurological disorders or high disability group (e.g., FoG+) compared to healthy people or low disability group (e.g., FoG-). Interestingly, Argento et al. found a greater cerebellar volume in people with MS with low disability versus high disability or healthy people, which was unexpected [47]. However, brain volume can increase in MS due to various reasons such as measurement errors, and biological factors (e.g., inflammation, hydration status) while the underlying mechanism and contributing factors should be further investigated [83]. Usually, people with neurological disorders experience a decrease in structural integrity [84-86]. Pathological brain changes lead to various cognitive and motor impairments that can negatively affect DT gait performance of people with neurological conditions [2]. The findings support this, as most of the included studies found a correlation between increased structural brain changes and decreased dual-task performance.

Specific brain regions that correlated with poor DT performance include striatum, PPN, and hippocampus in PD and SMA in MS. As explained, due to its involvement in motor and executive functions [15; 73], damages to striatum could lead to poor cognitive-motor dual-tasking [33]. Another structure called PPN has been implicated in gait disturbances in PD (e.g., FoG) [87] and attentional functions [88]. Therefore, PPN could potentially play a role in dual-tasking [53] and explain why Peterson et al. found the correlation only in PD with FoG versus without FoG (2014) [53]. Hippocampal atrophy is also common in PD [89] and is related to poor DT

performance in people with cognitive impairment [90]. Thus, striatum regions, PPN, and hippocampus might be involved in DT-walking in PD. Lastly, white and grey matter atrophy in SMA, which commonly occurs in MS [91], can negatively affect their DT performance [46].

In contrast to most studies, Sartor et al. (2017) found a significant positive relationship between greater white matter lesions and better DT performance in older adults with PD [44]. Coghe et al. (2018) also reported the positive correlation with brain volume including white and grey matter in people with MS [27]. There were no similar findings and the literature suggests the opposite in which lower structural integrity including white matter lesions are associated with motor and cognitive deficits in PD [92] and MS [93, 94] and poorer DT performance in general [95-97].

Limitations and future directions

One of the biggest limitations is a variability in study design (e.g., cognitive tasks used, gait measures), which hinders a direct comparison between the studies and generalizability of findings. Further, many did not report cognitive DT performance and thus it is difficult draw a clear conclusion regarding cognitive DTC and overall changes in DT performance. In addition, after screening, there were no studies on people with AD. People with AD might be particularly difficult to recruit due to several reasons such as a rapid disease progression, and comorbidities [98]. Most of the included studies recruited people with mild to moderate neurological conditions so that they can complete the tasks. However, people with AD are often diagnosed at a later stage of disease, hindering the recruitment of people with mild AD [99].

Future studies could use a standardized reporting of DT performance and report both cognitive and gait performances to reduce variability and facilitate a better synthesis of data, possibly meta-analysis. For people with AD, tasks that are less demanding or portable imaging

techniques (e.g., fNIRS) could be used to test this population at home or places that are more accessible. If possible, studies could examine how the brain as a whole and specific brain areas respond under DT conditions using combined imaging techniques (e.g., MRI and fNIRS). Understanding these neural correlates could help create targeted rehabilitation strategies that improve DT performance. Also, analyzing different patterns of brain activity and DT performance could identify individuals at risk for cognitive and/or motor declines (e.g., those who show increased brain activity but decreased DT performance).

Conclusion

This systematic review investigated DT-walking and associated neural correlates in people with neurological conditions. The results showed that people with neurological disorders are more likely to experience motor or cognitive DTC than healthy individuals. Overall, lower structural integrity of the striatum regions, PPN, and hippocampus in PD and SMA in MS may be associated with poor DT performance. The functional brain findings showed that the PFC and SMA might be associated with DTC in people with neurological disorders in general. The results align with the CRUNCH model and neural dedifferentiation hypothesis in which a directionality of brain activation changes and its effect on performance can vary, which could be affected by many different factors (e.g., neural reserve). Taken together, several neural correlates have been identified in this review, however, the neural basis of DT-walking is complex and further studies are needed to clarify the association between these potential neural correlates and DT-walking in people with neurological conditions.

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7. Figures and tables

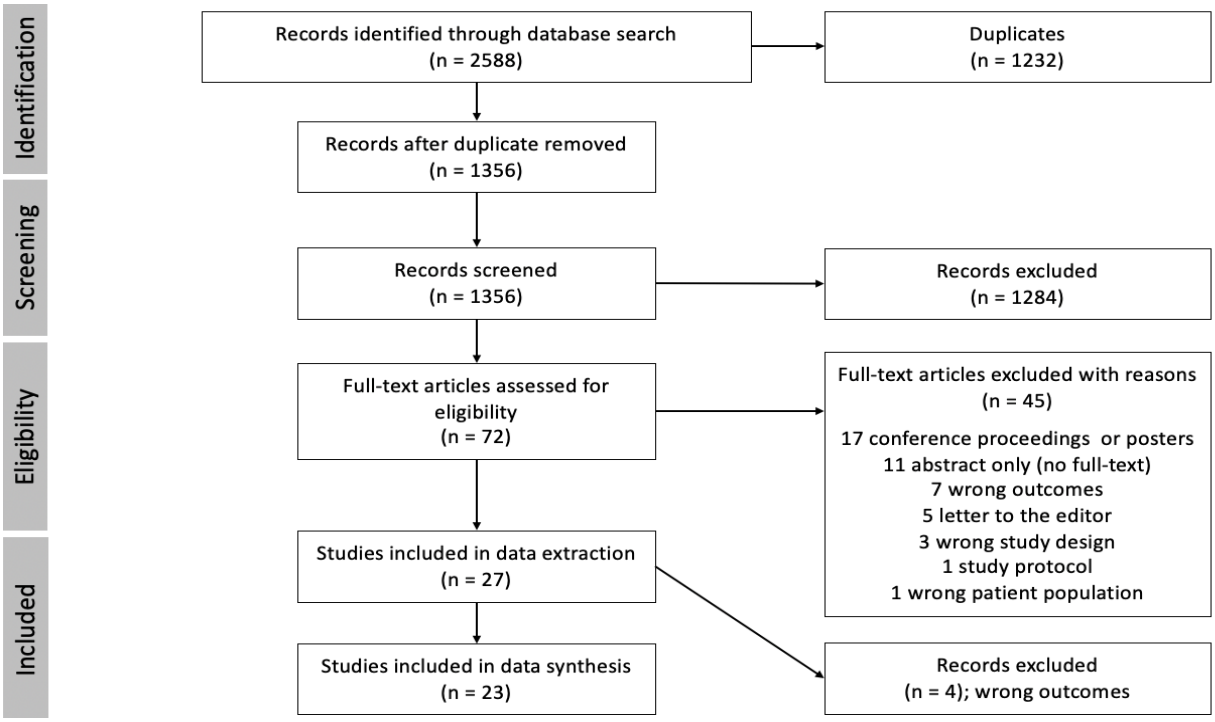

Figure 1. Prisma diagram for the screening and inclusion of articles.

Table 1. JBI quality assessment results for included studies

Articles	Items							
	1	2	3	4	5	6	7	8
Argento et al 2020	O	O	O	O	O	Δ	O	O
Chatterjee et al 2019	O	O	O	O	O	O	O	O
Coghe et al 2018	O	O	O	O	O	O	O	O
Dagan et al 2020	O	O	O	O	O	O	O	O
Fritz et al 2019	O	O	O	O	O	O	O	O
Hawkins et al 2018	O	O	O	O	O	O	O	O
Hermand et al 2020	O	O	X	Δ	O	O	O	O
Hermand et al 2019	O	O	O	Δ	O	Δ	O	O
Hernandez et al 2016	O	O	O	O	O	O	O	O
Hirata et al 2020	O	O	O	O	O	O	O	O
Liparoti et al 2019	O	O	O	O	O	O	O	O
Liu et al 2018	O	O	O	O	O	Δ	O	O
Maidan et al 2016	O	O	O	O	O	O	O	O
Mori et al 2018	O	O	O	O	O	O	O	O
Orcioli-Silva et al 2020	O	O	O	O	O	O	O	O
Peterson et al 2015	O	O	O	O	O	O	O	O
Rosenberg-Katz et al 2016	O	O	O	O	O	O	Δ	O
Saleh et al 2018	O	O	O	O	O	O	O	O
Sartor et al 2017	O	O	O	O	O	O	O	O
Stuart et al 2020	O	O	O	O	O	O	O	O
Toda et al 2019	O	O	O	O	O	O	O	O
Vervoort et al 2016	O	O	O	O	O	O	O	O
Vitorio et al 2020	O	O	O	O	O	O	O	O

O: low risk of bias; Δ: unclear/no information available; X: high risk of bias

Table 2. Participant characteristics of included studies

Authors (year)	Study design	Sample size (n); Age M (SD) (years)	Disease duration M (SD) (years)	Baseline clinical measures M (SD)	
Parkinson's disease (PD)					
Dagan et al 2020	Cross-sectional	PD: 40; 68.38 (7.48)	8.83 (5.52)	UPDRS-III OFF = 42.25 (14.37) UPDRS-III ON = 35.25 (13.45) NFOG-Q = 18.79 (3.94) MMSE = 28.4 (1.7) Global cognitive score = 96.08 (9.50)	
Hirata et al 2020	Cross-sectional	PD: 21; 71.6 (5.6) HC: 12; 70.1 (7.4)	2.2 (1.9)	MoCA-J = 24.4 (3.2) UPDRS part III total score = 25.9 (13.1)	
Maidan et al 2016	Cross-sectional	PD: 68; 71.6 (0.9) HC: 38; 70.4 (0.9)	9.1 (0.7)	MMSE (/30): • PD: 28.2 (0.2) • HC: 28.8 (0.2) Computerized cognitive test (PD; HC): • Executive function: 87.9 (1.3); 102.8 (1.8) • Visual-spatial: 94.6 (1.9); 103.1 (3.3) • Attention: 88.6 (1.9); 101.1 (1.6)	UPDRS motor: 32.9 (1.7) Mobility tests: • FSST (s): 14.5 (0.9); 8.7 (0.5) 2MWT (m): 119.8 (4.3); 152.6 (4.3)
Orcioli-Silva et al 2020	Cross-sectional	PD: 20; 69.8 (5.9) HC: 30; 68.0 (5.6)	5.6 (3.1)	MMSE (0-30): • PD 26.9 (1.8) • HC 27.7 (1.6) MDS-UPDRS III (0-132): • OFF: 35.2 (11.3) • ON (0-132): 27.7 (11.4) Most affected limb (right/left): 8/12	
Peterson et al 2015	Cross-sectional	PD: 25 • FoG-: 12; 64.9 (6.9) • FoG+: 13; 66.2 (5.5)	• FoG-: 6.5 (4.2) • FoG+: 10.8 (6.2)	UPDRS: • FOG- 29.2 (6.9) • FOG+ 38.6 (9.7) MOCA: • FoG-: 27.8 (1.9) • FoG+: 26.5 (2.1)	Preferred gait velocity: • FoG-: 74.8 (9.01) • FoG+: 70.56 (9.60)
Rosenberg-Katz et al 2016	Cross-sectional	PD: • ID: 45; 65.16 (8.43) • PIGD: 30; 64.95 (7.71)	• ID: 5.62 (5.50) • PIGD: 5.69 (3.68) • TD: 5.36 (3.15)	UPDRS motor sum: • ID: 41.85 (14.70) • PIGD: 38.74 (10.47) • TD: 39.47 (15.30)	Global cognitive score: • HC: 95.88 (9.43) • ID: 94.49 (10.70) • PIGD: 90.04 (14.39)

		• TD: 30; 64.60 (8.85) HC: 28; 64.91 (8.76)		NFOG-Q: • ID: 4.50 (7.66) • PIGD: 8.16 (9.88) • TD: 0 (0) ABC scale: • ID: 84.50 (16.50) • PIGD: 79.20 (17.00) • TD: 94.55 (7.84)	• TD: 95.89 (10.79) Geriatric depression scale: • ID: 3.96 (3.20) • PIGD: 4.70 (3.14) • TD: 3.00 (3.19)
Sartor et al 2017	Cross-sectional	PD: • yPD: 22; 62 (49-69) • oPD: 36; 75 (70-89) HC: • yPn: 65; 57 (50-69) • oPn: 36; 77 (70-89)	–	MMSE (0-30): • yPn: 29 (15-30) • yPD: 29 (17-30) • oPn: 28 (16-30) • oPD: 28 (17-30) UPDRS III (0-132): • yPn: 7 (0-38) • yPD: 41(16-78) • oPn: 12 (0-46) • oPD: 38 (15-74) BDI II (0-63): • yPn: 11 (1-51) • yPD: 9 (5-34) • oPn: 11 (1-31) • oPD: 12 (3-20)	TMT-A (s): • yPn: 36 (20-180) • yPD: 51 (25-180) • oPn: 55 (28-180) • oPD: 68 (36-180) TMT-B (s): • yPn: 104 (49-300) • yPD: 254 (53-300) • oPn: 202 (64-300) • oPD: 300 (73-300)
Stuart et al 2020	Cross-sectional	PD: 25; 69.20 (3.99) • FoG+: 13; 69.69 (4.21) • FoG-: 12; 68.67 (3.85)	10.00 (6.27) • FoG+: 12.08 (6.18) • FoG-: 7.75 (5.77)	UPDRS III: 36.40 (11.67) • FoG+: 40.00 (14.01) • FoG-: 32.50 (7.15) FOG-Q: 883.39 (501.40) • FoG+: 924.92 (609.37) • FoG-: 839.44 (373.20) MoCA: 27.12 (3.83) • FoG+: 26.08 (3.62) • FoG-: 28.25 (3.62) FAB: 14.48 (3.04) • FoG+: 14.08 (3.23) • FoG-: 14.92 (2.91)	TMT-A: 51.48 (57.10) • FoG+: 65.25 (21.16) • FoG-: 36.56 (17.14) TMT-B: 98.35 (51.74) • FoG+: 123.55 (57.31) • FoG-: 71.04 (26.31) TMT B-A: 46.87 (35.57) • FoG+: 58.30 (42.66) • FoG-: 34.48 (21.29) CLOX1: 11.76 (2.32) • FoG+: 12.08 (1.38) • FoG-: 11.42 (3.06) CLOX2: 13.44 (1.66) • 12.92 (2.02) • 14.00 (0.95)
Toda et al 2019	Cross-sectional	PD: 64; 67.9 (8.6) HC: 20; 71.0 (7.1)		UPDRS-III: 11.1 (8.1) MMSE score: 28.9 (1.4) FAB: 15.1 (2.0) based on 53 PD individuals	

Vervoort et al 2016	Cross-sectional	PD : 73; 59.5 (10.2) • FoG+ = 13; 65.8 (9.9) • FoG- = 60; 58.2 (9.9) HC: 20; 57.7 (8.8)	6.2 (3.8) • FoG-: 5.8 (3.3) • FoG+: 7.9 (5.4)	MDS-UPDRS-III: 28.1 (13.2) • FoG-: 25.9 (12.0) • FoG+: 38.3 (13.9) NFOG-Q: • FOG+ 15.8 (7.5)	MMSE: • HC: 29.3 (0.8) • PD: 28.4 (1.6) • FoG-: 28.5 (1.6) • FoG+: 28.0 (1.6)
Vitorio et al 2020	Cross-sectional	PD: 48 • FoG+: 24; 70.3 (4.7) • FoG-: 24; 70.8 (7.6)	• FoG+: 10.1 (6.1) • FoG-: 7.2 (5.2)	MDS-UPDRS-III (score): • FoG-: 35.0 (10.3) • FoG+: 42.4 (13.2) MoCA: • FoG-: 27.2 (3.7) • FoG+: 26.0 (3.1) FAB: • FoG-: 14.6 (3.1) • FoG+: 14.6 (3.0) TMT-A (s): • FoG-: 36.5 (15.6) • FoG+: 51.9 (57.7)	TMT-B (s): • FoG-: 83.5 (38.5) • FoG+: 116.5 (56.1) TMT-(B-A) (s): • FoG-: 46.9 (30.4) • FoG+: 64.5 (44.9) CLOXI: • FoG-: 12.1 (2.0) • FoG+: 12.2 (1.4) CLOX2: • FoG-: 13.9 (0.9) • FoG+: 13.3 (1.6)
Multiple Sclerosis (MS)					
Argento et al 2020	Cross-sectional	MS: 20; 44.8 (6.2) HC: 18; 39.4 (11.9)	13.29 (9.8)	EDSS (median) = 3.25	
Coghe et al 2018	Cross-sectional	MS = 48; 41.1 (8.9) HC = 36; 40.1 (12.6)	–	EDSS: 2.4 (1.5) SCWT: 72.5 (47.9)	
Fritz et al 2019	Cross-sectional	MS = 18; 45.5 (8.2)	12.3 (6.7)	EDSS median (range): 2.25 (1.5-4)	
Hernandez et al 2016	Cross-sectional	MS: 8; 57 (5) HC: 8; 61 (4)	Not reported	RBANS: • MS 97 (15) • HC 110 (12)	EDSS not reported: included MS with mild to moderate disability
Liparoti et al 2019	Cross-sectional	MS: 22; 34.9 (9.4) HC: 21; 37 (11.8)	108.6 (89.7) (month) 9.05 (7.47) (years)	EDSS: • Pyramidal: 0.7 (0.5) • Cerebellar: 0.3 (0.5) SDMT: • HC: 51.8 (10.2) • MS: 20.4 (8.7) PASAT 3": • HC: 38.9 (11.5) • MS: 37.4 (12.8) PASAT 2”: • HC: 29.3 (9.4) • MS: 30.8 (11.8)	WLG: • HC: 23.7 (6.9) • MS: 20.2 (4.4) SCWIT: • HC: 62.9 (22.2) • MS: 61.8 (15.1) CII: • HC: 8.5 (4.3) • MS: 8.1 (3.9)

Saleh et al 2018	Cross-sectional	RR-MS = 14; 50 (8) HC = 14; 50 (9)	–	SDMT: • HC: 57.7 (5.77) • MS: 53.2 (12.4) BVMT-R raw score: • HC: 4.07 (2.05) • MS: 3.14 (1.96)	CVLT-II: • HC: 55.86 (8.8) • MS: 52.2 (9.26)
Stroke					
Chatterjee et al 2019	Cross-sectional	Stroke: 33; 59.6 (9.7)	19.2 (10.4) (months) 1.6 (0.87) (years)	FMA-LE score (/34): 24.7 (4.4) DGI: 13.6 (3.5) MMSE: 26.6 (3.1) ABC scale (%): 59.2 (19.6)	Affected Hemisphere (L/R): 16/17 10MWT (m/s): 0.6 (0.2)
Hawkins et al 2018	Cross-sectional	Stroke: 24; 58.0 (9.3) Elderly: 15; 77.2 (5.6) Young: 9; 22.4 (3.21)	18.3 (9.3) (months) 1.52 (0.77) (years)	FMA-LE score: • Stroke: 25.3 (4.0) ABC score (%): • Stroke: 59.1 (19.1) • Elderly: 83.0 (15.0)	MMSE: • Stroke: 25.9 (3.3) • Elderly: 27.4 (1.7)
Hermand et al 2019	Cross-sectional	Stroke: 11; 71.4 (10.1)	45.5 (34.5) (days) 0.12 (0.09) (years)	Barthel index (/100): 81.8 (11.0) Functional ambulation category (/5): 3.9 (1.0)	Stroke subtype (Ischemic/hemorrhagic): 9/2
Hermand et al 2020	Cross-sectional	Stroke: 21; 68.1 (9.4) • LoB: 8; 70.6 (10.5) • HiB: 13; 66.6 (10.4)	62.9 (30.9) (days) • LoB 54.5 (39.3) • HiB 68.1 (28.2)	Barthel Index (/100) = 89.8 (11.5) • LoB 76.3 (6.4) • HiB 98.1 (2.5)	Stroke subtype (Ischemic/hemorrhagic): 17/4
Liu et al 2018	Cross-sectional	Stroke: 23; 51.5 (10.7)	41.5 (41.4) (months) 3.46 (3.45) (years)	MMSE: 27.8 (2.2)	Stroke subtype (Ischemic/hemorrhagic): 12/11
Mori et al 2018	Cross-sectional	Stroke: 14; 61.1 (9.3) HC: 14; 66.3 (13.3)	–	MMSE: • Stroke: 29.2 (1.1) • HC: 28.7 (1.8) TMT-A (s): • Stroke: 42.6 (13.4) • HC: 38.1 (12.3) TMT-B (s): • Stroke: 105.1 (41.5) • HC: 113.0 (68.6)	10MWT (m/min): • Stroke 56.5 (13.8) • HC 74.6 (10.6) TUG (s): • Stroke 14.9 (4.1) • HC 10.3 (1.8) Stroke subtype (Ischemic/hemorrhagic): 5/9

M(SD): mean (standard deviation), PD: Parkinson's disease, MS: multiple sclerosis, HC: healthy controls, ON: on anti-Parkinsonian medication state, OFF: off anti-Parkinsonian medication state, FoG-: without freezing of gait, FoG+: with freezing of gait, ID: indeterminate patients, PIGD: postural instability gait difficulty, TD: tremor dominant, yPD: young adults with PD, oPD: older adults with PD, yPn: young adults without PD, oPn: older adults without PD, HiB: high Barthel index (slight dependency), LoB: low Barthel index (moderate dependency), UPDRS: unified Parkinson's disease rating scale, NFOG-Q: new freezing of gait questionnaire, FoG-Q: freezing of gait questionnaire, MMSE: mini-mental state examination, MoCA-J: Montreal cognitive assessment (Japanese version), MoCA: Montreal cognitive assessment, 2MWT: 2 minute walking test, MDS-UPDRS:

movement disorders society-unified Parkinson's disease rating scale, ABC: activities specific balance confidence scale, BDI II: Beck depression inventory II, TMT-A: trail making test A, TMT-B: trail making test B, FAB: frontal assessment battery, CLOX: Royall's clock drawing, EDSS: expanded disability status scale, SCWT: stroop color word test, RBRANS: repeatable battery for the assessment for neuropsychological status, SDMT: symbol digit modalities test, PASAT: paced auditory serial addition test, WLG: word list generation, SCWIT: Stroop color-word interference test, CII: cognitive impairment index, BVMT-R: brief visuospatial memory test-revised, CVLT-II: California verbal learning test, FMA-LE score: Fugl-Meyer lower extremity score, DGI: dynamic gait index, 10MWT: 10-meter walking test, TUG: timed up and go.

−: data not available

Table 3. Overview of included studies by condition x type of imaging technique used

Authors (year)	Imaging	Task Characteristics		Behavioural outcomes	Brain outcomes	Correlation analysis between DT performance and brain outcomes
Parkinson's disease (PD)						
		Motor	Cognitive			
Dagan et al 2020	fNIRS	Self-paced walking (19m path)	Serial-3 subtraction	DT vs ST: • ON & OFF: ↓ gait speed, ↑ stride time, and ↓ step length ($p < 0.0001$) • OFF: ↑ stride time CV ($p = 0.003$) ON vs OFF: • ↓ gait speed ($p < 0.0001$), ↓ step length ($p < 0.05$), ↑ stride time ($p < 0.05$), and ↑ stride time CV ($p < 0.05$) in OFF vs ON state • ↑ number of responses and cog errors in OFF vs ON during DT-walk ($p = 0.027$)	↑ HbO_2 PFC ($p = 0.001$) under DT vs ST only in OFF state No significant difference between ON and OFF state under DT-walk condition ($p = 0.849$)	−
ø Maidan et al 2016	fNIRS	Walking (back and forth 30m)	Serial-3 subtraction	DT vs ST: • PD ↓ gait speed and stride length ($p < 0.05$) • HC: no difference PD vs HC: ↓ gait speed, step length, and correct responses in PD vs HC (all $p < 0.001$)	PD: no significant difference in HbO_2 PFC ($p = 0.122$) between DT and ST HC: ↑ HbO_2 PFC ($p = 0.001$) under DT vs ST No significant difference ($p = 0.264$) between groups	PD: Small ↑ in HbO_2 during DT vs walking alone correlated with ↑ DTC for gait speed ($p < 0.001$) HC: large ↑ in HbO_2 during DT vs walking alone correlated with ↓ DTC for gait speed ($p < 0.001$)
ø Orcioli-Silva et al 2020	fNIRS	Self-paced walking (26.8m circuit; 2x7m	Digit vigilance task	DT vs ST: ON & OFF: ↓ step length ($p < .001$), velocity ($p = 0.001$), swing time ($p < .001$) and ↑ double support time ($p < .001$) during DT vs ST	↑ HbO_2 PFC under DT vs ST only in ON state ($p = 0.008$) PD vs HC: (no main effect of group)	−

		parallel path)		PD OFF & HC: ↓ step length ($p < 0.001$), velocity ($p < 0.001$), and swing time ($p < 0.001$); ↑ step time ($p < 0.001$), step width ($p = 0.005$), and double support time ($p < 0.001$) PD ON: ↓ swing time ($p < 0.001$) ON & HC: ↓ step length ($p < 0.001$), velocity ($p < 0.001$), and swing time ($p < 0.001$); ↑ step time ($p < 0.001$), double support time ($p < 0.001$), and step length variability ($p = 0.011$) Cognitive: no difference ($p > 0.05$) Group comparison: • ↓ step length ($p = 0.022$) in OFF vs ON • ↓ step length ($p = 0.002$), step velocity ($p = 0.042$), and ↑ step length variability ($p = 0.001$) in OFF vs HC • ↓ step length ($p = 0.022$), and ↑ step length variability ($p = 0.016$) in ON vs HC	• ON vs HC: ↑ HbO_2 PFC (left and right PFC $p < 0.001$) during DT vs ST • OFF vs HC: ↑ HbO_2 PFC (left PFC $p = 0.038$; right PFC = 0.002) during DT vs ST	
Stuart et al 2020	fNIRS	Walking (back and forth 9m)	AX-CPT	DT vs ST: ↓ speed, stride length, and foot strike angle (all $p < 0.001$)	DT vs ST: no significant difference in HbO_2 PFC ($p = 0.975$)	No significant results
Vitorio et al 2020	fNIRS	Self-paced walking (back and forth 9m)	AX-CPT	DT vs ST: • ↓ speed ($p = 0.029$), stride length ($p < 0.001$), and foot strike ($p = 0.013$) • Cog-accuracy: no difference ($p > 0.05$) FoG+ vs FoG- • No difference ($p > 0.05$)	DT vs ST: no significant difference in PFC HbO_2 ($p > 0.05$) ↑ PFC HbO_2 during late phase of ST & DT walking in FoG+ vs FoG- ($p = 0.031$)	↑ Early HbO_2 correlated with ↓ step time variability only in FoG+ ($p = 0.023$)
*ø Hirata et al 2020	MRI	Fast-paced walking (15m)	Serial-7 subtraction	DTC walking (%) (PD; HC): • Stride length: 17.9 (12.0); 7.5 (9.6) • Stride duration: 18.9 (12.7); 11.1 (11.2) • Stride velocity: 29.5 (15.8); 15.9 (12.8) PD vs HC: ↓ DTC of stride length and velocity in HC vs PD (both $p = 0.020$)	Average uptake value of DAT-SPECT, mean (SD): Sensorimotor region of the striatum R and L: 0.84 (0.47); 0.76 (0.36) Executive region of the striatum R and L: 1.50 (0.47); 1.50 (0.47)	PD: ↑ bilateral CVs of stride length ↓ DAT uptake left ($p = 0.036$) & right ($p = 0.036$) executive regions; right limbic region of striatum ($p = 0.048$) HC: no data available

					Limbic region of the striatum R and L: 1.39 (0.35); 1.34 (0.37)	
Peterson et al 2015	MRI	Walking (20m hallway)	Auditory choice reaction head-turning task	DT vs ST: • ↓ stride length during DT vs ST-walk ($p < 0.001$) in FoG+ vs FoG- ($p = 0.02$) • ↑ number of head turn errors ($p < 0.05$) Group comparison: • ↓ Stride length in FoG+ vs FoG- during DT ($p < 0.05$) • ↑ stride length variability in FoG+ vs FoG- ($p = 0.018$)	↑ PPN laterality (structural connectivity) in FoG- in right hemisphere vs FoG+ ($p < 0.05$)	↑ DTC of stride length ↓ PPN laterality in PD ($p < 0.001$) • When analyzed separately: FoG+ ($p < 0.01$); FoG- ($p > 0.05$)
ø Rosenberg-Katz et al 2016	MRI	Walking	Serial-3 subtraction	DT vs ST: = Group comparison: • ↓ DT gait speed in PIGD vs TD ($p = 0.009$)	PIGD vs TD: ↓ globus pallidus ($p = 0.04$) and amygdala ($p = 0.018$) volume PIGD vs HC: ↓ caudate nucleus ($p = 0.003$), putamen ($p = 0.002$), and amygdala ($p = 0.0002$) volumes TD vs HC: ↓ caudate nucleus volume ($p = 0.05$) ID vs HC: ↓ caudate nucleus ($p = 0.009$), putamen ($p = 0.001$), and amygdala ($p = 0.013$) PIGD vs ID: ↓ amygdala ($p = 0.02$)	PD: ↑ hippocampal volume correlated with ↑ DT speed ($p < 0.002$) HC: no data available
*ø Sartor et al 2017	MRI	Self-paced walking (20m walkway)	Serial-7 subtraction	DTC walking (%): • yPD: 13.1 (-8.5 to 37.1) • oPD: 19.9 (-1.2 to 43.4) • yPn: 9.1 (-7.8 to 44.2) • oPn: 13.7 (-19.2 to 37.1) DTC cognitive (%): • yPD: -2.8 (-61.6 to 48.2) • oPD: -10.2 (-203.8 to 84.6) • yPn: -17.5 (-107.8 to 46.2) • oPn: -20.1 (-101.1 to 79.6)	No significant WMC difference (presence and severity) between groups ($p < 0.05$)	Negative correlation between the Fazekas score & DTC ($p < 0.05$) (of motor and cognitive performance in older adults with PD only) HC: no significant correlations

				Group comparison: no significant difference in DTC between groups; ↓ speed in oPD vs yPn ($p = 0.0053$)		
ø Toda et al 2019	MRI	Walking (10m walkway)	Serial subtraction	DT vs ST: • PD: ↓ speed, ↓ stride length, ↑ gait cycle, ↑ step time variability, and ↑ left-right instability (all $p < 0.001$) • HC: ↓ speed, ↑ gait cycle, and ↑ left-right instability (all $p < 0.05$) PD vs HC: ↓ speed, ↓ stride length, ↑ step time variability in PD vs HC (all $p < 0.01$)	PVH score: median, 2 points; interquartile range 1-4 points WMH score: median, 4 points; interquartile range 1-7	PD: ↑ PVH ↓ DT gait speed ($p < 0.01$), and stride length ($p < 0.01$) • Specifically, speed/stride length negatively correlated with frontal/occipital cap (all $p < 0.01$) HC: no data available
ø Vervoort et al 2016	rs-fMRI	Walking (back and forth 6m walkway)	Auditory stroop task	DT vs ST: = Group comparison: • No significant difference in DT gait performance between PD and HC • ↑ stance times, ↓ swing times, and ↑ double support times ($p < 0.05$) in FoG+ vs FoG-	Hypo-connectivity (PD < HC): between left M1 and right M1/right PMC; Left IPL and bilateral caudate, left SNc, and right PPN (FoG+ < FoG-): between left caudate and right superior temporal lobe/left cerebellum; right caudate and bilateral dorsal putamen/left GP/bilateral temporal lobe Hyper-connectivity (PD > HC): between left cerebellum and bilateral PMC or bilateral M1; Right IPL and bilateral PMC or left M1; left SNc and left M1 (FoG+ > FoG-): between right precuneus and left dorsal putamen (all $p < 0.05$)	↓ connectivity btw left caudate & superior temporal lobe correlated with worse DT step time, and swing time ↑ connectivity btw left dorsal putamen & right precuneus correlated with worse DT step, swing, and double support time FoG-specific (all $p < 0.05$) HC: no data available
Multiple sclerosis (MS)						
ø Hernandez et al 2016	fNIRS	Self-paced walking (14ft long walkway)	Letter recitation	DT vs ST: • ↓ gait speed ($p < 0.001$) (PD and HC) PD vs HC:	MS: ↑ HbO_2 PFC during DT vs ST compared to HC ($p < 0.01$)	–

				• No sig difference in gait speed (p = 0.43) and the number of correct responses during DT (p = 0.14) between PD and HC • No sig difference in gait speed during DT between low and high EDSS	• Larger ↑ in HbO_2 PFC during DT in low EDSS vs high EDSS (p < 0.05)	
*ø Saleh et al 2018	fNIRS	Self-paced walking (straight hallway)	Serial-7 subtraction	DTC (%) (MS; HC): • Walking speed: -16.8 (15.7); -12.5% (11.3%) • Cognitive (number of answers): -19.3 (30); 11% (39%) HC vs MS: • ↑ number of correct responses (p < 0.05) in HC vs MS • No difference in gait speed (p > 0.05)	MS: DT vs single walk: no change in rPMC activity (p > 0.05); DT vs single cog: ↑ rPMC (p = 0.002), lSMA (p = 0.016), rSMA activity (p = 0.005) HC: DT vs single walk: ↑ rPMC (p = 0.029); DT vs single cog: ↑ rPMC (p = 0.002), lSMA (p = 0.016), rSMA activity (p = 0.005) DT vs single cognitive: no main effect of group DT vs single walk: higher in HC vs MS	MS: ↑ lSMA/rSMA activation correlated with ↓ walking speed (α_m < 0.035) HC: no significant correlations
ø Argento et al 2020	MRI	Fast-paced walking (15m walkway)	Semantic word list generation or serial-3 subtraction	DT vs ST: • MS: no difference in mt covered (p > 0.05) • HC: ↓ mt covered during DT-word (p = 0.003) and DT-count (p = 0.012) vs ST Group comparison: • ↑ mt in hpPMS vs IpPMS during DT-word (p = 0.043) and DT-count (p = 0.008) trials • ↓ mt during DT-word and count trials (p = 0.039; 0.011); ↓ DT-word correct counts (p = 0.002) in MS vs HC	↑ cerebellum vermis-VIIIa (p = 0.065) & vermis-IX (p = 0.034) in hp vs Ip/HC#	–
ø Coghe et al 2018	MRI	Self-pace walking	Stroop color and word test	DT vs ST: ≠ MS vs HC: • ↓ mean (DT + ST) cadence (p = 0.001) and velocity (p < 0.001) in MS vs HC	↓ brain volume & grey matter volume in MS vs HC (all p < 0.001)	Only in MS (no correlations in HC): Negative correlations with DTC: WM and velocity (p = 0.024)

						GM and swing phase (p = 0.005), velocity (p = 0.044), and cadence (p < 0.001); Cortical GM and velocity (p = 0.020); BV and swing phase (p = 0.032), velocity (p = 0.002), cadence (p = 0.005), and stride length (p = 0.007) Positive correlations with DTC: WM (p = 0.013)/GM (p = 0.021) and stride time; GM and double support time (p = 0.045); Cortical GM and stride time (p = 0.020); BV and stride time (p < 0.001), and double support time (p = 0.003) Regression analysis: GM (p < 0.001) and BV (p = 0.009) was a significant predictor of DTC of cadence
Fritz et al 2019	MRI	Self-paced walking	Serial-3 subtraction or letter recitation	DT vs ST: • ↓ velocity (p = 0.048) and ↑ walk time (p = 0.001) during DT-serial vs ST	SMA lesions predominantly in juxtacortical 12.2 ± 12.0 (0–45) & periventricular 12.4 ± 10.5 (1–49) regions vs other regions. fMRI: ↑ activity only in SMA while performing ankle dorsiflexion (p < 0.05) SMA structural MRI measures mean (SD): FA: 0.346 (0.029); AD: 1.44 (0.113), RD: 0.911 (0.116), and MD: 1.09 (0.114)	No significant correlations between lesion load/fMRI measures and DT performance Positive correlations with structural MRI measures: AD & DT step length CV (p = 0.039), DT stance time CV (p = 0.016), DT double support time CV (p = 0.034) RD & DT stance time CV (p = 0.012) MD & DT stance time CV (p = 0.009), and DT double support time CV (p = 0.034)
ø Liparoti et al 2019	MRI	Self-paced walking	Serial-7 subtraction	DT vs ST: ↑ double support time in MS (p < 0.05)	↓ normalized white matter volume and brain volume in MS vs HC (p < 0.05)	No significant results in MS or HC

				MS vs HC: ↑ stance time ($p < 0.05$), swing time ($p < 0.01$), ↑ cycle time ($p < 0.01$), ↑ double support time ($p < 0.05$) in MS vs HC under DT		
Stroke						
Chatterjee et al., 2019	fNIRS	Self-paced walking (18m oval-shaped path)	Serial-7 subtraction	DT vs ST: • ↓ gait speed ($p < 0.0001$), ↓ stride length ($p < 0.0001$), and ↑ step width ($p < 0.001$) • ↓ Correct number of responses ($p = 0.01$) Low vs high cognitive: • ↓ gait speed ($p = 0.003$), shorter stride length ($p = 0.02$) in low vs high	↑ PFC activity during DT vs single walk ($p = 0.001$) and single cognitive ($p = 0.06$) High vs low cognitive: • ↑ PFC activity ($p = 0.01$) during DT in high vs low	↑ HbO_2 correlated with ↓ DT-cog performance ($p = 0.02$); no significant correlations with DT-walk ($p > 0.05$)
ø Hawkins et al 2018	fNIRS	Self-paced walking (18m oval path; 5.2m instrumented walkway)	Verbal fluency task	DT vs ST: • ↓ gait speed ($p < 0.001$) during DT vs ST Stroke vs HC: • ↓ gait speed in stroke vs HC under DT ($p < 0.001$)	↑ PFC activity during DT vs single walk • Early walking period ($p = 0.010$) • Late walking period ($p = 0.004$) No group differences ($p > 0.05$)	No significant correlations ($p > 0.05$)
Hermand et al 2019	fNIRS	Walking (8m walkway)	2-back or 1-back task	DT vs ST: ↓ gait speed, and ↑ gait variability under DT vs ST walk (all $p < 0.05$) • No sig difference between DT-low (1-back) and DT-high (2-back) % of correct answers: no difference ($p > 0.05$) • ↓ during DT-high vs DT-low ($p < 0.01$)	Stroke: no sig difference between ST-walk, DT-low, and DT-high ($p > 0.05$)	No significant correlations ($p > 0.05$)
Hermand et al 2020	fNIRS	Walking (8m walkway)	2-back task	DT vs ST: no difference (HiB + LoB) • ↑ gait variability in HiB under DT vs single walk ($p = 0.039$) • ↓ % good answers in HiB under DT vs single cognitive ($p < 0.05$) HiB vs LoB: ↓ gait speed ($p = 0.0018$), and ↑ gait variability ($p = 0.0013$) in LoB vs HiB under DT	HiB + LoB: no difference • ↑ PFC HbO_2 and HbO_2-unaffected in DT vs ST-cog in LoB ($p < 0.05$; 0.01) HiB vs LoB: ↑ PFC HbO_2 (unaffected side) in LoB vs HiB during DT ($p = 0.036$); no	–

					difference for affected side ($p > 0.05$)	
Liu et al 2018	fNIRS	Self-paced walking (4.75m walkway)	Serial-3 subtraction	DT vs ST: • ↓ gait speed ($p < 0.01$), ↓ cadence ($p < 0.05$), ↓ stride length ($p < 0.01$), and ↑ stride time ($p < 0.05$)	↑ activity in PFC of the lesioned hemisphere, SMA of the non-lesioned hemisphere, and most bilateral PMC (all $p < 0.05$) in DT vs ST	Negative correlations: SMA of the lesioned hemisphere activity & speed, and stride length; bilateral PMC activity & cadence Positive correlations: SMA of the lesioned hemisphere activity and SAR; bilateral PMC activity and stride time (all $p < 0.05$)
ø Mori et al 2018	fNIRS	Self-paced walking (2.5m circle pathway)	Serial-3 subtraction	DT vs ST: ⩧ Stroke vs HC: ↑ DTC on acceleration magnitude and mistake rate in stroke vs HC	Stroke or HC: no significant difference between DT and ST ($p > 0.05$) ↑ right ($p < 0.001$), middle ($p = 0.009$), and left ($p = 0.002$) PFC activity during DT in HC vs stroke	Stroke: ↑ right PFC activation correlated with ↓ DTC on acceleration magnitude ($p = 0.013$); no significant correlations with DTC cog HC: no significant correlations with DTC motor; ↑ left PFC activation correlated with ↓ DTC on correct rate ($p = 0.013$);↑ middle ($p = 0.028$) and left ($p = 0.036$) PFC activation correlated with ↓ DTC on the mistake rate

fNIRS: functional near infrared spectroscopy, fMRI: functional magnetic resonance imaging, MRI: magnetic resonance imaging, PD: Parkinson's disease, MS: multiple sclerosis, HC: healthy controls, ON: on anti-Parkinsonian medication state, OFF: off anti-Parkinsonian medication state, FoG-: without freezing of gait, FoG+: with freezing of gait, ID: indeterminate patients, PIGD: postural instability gait difficulty, TD: tremor dominant, yPD: young adults with PD, oPD: older adults with PD, yPn: young adults without PD, oPn: older adults without PD, HiB: high Barthel index (slight dependency), LoB: low Barthel index (moderate dependency), IpPMS: low performers' patients with multiple sclerosis, hpPMS: high performer' patients with multiple sclerosis, DT: dual task, ST: single task, HbO_2: oxygenated hemoglobin, PFC: prefrontal cortex, DTC: dual-task cost, AX-CPT: continuous performance task, SD: standard deviation, DAT-SPECT: dopamine transporter single-photon emission computed tomography, CV: coefficient variability, R/r: right, L/l: left, PPN: pedunculopontine nucleus, WMC: white matter change, PVH: periventricular hyperintensity, WMH: white matter hyperintensity, M1: primary motor cortex, PMC: primary motor cortex, IPL: inferior parietal lobe, SNc: substantia nigra pars compacta, GP: globus pallidus, SMA: supplementary motor area, WM: white matter, GM: grey matter, BV: brain volume, AD: axial diffusivity, RD: radial diffusivity, MD: mean diffusivity, SAR: spatial asymmetry ratio, mt: meters covered, EDSS: expanded disability scale.

⩧: data not available (e.g., *p*-values, DTCs (%))
*: only reported dual-task cost (percent change)
- : no correlation analysis has been conducted
#: full sample was not reported only the subgroup analyses
ø: studies that included healthy individuals

4. GENERAL DISCUSSION

The purpose of this systematic review was to identify shared or distinct neural correlates of DT walking in people with neurological conditions by analyzing studies that examined the relationship between brain imaging and dual-task walking performance in people with PD, MS, stroke, and AD. Most of the included studies (n = 17) reported a decrease in walking performance (e.g., reduced gait speed, stride length) under the DT versus single-walk condition. In terms of cognitive changes, half of the studies found poorer performance during dual tasking compared to single-cognitive condition. In general, people with neurological disorders performed poorer under dual-task conditions than age-matched healthy individuals.

The brain findings are much more diverse and complicated. Almost equal number of studies reported an increase or no difference in brain activity under DT versus single task conditions. When there was an increase in brain activity (e.g., PFC, supplementary motor area (SMA)), this correlated with poorer dual-task performance in general but it also correlated with better or no significant changes in performance. There were similarities between brain activity in healthy people and people with neurological conditions, but a few (n = 3) showed smaller or greater brain activation (Hernandez et al., 2016; Mori et al., 2018; Saleh et al., 2018), and the latter did not correlate or positively correlated with DT performance.

Most structural imaging studies found a negative association between lower brain volume, and greater white or grey matter changes in people with neurological disorders compared to healthy controls. These structural changes were associated with decreased DT performance in most cases (e.g., slower gait speed) while no such correlations were found in healthy individuals. Specific brain areas that showed this negative relationship include the striatum regions, pedunculopontine nucleus (PPN), and hippocampus in people with PD and SMA in MS individuals. A detailed

discussion of cognitive and walking performance under single- and dual-task conditions, functional and structural brain outcomes including neural correlates will be presented below in the order given.

4.1 Dual-task performance of people with neurological conditions

4.1.1 Walking performance

Only two studies instructed participants to walk fast while the rest used normal-paced walking. The findings show that most people with neurological disorders demonstrate a decline in motor performance (e.g., decreased gait speed) under the DT condition compared to single-walking. This shows that the DT condition was more demanding (physically and/or cognitively) than single task walking and led to a greater decline in performance, which aligns with the DT theories (e.g., capacity sharing theory) that predict a decrease in DT performance when demand exceeds capacity (Kahneman, 1973; Strobach et al., 2018). Further, people with neurological disorders demonstrated poorer DT walking performance than healthy individuals. It has been supported that neuronal damage can negatively affect dual-tasking ability of people with neurological disorders compared to those without such health conditions (Pizzamiglio et al., 2017). Based on the findings of included studies, structural (e.g., lower hippocampal volume in PD) (Rosenberg-Katz et al., 2016) or functional (e.g., increased PFC activity in PD and stroke) (Liu et al., 2018; Maidan et al., 2016) brain changes could have contributed to poorer DT walking performance when compared with healthy people. The relationship between behavioural and neural measures will be presented in greater detail in section 4.2 and 4.3.

Various gait measures were examined in the included studies but gait speed and stride length were the most commonly reported. Gait speed, stride length, stride velocity, step length, step velocity, swing time, cadence, foot strike angle decreased while stride time, step width, step

time, double support time, and gait variability increased from single-walking to DT. These DT related gait changes have been associated with falls in older adults (Soangra & Lockhart, 2017) and people with neurological disorders (Modarresi et al., 2018). For example, increased double support time and step length variability are related with falls in people with dementia (Modarresi et al., 2018). It has been shown that gait speed is a good indicator of general health and mortality in older adults (White et al., 2013) and reduced speed and stride length have been related with white matter disease and stroke (Verghese et al., 2007).

While changes in gait speed have been a common outcome measure of dual-tasks, there is some evidence that gait variability might be more closely related to fall risk than gait speed (Soangra & Lockhart, 2017). Further, studies exploring falls and falls risk using gait variability measures have argued that increased gait variability is a marker for falls in the populations included in this review (Allali et al., 2016; Kao et al., 2014; Moon et al., 2016; Schmitt et al., 2020). Therefore, if the goal is to reduce falls risk, then gait variability may be a better outcome measure. The future studies could examine different features of gait including gait variability to characterize gait patterns of people with neurological disorders in more detail. This in turn will allow people to better predict fall risk and potential consequences that individuals with neurological disorders might face due to increased gait variability during DT performance.

4.1.2 Cognitive performance

Around one third of the studies compared cognitive performance under dual- and single task conditions. Among these studies, half observed a decrease in DT cognitive performance. These studies observed a decline in both motor and cognitive performance (mutual interference), which seems to commonly occur in people with neurological disorders due to limited dual-tasking capacity (Bayot et al., 2018; Plummer et al., 2013). Other studies found improvements or no

difference, but this was still combined with poor DT walking performance, which suggests that people with neurological disorders from these studies might have prioritized a cognitive task over walking (Yogev-Seligmann et al., 2012). This is called posture second strategy (Yogev-Seligmann et al., 2012), which contradicts the posture first principle that proposes under challenging conditions (e.g., dual-tasking), healthy individuals tend to prioritize balance over a secondary task (e.g., cognitive task) to prevent falling (Holmes et al., 2010). However, the included studies did not instruct participants to focus on a particular task and when there are no instructions on task prioritization people may use a posture second strategy (Jansen et al., 2016).

Yogev-Seligmann et al. (2012) further explained that a task prioritization during walking is dynamic and can be influenced by various factors. The primary contributing factors include individuals' physical capacity (how well individuals cope with postural threat) and ability to accurately assess surrounding hazards and one's limitations (Yogev-Seligmann et al., 2012). Other contributing factors include familiarity of tasks, personality, and type of a secondary task (e.g., cognitive task) used (Yogev-Seligmann et al., 2012). The paper further explained that healthy individuals assess these factors accurately and focus on a cognitive task when walking performance can be maintained and under a more challenging condition, these individuals will shift their attention to walking to prevent falling and ensure safety, utilizing an appropriate strategy as the condition changes (Yogev-Seligmann et al., 2012). However, people with neurological disorders such as PD might make an inappropriate assessment of these factors and may prioritize a cognitive task over walking even when there is a high postural threat (Yogev-Seligmann et al., 2012). Likewise, some participants from the included studies that have shown better or no changes in DT cognitive performance but decreased gait performance might have used a posture second strategy, which can increase falls risk.

Since only seven studies compared cognitive performance under dual- and single task conditions and reported mixed results, we cannot be conclusive about cognitive DTC in people with neurological disorders. In addition, it is difficult to describe overall changes in DT walking performance when only gait data is presented because cognitive performance might have increased or decreased or stayed stable (Plummer et al., 2015). Overall, the findings of DT cognitive performance varied much more than walking performance, and this could be potentially due to a variability in types of cognitive tasks used. Compared to walking, the included studies used diverse cognitive tasks testing a different set of cognitive functions with various levels of difficulty, which can make a certain combination of DT relatively more or less challenging than others and this can differently affect DT performance and lead to mixed results. For example, working memory tasks such as n-back tasks have been known to affect dual-task cognitive performance more than simple reaction time tasks (Salzman et al., 2021; Wollesen et al., 2019). Leone et al. (2020) also reported that digit span backward, which is another working memory task, produce most interference under DT conditions, affecting gait velocity and cognitive task accuracy.

The results of the included studies don't directly support the above findings, as some studies (Hermand et al., 2019; Hermand et al., 2020) that utilized n-back tasks reported no difference in cognitive performance between dual- and single task conditions. However, it should be noted that the included studies only measured accuracy or errors made and did not compare changes in reaction time. It has been suggested measuring both accuracy and reaction time provides more comprehensive view on changes of cognitive performance from single- to dual-task conditions (Vaportzis et al., 2013). A reaction time tends to decrease in older adults while they can be quite accurate on cognitive tasks compared to healthy people (Vaportzis et al., 2013). In addition, it has been shown that older adults tend to maintain accuracy over speed during dual

tasking (Wolkorte et al., 2014). A decrease in reaction time (cognitive DTC) could have also occurred in people with neurological disorders while accuracy is maintained and thus measuring only one of the cognitive variables can lead to biased conclusions.

4.1.3 Comparison between neurological conditions

Compared to people with PD, people with MS and stroke relatively had a lower level of physical and/or cognitive disability based on the clinical measures taken (e.g., UPDRS). This could possibly explain why there was a higher proportion of MS and stroke studies that found no significant difference in DT performance (motor or cognitive) compared to single tasking or between people with neurological disorders and healthy individuals. There is evidence that disease severity is associated with dual-task gait speed (e.g., slower speed) in people with neurological disorders (e.g., PD) (Kelly et al., 2012) suggesting disease severity as one of the contributing factors for poor DT walking performance. This trend can also be observed within people with PD but was less apparent in people with MS and stroke as studies used different standardized tests to assess baseline cognitive and physical functions, which makes difficult to directly compare disease severity within the population. In addition, in the studies reviewed, people with PD were relatively older than people with MS or stroke and this might have also contributed to poorer DT performance in people with PD. It has been shown that older adults show poorer DT performance compared to young adults or middle-aged individuals (Brustio et al., 2017).

4.2 Functional brain outcomes

4.2.1 Functional near-infrared spectroscopy findings

About half of the studies observed an increase in brain activity during DT walking versus single walking while the rest found no difference between the task conditions. Similarly, in terms of correlations between brain imaging and behavioural outcomes, 44% found an association

between increased brain activity and poorer DT performance while others found a relationship between improved DT performance and increased brain activity or no associations. Since the PFC plays an important role in dual-tasking and executive functioning (Watanabe & Funahashi, 2018), most fNIRS studies examined the relationship between the PFC and behavioural changes. Research has consistently reported the involvement of PFC in DT walking in different populations including people with neurological disorders (Mirelman et al., 2014; Mori et al., 2018). Findings of the included studies also seem to indicate an association between the PFC and DT walking in people with neurological conditions, however, the direction of this correlation (e.g., positive or negative) varied across the studies.

The PFC activity in people with PD and stroke either increased or did not significantly change during DT walking compared to single tasking. In terms of correlations, the results were mixed and all possible outcomes were reported by almost equal number of studies for PFC. In PD, an increase in PFC activity correlated with better or poorer DT performance while in stroke, it correlated with better or poorer dual-task performance or did not correlate with behavioural measures. People with MS also showed poorer DT performance and an increase in PFC activity, however, a correlation analysis has not been conducted. To a lesser extent, motor areas such as premotor cortex and SMA have been examined. In both people with MS and stroke, two studies reported an increase in activity of these regions during DT walking compared to single tasking (motor or cognitive) (Liu et al., 2018; Saleh et al., 2018). The association between a greater SMA activity and a decrease in DT performance has been found in both studies. The SMA is involved in planning and executing voluntary movements and communicate with the PFC, suggesting its role in executive functioning (Cañas et al., 2018) and dual-tasking (Saleh et al., 2018). To further

support, a recent study found an increase in DT gait speed when SMA was stimulated with repetitive transcranial magnetic stimulation (Goh et al., 2019).

4.2.2 Functional magnetic resonance imaging findings

One fMRI study examined the functional connectivity between and within regions that are important for motor control and DT related areas (e.g., fronto-parietal regions) (Vervoort et al., 2016). The study found a significant association between decreased DT performance and hyperconnectivity within striatum regions (putamen and nucleus) or hypoconnectivity between caudate nucleus and temporal lobe specifically in PD with FoG. This suggests that the striatum regions might play an important role in DT walking in people with PD with FoG, which is not surprising since the striatum regions are commonly affected in PD (Zhai et al., 2017) and are important for carrying out motor movements and executive functioning (Moustafa et al., 2016; Elliott, 2003). The reduced connection between caudate and temporal lobe might be associated with the cognitive task performed (auditory Stroop task) as these structures work together to process auditory stimuli during dual tasking (Plakke & Romanski, 2014).

4.2.3 CRUNCH model and neural dedifferentiation

Taken together, the functional imaging studies seem to indicate the involvement of PFC and SMA in DT walking in people with PD, MS, and stroke. However, the direction of brain activity changes and its effect on DT walking performance remain unclear and seem to vary across the studies, which align with DT neuroimaging literature (Leone et al., 2017; Watanabe & Funahashi, 2018). These mixed findings could be potentially explained by the CRUNCH model (Festini et al., 2018) and neural dedifferentiation hypothesis (Cassady et al., 2020) that were introduced previously.

Studies have reported an increase in brain activation in older adults compared to young adults, which typically involves a greater or bilateral recruitment of frontal regions, and studies have interpreted this as a compensatory process for age-related decline in performance (Festini et al., 2018). In response, several theories have been developed to explain age-related brain activity differences (Festini et al., 2018). The CRUNCH is one of them and could be particularly relevant for dual-tasking as it accounts for a level of task difficulty (Festini et al., 2018). The model predicts an increase in brain activity of older adults under low task demands (e.g., single cognitive or motor) compared to young adults, however, as the condition becomes more challenging (dual-task), a resource celling (crunch point) can be reached and further compensation won't occur (Festini et al., 2018). The same notion can be applied to people with neurological disorders that they might have increased their brain activity to compensate for disease-related impairments and brain changes. In fact, about half of the included studies observed a higher brain activity under dual- versus single task conditions. However, it should be noted that there were studies with no control groups. In this case, a greater brain activity could be simply a response to increasing task demands from single- to dual task (Klingberg et al., 2000) or the result of neural compensation (Festini et al., 2018).

On the other hand, some participants might have reached their crunch point earlier during single tasking and may have experienced a difficulty in increasing brain activity during dual tasking. This may have resulted in no significant difference in brain activity between the task conditions, which was reported by around half of the included studies. However, most participants still showed a significant decrease in DT performance (e.g., slower gait), showing that the DT condition was demanding, which supports the CRUNCH model. In fact, Hermand et al. (2019)

used the same argument to explain why there was a decrease in DT walking performance but no changes in PFC activity in people with stroke.

The CRUNCH model should be discussed further to explain the relationship between brain activation and performance changes. When an increase in brain activity is associated with better performance, it is considered as successful compensation (Ji et al., 2018). For example, in the included studies, the positive correlation between greater PFC activity and increased DT performance (motor or cognitive) reported in people with PD (Vitorio et al., 2020) and stroke (Mori et al., 2018) support the CRUNCH model. However, when the crunch point is reached, there will be no longer an increase in brain activity or a decrease in brain activity and/or performance is expected (Festini et al., 2018). This can potentially explain why there was an association between decreased functional connectivity between the caudate and superior temporal lobe and worse DT step and swing time in people with PD (Vervoort et al., 2016).

In contrast to the studies that found compensation, some studies reported an association between increased brain activity and poorer DT performance or no significant associations, which do not fit the CRUNCH model but can be explained by the neural dedifferentiation hypothesis. The neural dedifferentiation hypothesis also involves an upregulation of brain activity; however, it is associated with decreased (Cassady et al., 2020) or no changes in performance (Gertel et al., 2020). As previously mentioned, neural dedifferentiation in older adults is thought to be the result of a loss of neural specificity as the brain undergoes age-related changes (Cassady et al., 2020). This typically leads to a more widespread brain activation, which is not adaptive and considered as a reduced ability of the brain to selectively respond to given tasks and thus it has no impact on performance (Gertel et al., 2020), which can decrease if the condition is challenging enough (Cassady et al., 2020; Li et al., 2018). Morcom and Henson (2018) found that there was an

upregulation of PFC activity with increasing age but this did not predict better cognitive performance (memory task), suggesting functional impairment of PFC. Therefore, the neural dedifferentiation hypothesis supports the negative relationship between increased brain activation and poorer DT performance (Chatterjee et al., 2019; Maidan et al., 2016; Saleh et al., 2018; Liu et al., 2018) or no correlations despite elevated brain activity (Hawkins et al., 2018) reported by the included studies.

To summarize, an increase in brain activity does not necessarily translate to better performance and could reflect neural dedifferentiation when it is associated with poorer performance (Gertel et al., 2020). This relationship could be affected by various factors such as individual differences (e.g., older age and neural reserve), and types of tasks used (e.g., working memory vs simple reaction time task) (Ji et al., 2018). For example, even if people are affected by the same neurological condition, individuals with more neural reserve, which is defined as efficiency and/or capacity of one's brain network associated with a task, might be able to reduce the effect of neuronal changes by recruiting compensatory brain activity as described by the CRUNCH model compared to those with less reserve, who could demonstrate neural dedifferentiation instead (Stern, 2009). In addition, several studies have demonstrated that neural dedifferentiation occurs while performing visual tasks and thus has shown its association with visual cortex, however, it is uncertain whether dedifferentiation would occur for other brain areas or tasks (Gagnon et al., 2019). It has been suggested neural dedifferentiation might not occur equally in all brain regions (Papegaaij et al., 2017) and may be influenced by types of stimuli (Srokova et al., 2020), which should be investigated further.

4.2.4 Healthy individuals versus people with neurological disorders

In healthy people, there was a significant correlation between increased brain activity (e.g., PFC) and better DT performance, which aligns with the CRUNCH model (Festini et al., 2018). One of the included studies observed an increase in PFC activity in both people with PD and healthy individual during dual tasking, however, this was associated with decreased gait speed in PD while it was associated with increased gait speed in healthy controls (Maidan et al., 2016). This finding demonstrates that healthy individuals were able to better manage DT conditions compared to people with PD. In general, healthy people performed better than people with neurological disorders. However, some studies also reported no significant correlations between brain imaging (e.g., SMA) and DT performance in healthy people, which could be due to small changes in brain activity and/or performance (Causse et al., 2017). A decrease in DT walking performance was still observed but the degree of decline was much less than people with neurological conditions. It is important to note that most healthy individuals were older adults. Thus, it is possible that they are experiencing age-related cognitive and motor decline, which can contribute to decreased DT performance (Beurskens & Bock, 2012) even without neurological conditions.

4.3 Structural brain outcomes

All studies used MRI and most found a decline in structural integrity of the brain (e.g., brain volume) in people with neurological disorders versus healthy people. A few studies performed a subgroup analysis (e.g., FoG+ vs FoG-) and reported lower structural integrity or connectivity in low performing compared to high performing group. For example, PPN connectivity was higher in FoG- compared to FoG+ (Peterson et al., 2014). These findings align with the literature in which people with neurological conditions experience a greater reduction in brain volume including white and grey matter compared to age-matched healthy individuals (Kotov, 2017). People with neurological conditions experience both whole brain volume reduction

and a regional volume loss (Kotov, 2017). In addition, cerebral atrophy usually occurs more extensively as the disease severity increases (Staffaroni et al., 2020). For example, a greater grey matter loss in SMA, cingulate cortex, and temporal lobe in FoG versus without FoG has been observed (Vastik et al., 2017).

In contrast to these findings, Argento et al. (2020) reported an increase in cerebellar volume in high performing people with MS compared to low performing group or healthy people. Uher et al. (2020) showed that brain volume increase can occur in people with MS due to different factors such as measurement errors and biological processes (e.g., edema). Especially during white matter lesion formation, inflammation can occur, which can last for a few weeks and distort measurements of brain volume or atrophy (Andravizou et al., 2019). It is also possible that the brain volume increased through neurogenesis (Ksiazek-Winiarek et al., 2015), which might have contributed to better DT walking performance in high performing MS individuals versus low performing group. However, this group still performed worse than healthy individuals and functional adaptations (e.g., increased synaptic transmissions) seem to occur in people with MS not structural ones (Ksiazek-Winiarek et al., 2015). The exact mechanism underlying this phenomenon in MS and contributing factors should be further investigated (Uher et al., 2020).

4.3.1 Structural neural correlates of dual-task walking

As previously mentioned, various studies have suggested an interaction between structural brain integrity, cognitive and motor impairments, and DT performance (Coghe et al., 2018; Li et al., 2018; Sakurai et al., 2019; Urban et al., 2017). In accordance with the literature, most of the included studies observed an association between greater neuronal damage and poorer DT walking performance.

Parkinson's Disease. Specifically for PD, lower structural connectivity or integrity of striatum, PPN, and hippocampus correlated with increased DT stride length variability, decreased stride length, and slower gait speed respectively. The association between striatum and increased DT gait variability could be due to the involvement of striatum in modulation of gait (Gilat et al., 2017) and executive functioning (Gaßner et al., 2017; Nieuwhof et al., 2017). Specifically, the striatum regions work with the frontal area to allow shifting in attention, which is essential for dual-tasking (Salazar et al., 2017). In addition, since striatum (e.g., basal ganglia) are essential for producing rhythmic movements, people with PD are more likely show gait variability compared to healthy individuals (Puyjarinet et al., 2019), which can increase under DT conditions (Salazar et al., 2017).

PPN is another subcortical structure that has been implicated in gait deficits in PD such as freezing of gait (Bekkers et al., 2018). Therefore, it has become a target for deep brain stimulation to improve gait (e.g., longer stride length) in people with PD (Collomb-Clerc & Welter, 2015). Since PPN is also important for attentional control (Yarnall et al., 2011), damages to PPN could negatively affect DT walking performance and could explain why there was a decrease in stride length in PD with FoG under the DT condition (Peterson et al., 2014).

Lastly, hippocampus is well known to play a role in cognitive functioning (e.g., memory), however, it is also involved in coordinating movement (Wennberg et al., 2017). Hippocampal atrophy, which commonly occurs in people with PD (Regensburger, Prots & Winner, 2014), has been associated with decreased gait speed (Rosso et al., 2017; Wennberg, Savica & Mielke, 2017). Further, degeneration of hippocampus in people with cognitive impairment has been associated with poor DT performance (Longhurst et al., 2020), showing that hippocampal atrophy might also lead to poor DT walking performance in people with PD.

Multiple Sclerosis. Studies on MS showed an association between lower SMA integrity and worse dual-task walking performance (e.g., increased gait variability). In people with MS, a loss of white and grey matter in SMA frequently occurs (Gomez et al., 2013). This brain region works with other areas (e.g., basal ganglia) to control different gait parameters such as stride length (Auvinet et al., 2017). In addition, several studies have shown the link between SMA and DT walking performance (Goh et al., 2019; Saleh et al., 2018; Wu & Hallett, 2008). Therefore, structural changes to SMA in people with MS can lead to increased gait variability under DT conditions (Fritz et al., 2019).

Structural imaging results seem to be more consistent than functional imaging outcomes as most of the structural findings showed a correlation between lower brain integrity and worse DT performance. While structural imaging techniques are used to obtain static brain measurements (e.g., volume) (Hirsch et al., 2015), functional imaging techniques (e.g., fNIRS) measure real-time changes in brain activity while performing tasks (Mirelman et al., 2014) and thus can be influenced by different environmental factors (Orihuela-Espina et al., 2010). For example, increased task difficulty (e.g., working memory vs simple reaction time tasks) could lead to an up-regulation of brain activity in areas that are associated with a given task (Zhang et al., 2018). In addition, since cognitive reserve is associated with neural networks (Pietzuch et al., 2019), individual differences in cognitive reserve and brain resilience could lead to changes in task-related brain activity (Elshiekh et al., 2020). Other physiological changes such as heart rate and blood pressure could also affect the level of HbO_2 (Plichta et al., 2011) and consequently functional imaging results. Taken together, measurements of functional imaging are more dynamic and could be more susceptible to environmental factors other than tasks given compared to structural imaging (MRI), which may have contributed to heterogeneity in measurements/results.

In general, studies that investigated global brain volume changes such as whole brain volume, and white or grey matter volume showed more varied results. Liparoti et al. (2019) found no significant association between white matter volume and DT gait. Sartor et al. (2017) and Coghe et al. (2018) reported a positive correlation between lower brain volume and DTC, which contradicts other studies. In addition, Coghe et al. (2018) found a negative correlation between lower brain volume (e.g., grey matter) and higher DTC-cadence, which fits with the results reported by the majority of structural imaging studies. Sartor et al. (2017) suggested that depressive symptoms of people with PD might have disengaged the participants under less challenging (single task) conditions compared to dual task, leading to unexpectedly poor single task performance. However, it is uncertain whether this had a significant effect as depressive symptoms of the participants were minimal, which was assessed using a standardized test (Beck-Depression Inventory II).

The literature seems to support the association between increased white matter lesions and poorer DT walking or balance performance in various populations including people with mild cognitive impairments (Doi et al., 2015; Snir et al., 2019), dementia (Hairu et al., 2021), healthy older adults (Castro-Chavira et al., 2019; Ghanavati et al., 2018). However, Herman et al. (2013) found no associations between the two measures in people with PD. One of the included studies in this review also found no significant correlations between DT performance and white matter lesions and only found its association with periventricular hyperintensities specifically with frontal and occipital regions (Toda et al., 2019). Further, Longhurst et al. (2020) reported a relationship between lower cerebellar gray matter volume and better DT motor performance, supporting positive correlations reported by Sartor et al. (2017) and Coghe et al. (2018). This study explained that lower volume in motor areas might have shift the attention to motor task, leading to better DT

motor (Timed Up and Go) performance (Longhurst et al., 2020), suggesting a connection between structural and functional brain changes such that decreased white or grey matter volume might have led to higher brain activity (Lucas et al., 2019) and possibly better performance according to the CRUNCH model (Festini et al., 2018). However, it is uncertain whether this occurred in the studies conducted by Sartor et al. (2017) and Coghe et al. (2018) as they did not focus on a specific brain area. In line with the result of Longhurst et al. (2020), it has been shown that grey matter changes can be associated with increased or decreased DTC depending on the region of the brain (Tripathi et al., 2019). Also, each gait parameter is associated with grey matter volume in shared and different regions of the brain (Wilson et al., 2019). These findings suggest that the relationship between white or grey matter volume and dual-tasking might be dependent on specific brain area and gait parameter examined and focusing on global brain volume changes may produce mixed results, which could possibly explain why Coghe et al. (2018) found both negative and positive correlations.

4.4 Brain outcomes: comparison between neurological conditions

In terms of brain (structural or functional) outcomes and associations between the brain and behavioural measures, there was no noticeable trend that could characterize a specific population in the groups targeted by this systematic review. Mostly, structural imaging studies that examined PD and MS showed significant association between structural changes and poorer DT performance. One study from each population (Coghe et al., 2018; Sartor et al., 2017) found the opposite association. Liparoti et al. (2019) and Toda et al. (2019) found no significant correlations between white matter changes and DT performance in both MS and PD respectively. However, there was a higher proportion of PD studies that reported no difference in brain activity between the task conditions but a decrease in DT motor performance. Participants with PD compared to

MS and stroke were older and had higher levels of disability (moderate to severe). The disease duration for participants with MS was longer than PD. However, as previously mentioned, people with PD were older than individuals with MS and there is evidence that the disease progresses more rapidly in older adults (Levy, 2007), which could explain why the disease severity of participants with PD was higher than people with MS.

Further, age is an important factor that affects one's cognitive and motor function (Buchman et al., 2014) and older adults tend to reach their physical and/or cognitive limit faster than younger adults (Lordan et al., 2020). Thus, it is possible that older participants (PD) reached their limit faster and couldn't increase their brain activity further under the DT condition compared to middle-aged individuals (MS or stroke) who were able to upregulate their brain activity during dual tasking. Similarly, there is evidence that people with high versus low disease severity experience more difficulty in increasing the brain activity while performing a cognitive task (Clement & Belleville, 2010). However, it is less clear how disease severity might modulate the brain activity during dual tasking. One of the included studies found that people with stroke with low versus high cognitive score show a lower PFC activity during dual tasking and poorer DT performance (e.g., slower gait speed) (Chatterjee et al., 2019), which supports the trend observed. However, other studies reported that people with MS or PD with high disability compared to low disability exhibit a greater brain activation but this did not lead to better performance (Hermand et al., 2020; Vitorio et al., 2020).

4.5 Brain areas selected

As previously mentioned, most of the functional imaging studies examined the PFC. Compared to PD, a higher proportion of stroke studies reported non-significant correlations between the PFC activity and DT performance. As explained, the PFC is essential for dual-tasking

(Beste et al., 2018) and it is commonly affected by neurological disorders including (Brück et al., 2003) PD and stroke (Shi et al., 2017) but the anterior cerebral artery that directly supplies the PFC is less affected in stroke (Hui et al., 2021) while prefrontal atrophy can be observed in early stage of PD (Brück et al., 2003). There is evidence that the middle cerebral artery is most affected by stroke, which supplies regions such as basal ganglia, and parts of temporal, parietal, and frontal lobe (Hui et al., 2021). These areas were not examined by the studies and since fNIRS can only measure cortical brain activity, the basal ganglia activity cannot be measured using fNIRS (Schaal et al., 2019). Moreover, the studies that found no significant results included participants that recently had stroke while lesions tend to get worse and spread over time (Seghier et al., 2014). Therefore, these factors might have contributed to non-significant results reported by stroke studies.

In addition, it would be interesting to note the effect of cognitive task on brain areas activated. For example, it has been shown that arithmetic tasks (e.g., serial-subtraction) activate regions of parietal lobe and frontal gyrus (e.g., superior, medial, middle, inferior) (Abd Hamid et al., 2011) in which the latter contains PFC (Harms et al., 2010) and SMA (Talati & Hirsch, 2005). This could partially explain an increase in SMA or PFC activity under DT versus single cognitive condition observed by the studies that utilized serial subtraction tasks (Chatterjee et al., 2019; Saleh et al., 2018). However, it should be noted that others found no significant changes (Maidan et al., 2016; Mori et al., 2018). Similarly, n-back tasks involve an activation of parts of premotor cortex and dorsolateral and ventrolateral PFC (Owen et al., 2005). However, the included studies found no significant difference in brain activity between dual- and single task conditions in people with stroke (Hermand et al., 2019; Hermand et al., 2020). As previously mentioned, this could be because the participants were not able to increase their PFC activity according to the CRUNCH

model (Festini et al., 2018) or the DT condition was not challenging enough as Hermand et al. 2020 found no changes in performance and Hermand et al. 2019 found no decrease in performance when the task difficulty increased (e.g., 1-back to 2-back), which could be associated with low disease severity of the participants (Kelly et al., 2012). The cognitive tasks utilized by functional imaging studies were associated with the brain areas (e.g., PFC) that were examined in most cases (Abd Hamid et al., 2011; Owen et al., 2005; Schlösser et al., 1998) and while some found a significant increase in activity of those brain areas during dual- versus single tasking, others found no significant changes, which suggest the effects of other factors (e.g., neural reserve, age) that have been discussed previously.

Regarding structural brain changes, PD and MS studies examined different brain areas. Though, both examined whole brain volume changes including white matter changes and showed mixed results (Coghe et al., 2018; Liparoti et al., 2019; Toda et al., 2019) and as previously explained, examining these global changes versus a specific brain area could produce more inconsistent findings (Longhurst et al., 2020; Tripathi et al., 2019). PD studies mostly examined the striatum and related structures such as PPN and found significant correlations between lower structural integrity and decreased DT performance, which is expected as these regions are predominantly affected in PD and lead to cognitive and motor deficits (Molina et al., 2020; Prakash et al., 2016; Yarnall et al., 2011). The studies on MS also investigated brain areas that are frequently implicated in multiple sclerosis such as cerebellum (Wilkins et al., 2017), and SMA (Gomez et al., 2013). Only one study found no significant associations between white matter volume and DT performance in people with MS (Liparoti et al., 2019). However, Haider et al. (2016) specifically indicated that periventricular white matter lesions dominate in MS. Moreover, one of the included PD studies reported a correlation between greater periventricular white matter

changes and decreased DT performance (Toda et al., 2019). Therefore, it is possible that white matter lesions particularly in periventricular area might also play a role in DT walking in MS but this was not tested by the included studies.

5. CONCLUSION

5.1 Summary

Findings from the included studies helped identify neural correlates of DT walking in people with PD, MS, and stroke. The magnetic resonance imaging studies revealed that lower structural integrity of striatum regions, PPN, and hippocampus in people with PD is associated with poorer DT walking performance. In people with MS, greater structural changes in SMA correlated with decreased DT walking performance. The functional imaging (e.g., fNIRS) revealed that PFC and SMA might be associated with DT walking performance but findings demonstrated more mixed results. In general, people with neurological disorders tend to increase their brain activity (e.g., PFC) during DT walking and this was associated with poorer DT performance but was also associated with better performance in people with stroke and PD. This dynamic relationship between the brain and DT walking can be explained by the CRUNCH model (Festini et al., 2018) and neural dedifferentiation hypothesis (Cassady et al., 2020; Gertel et al., 2020), which demonstrate that a higher brain activity may allow for maintenance of performance under certain circumstances (Festini et al., 2018) but not others (Gertel et al., 2020). Several factors could be involved in this relationship such as individual differences (e.g., age, neural reserve) and type of task used (Ji et al., 2018). These structural and functional brain changes along with other contributing factors might produce the combined effect on reduced cognitive and/or motor performance of people with PD, MS, and stroke under DT walking compared to single task conditions and in general more than healthy individuals, which is in line with the literature (McIsaac et al., 2018; Kelly et al., 2012) and supported by the included studies.

5.2 Limitations and future directions

Several limitations should be addressed. First, there was a lot of variability in study design in terms of cognitive tasks used and gait parameters examined. As previously stated, six different types of cognitive tasks were used and even though gait speed and stride length were most commonly measured, other spatiotemporal gait measures (e.g., double support time, cadence) have been examined. Moreover, studies used different standardized tests to measure baseline cognitive and motor impairments. For example, UPDRS was used by all PD studies, however, only a few MS studies reported EDSS and stroke papers did not utilize scales that are used to measure stroke severity (e.g., NIH stroke scale/score) (Sung et al., 2016). This hinders a direct comparison between the studies and generalizability of findings. In addition, only seven studies reported cognitive performance changes from single- to dual task, which makes difficult to conclude or predict about cognitive DTC and overall changes in DT walking performance as there could be a trade-off between walking and cognitive performance.

Further, several trends regarding brain and behavioural outcomes that have been discussed are based on a small number of studies and when comparing the populations, the difference was very subtle, which decreases the power of trends observed. Another limitation of this review is that there were no studies on people with AD after screening. This can be possibly because this population is difficult to recruit due to several reasons such as a rapid disease progression, comorbidities, and lack of diagnostic tools (Watson et al., 2014). Most of the included studies recruited participants with low to moderate disease severity in order to facilitate a completion of tasks. However, people with AD are often diagnosed at the later stage of disease, hindering a recruitment of people with mild AD (Clement et al., 2019).

5.2.1 Future direction

For future studies, it would be important to follow a standardized dual-task reporting guideline and include both cognitive and motor performances to reduce variability and facilitate a better synthesis of data, possibly meta-analysis. For people with AD or other similar populations that are difficult to recruit, tasks that are less demanding or portable imaging techniques (e.g., fNIRS) could be used to test this population at home or places that are more accessible. Further, studies using multimodal imaging (e.g., MRI and fNIRS) to examine different regions of the brain could add valuable information regarding interrelationship between structural and functional brain changes and possible effects of structural brain changes on functional brain activations. These studies could identify or confirm specific brain regions/measures associated with DTC-walking that could be targeted during rehabilitation to improve DT performance. In addition, analyzing different patterns of brain activity and DT performance could reveal individuals at risk for cognitive and/or motor declines (e.g., those who show increased brain activity but decreased DT performance.

It has been shown that non-pharmacological treatments such as aerobic exercise can improve PFC activity in older adults (Basso et al., 2015). In addition, improving executive functions through DT training (Falbo et al., 2016) and stimulating the PFC using transcranial direct current stimulation (Manor et al., 2016) was associated with better DT performance. By targeting specific brain regions and individuals who are at high risk of falls among people with neurological disorders, their dual-tasking ability can be improved and consequently their mobility and quality of life.

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APPENDIX

Examples of search/key terms used for literature search (Medline)

# ▲	Searches	Results	Type	Actions	Annotations
1	Alzheimer Disease/	95690	Advanced	Display Results | More	
2	Alzheimer*.ti,ab.	148625	Advanced	Display Results | More	
3	exp Stroke/	138036	Advanced	Display Results | More	
4	stroke*.ti,ab.	253737	Advanced	Display Results | More	
5	Multiple Sclerosis/	53113	Advanced	Display Results | More	
6	multiple sclerosis.ti,ab.	75900	Advanced	Display Results | More	
7	Parkinson Disease/	67671	Advanced	Display Results | More	
8	Parkinson* disease*.ti,ab.	95207	Advanced	Display Results | More	
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	617839	Advanced	Display Results | More	
10	dual-task.ti,ab.	4547	Advanced	Display Results | More	
11	dual-task performance.ti,ab.	701	Advanced	Display Results | More	
12	dual-tasking.ti,ab.	651	Advanced	Display Results | More	
13	dual-task training.ti,ab.	136	Advanced	Display Results | More	
14	dual-task intervention.ti,ab.	10	Advanced	Display Results | More	
15	dual-task paradigm.ti,ab.	646	Advanced	Display Results | More	
16	dual-task cost.ti,ab.	177	Advanced	Display Results | More	
17	cognitive-motor.ti,ab.	1344	Advanced	Display Results | More	
18	Motor-cognitive.ti,ab.	1411	Advanced	Display Results | More	
19	Cognitive-motor interference.ti,ab.	107	Advanced	Display Results | More	
20	Motor-cognitive interference.ti,ab.	8	Advanced	Display Results | More	
21	cognitive dual-task*.ti,ab.	212	Advanced	Display Results | More	
22	motor dual-task*.ti,ab.	122	Advanced	Display Results | More	
23	Divided attention.ti,ab.	1749	Advanced	Display Results | More	
24	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	8761	Advanced	Display Results | More	
25	Gait/	28260	Advanced	Display Results | More	
26	gait.ti,ab.	50655	Advanced	Display Results | More	
27	gait control.ti,ab.	270	Advanced	Display Results | More	
28	gait performance.ti,ab.	994	Advanced	Display Results | More	
29	Walking/	33528	Advanced	Display Results | More	
30	walking.ti,ab.	72992	Advanced	Display Results | More	
31	Walking Speed/	1507	Advanced	Display Results | More	
32	walking speed.ti,ab.	6579	Advanced	Display Results | More	
33	ambulation.ti,ab.	11296	Advanced	Display Results | More	
34	Locomotion/	25879	Advanced	Display Results | More	
35	Locomotion.ti,ab.	27863	Advanced	Display Results | More	
36	Kinematics.ti,ab.	22229	Advanced	Display Results | More	
37	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	183218	Advanced	Display Results | More	
38	9 and 24 and 37	620	Advanced	Display Results | More	