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Review
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Cognitive–motor Interference in Individuals With a Neurologic Disorder: A Systematic Review of Neural Correlates

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Running head: Neural Correlates of CMI in Neurologic Disorders

Abstract

Background: Performing a cognitive task and a motor task simultaneously is an everyday act that can lead to decreased performance on both tasks.

Objective: To provide insight into the neural correlates associated with cognitive–motor dual tasking in individuals with a neurologic disorder.

Method: We searched the PubMed and Web of Science databases for studies that had been published up to January 16th, 2019. Studies investigating the neural correlates of cognitive–motor dual task performance in individuals with a variety of neurologic disorders were included, independently from whether the study included healthy controls. Clinical and imaging data were abstracted for the comparison between single tasks and a dual task in the individuals with a neurologic disorder and for the comparison between the healthy controls and the individuals with a neurologic disorder.

Results: Eighteen studies met the inclusion criteria. Study populations included individuals with Parkinson disease, multiple sclerosis, mild cognitive impairment, Alzheimer disease,

traumatic brain injury, and stroke. Neuroimaging types used to study the neural correlates of cognitive–motor dual tasking during upper limb or gait tasks included fMRI, functional near-infrared spectroscopy, EEG, and PET.

Conclusion: Despite large heterogeneity in study methodologies, some recurrent patterns were noted. Particularly, in neurologic patients, an already higher brain activation during single tasks was seen compared with healthy controls, thereby compromising the patients' ability to further adapt brain activation with increasing load during dual tasking and resulting in reduced behavioral dual task performance.

Systematic Review Registration: Prospero (Identifier CRD42019129975).

Key Words: cognitive–motor interference, dual tasking, neurologic disorders, neural correlates, neuroimaging

AD = Alzheimer disease. **CMI** = cognitive–motor interference. **CMRglc** = cerebral metabolic rate of glucose consumption. **DT** = dual task. **DTC** = dual task cost. **fNIRS =** functional near-infrared spectroscopy. **HC** = healthy controls. **MS** = multiple sclerosis. **PD** = Parkinson disease. **PFC** = prefrontal cortex. **PMC =** premotor cortex. **SMA =** supplementary motor area. **ST** = single task. **TBI** = traumatic brain injury.

Dual tasking is an everyday act that can be defined as "the concurrent performance of two tasks that can be performed independently, measured separately and have distinct goals" (McIsaac et al, 2015, p 2). Examples include simultaneously walking and talking, walking and navigating through a crowd, and walking and typing a message. The simultaneous execution of two tasks can lead to various changes in performance, involving combinations of facilitation, interference, or no change. These changes are called cognitive–motor interference

(CMI) when they result in reduced performance (Leone et al, 2015; Plummer et al, 2013). Dual task cost (DTC) is a behavioral measure that is often used to quantify CMI; it is the percentage change of dual task (DT) performance compared with single task (ST) performance (Leone et al, 2015).

The central capacity sharing and bottleneck theories are well-recognized theoretical models that have been used to explain CMI (Wajda et al, 2017). The first model relates CMI to limitations in brain capacity (especially attention) that can be allocated to tasks. In this model, during dual tasking, less capacity is available for each individual task, potentially leading to CMI (Tombu and Jolicoeur, 2003, 2005). The second model states that CMI arises when the two separate tasks in the DT depend on the same neurologic structures (Pashler, 1994; Ruthruff et al, 2001), which for example may be the prefrontal cortex, premotor cortex, or supplementary motor area.

A systematic review on neural correlates of cognitive–motor dual tasking in healthy individuals showed that the brain areas that are involved in cognitive–motor DTs are task dependent and are similar to those that are involved in STs, indicating a lack of a specific brain area for cognitive–motor DTs (Leone et al, 2017). The authors of the review noted that perhaps the brain is sufficiently able to perform both tasks simultaneously in healthy adults.

In individuals with neurologic disorders, cognitive and motor impairments are common, as is CMI (McIsaac et al, 2018; Yogev-Seligmann et al, 2008). For example, several studies have reported that individuals with Parkinson disease (PD) and those with multiple sclerosis (MS) showed higher CMI than healthy controls (HC), negatively impacting their daily functioning and risk of falls (Bayot et al, 2018; McIsaac et al, 2018; Montero-Odasso et al, 2012). Better insight into the underlying neural correlates of dual tasking can lead to an improved understanding of CMI that will allow clinicians to tailor clinical interventions to improve DT performance. The aim of this systematic review was to compare neural correlates

between DTs and STs in individuals with neurologic disorders and between individuals with neurologic disorders and HC. We also planned to examine how these differences relate to behavioral findings of CMI.

METHOD

Search Strategy

We searched PubMed and Web of Science until January 16th, 2019, using the following search terms: cognitive motor interference OR dual task* AND neural pathways [MeSH] OR brain [MeSH] OR neuroimaging [MeSH] OR functional connectivity OR electroencephalography OR functional magnetic resonance imaging OR event-related potential OR magnetoencephalography OR spectroscopy OR NIRS OR positron emission tomography AND nervous system diseases [MeSH] OR multiple sclerosis OR Parkinson disease OR mild cognitive impairment OR Alzheimer disease OR stroke OR traumatic brain injury NOT animals.

Inclusion and Exclusion Criteria

We included studies that investigated the neural correlates of cognitive–motor DT performance in individuals with a neurologic disorder, independently from whether the study included HC. We defined a cognitive–motor DT as the simultaneous performance of both a cognitive task and a motor task that could be performed independently and measured separately and have distinct goals (McIsaac et al, 2015). The neural correlates included brain activation patterns, functional connectivity, metabolic correlates, and electrical patterns. In order to be included in our review, the neural correlates being studied had to be measured during, or correlated to, cognitive–motor DT performance by a neuroimaging technique or

neurophysiological instrument (eg, fMRI, functional near-infrared spectroscopy [fNIRS], PET, event-related potential, EEG, magneto-encephalography).

We excluded studies that (a) applied a motor–motor or cognitive–cognitive DT; (b) investigated solely the effects of an exercise intervention, therapy, drugs, or stimulation on dual tasking; and (c) included participants under 18 years of age. Conference papers and articles written in a language other than English were also excluded. The search was independently performed by two authors (M.G., K.G.), who first screened the titles and abstracts of the identified studies and then the full texts of the remaining studies, to ensure that the studies met the inclusion criteria. Any differences of opinion were discussed with and arbitrated by a third author (R.V.). The systematic review was registered through Prospero (Identifier CRD42019129975).

Quality Assessment

We used a modified version of the Downs and Black checklist (Downs and Black, 1998) to determine the methodological quality of the included studies. We discarded nine of the 27 items from the original checklist because they were not applicable for assessing cross-sectional observational studies (items 10, 13, 14, 17, 19, 22, 23, 24, 26). In item 8, on adverse events, we replaced “used intervention” with “neuroimaging method.” And, we added a new item, item 19, to check whether the study corrected for multiple comparisons. The adjusted checklist is provided as the supplemental digital content, http://links.lww.com/CBN/XXX. Item 16 was not applicable in studies without a control group. Therefore, the quality assessment score was a maximum of 19 for studies with a control group and a maximum of 18 for studies without a control group. M.G. and K.G. independently assessed the methodological quality of the studies. Any differences of opinion were discussed with R.V. until consensus was reached.

Data Extraction

We extracted the following information from each of the studies: participant characteristics (eg, diagnosis, age, number of subjects), type of neuroimaging technique used, DT paradigm, behavioral outcomes, and key findings and interpretations according to the study authors. We grouped the results by neuroimaging technique. In the following section, we describe (a) the behavioral outcomes and the neural correlates found in the DT compared with the STs for individuals with neurologic disorders and (b) the group differences in behavioral performance and neural correlates of dual tasking between individuals with neurologic disorders and HC. We also report correlations between the individuals' brain activation patterns and their behavioral DT performance.

RESULTS

Figure 1 presents a flow diagram of our literature search (Moher et al, 2009). Our electronic search yielded 381 studies from PubMed and 145 studies from Web of Science. After removing the duplicates, we screened a total of 450 articles. Based on the inclusion criteria, 420 articles were discarded while screening study titles and abstracts. Thorough examination of the remaining studies resulted in an exclusion of another 12 articles. We manually checked the reference lists of included studies for additional relevant studies that did not appear in our search but did not find any.

< Insert Figure 1 near here >

Eighteen articles ultimately met our criteria for inclusion in our review. Table 1 provides an overview of the data we extracted from those studies, and Table 2 shows the results of the quality assessment. None of the studies reported on power, and most did not report on blinding (n = 16), adverse events (n = 13), whether the population source was representative (n = 14), or whether patients were recruited from the same population (n = 9).

< Insert Table 1 and Table 2 near here >

Functional Near-infrared Spectroscopy

fNIRS is a non-invasive neuroimaging technique that measures changes in oxygenated hemoglobin. An increase in oxygenated hemoglobin reflects an increase in brain activity. Nine of the 18 studies used fNIRS, of which six included HC. Figure 2 shows that fNIRS was always conducted during a walking task and was combined with either a mental-tracking task (subtracting 3s, subtracting 7s, alternating alphabet), a working memory task (digit span forward, counting), or a verbal fluency task (word list generation: phonemic).

< Insert Figure 2 near here >

Contrast Between DT and STs in Individuals With Neurologic Disorders

Table 3 shows the DT versus ST contrasts for behavioral performance and brain activation patterns found using fNIRS and fMRI in individuals with a neurologic disorder. All of the studies that used fNIRS reported decreased behavioral motor performance in DT walking compared with ST walking, regardless of the cognitive task used. Four of the studies also showed decreased behavioral cognitive performance on serial subtractions and

alternating alphabet in the DT compared with the ST in individuals with stroke and those with MS (Al-Yahya et al, 2016; Chaparro et al, 2017; Mori et al, 2018; Saleh et al, 2018).

< Insert Table 3 about here >

Six of the nine studies that used fNIRS as the imaging technique reported a significant increase in prefrontal cortex (PFC) activation during DT walking compared with ST walking in individuals with MS (Chaparro et al, 2017; Hernandez et al, 2016), stroke (Al-Yahya et al, 2016; Liu et al, 2018), and MCI (Doi et al, 2013), or compared with rest in individuals with PD (Nieuwhof et al, 2016) (Table 3). Chaparro et al (2017) reported that PFC activation during non-body-weight-support DT walking was higher than during ST walking in individuals with MS. However, the participants were unable to maintain this increased activation; rather, they showed a reduction of PFC activation over the duration of the task.

Liu et al (2018) reported, additionally to the PFC, that the bilateral premotor cortex (PMC) and the non-lesioned supplementary motor area (SMA) showed increased activation during the DT compared with the ST in chronic stroke patients. Saleh et al (2018) also examined the PMC and SMA, but not the PFC, and reported increased right PMC and bilateral SMA activation during the DT compared with the cognitive ST, but not compared with the motor ST, in individuals with MS.

In contrast to the former studies, two studies did not observe a significant increase in PFC activation during the DT (walking while subtracting 3s) versus ST walking in individuals with PD and those with stroke (Maidan et al, 2016a; Mori et al, 2018).

Between-Group Differences in Behavioral Performance and Brain Activation

Of the nine studies that used fNIRS, six compared neurologic patients (MS, PD, and stroke) with HC (Table 4). Four of the studies reported a significantly higher motor or cognitive DTC in individuals with MS, PD, or stroke than in HC (Chaparro et al, 2017; Maidan et al, 2016a; Mori et al, 2018; Saleh et al, 2018). Of these, Mori et al (2018) reported lower PFC activation during the DT in individuals with stroke, and Chaparro et al (2017) and Maidan et al (2016a) reported higher PFC activation during the ST in individuals with MS and those with PD compared with HC, respectively. Additionally, individuals with PD did not increase PFC activation during the DT, whereas HC did (Maidan et al, 2016a). Saleh and colleagues (2018) reported a higher cognitive DTC in individuals with MS compared with HC; the motor DTC was higher but not significantly different. This behavioral finding corresponded with higher PMC activation during the ST and less increase in right PMC activation from ST to DT in individuals with MS compared with HC.

< Insert Table 4 near here >

In contrast, two of the fNIRS studies found no significant difference in DTC between individuals with MS or stroke and HC, reporting similar (Al-Yahya et al, 2016), or even larger, PFC activations (Hernandez et al, 2016) (Table 4).

Functional MRI

fMRI is a non-invasive neuroimaging technique that measures brain activity during task performance by detecting changes associated with blood flow. Seven of the 18 studies we reviewed used fMRI, of which six included HC. Three of the studies that used fMRI used a simulated walking task (ie, alternating ankle movement or imagined walking), and four of the

studies used an upper limb task (ie, finger-tapping or button-pressing or visuomotor tracking), which were all combined with a different cognitive task (Figure 2).

Contrast Between DT and STs in Individuals With Neurologic Disorders

Table 3 shows the DT versus ST contrasts for behavioral performance and brain activation patterns found using fMRI in individuals with a neurologic condition. As previously reported (Leone et al, 2017; Nijboer et al, 2014), results are discussed according to brain activation found during the DT relative to the STs. Under-additive, additive, or over-additive activation patterns occur when the observed DT activation is less than (under-), equal to (additive), or higher than (over-) the sum of the two ST activations, respectively, or in newly recruited areas (over-additive). Miscellaneous activation is a mix of those patterns. None of the included studies reported exclusively under-additive or additive patterns.

Over-additive. Four of the seven studies that used fMRI as the imaging technique reported an over-additive activation pattern during DT performance (Al-Yahya et al, 2016; Gao et al, 2017; Nieuwhof et al, 2017; Rasmussen et al, 2008). In their study of individuals with PD, Nieuwhof et al (2017) focused on the bilateral putamen because of their a priori hypotheses on the role of striatal dysfunction. The authors found that the ventro-anterior putamen was preferentially involved in the cognitive task, and the dorso-posterior putamen was preferentially involved in the motor task. Furthermore, during the DT, the ventro-posterior putamen was recruited by only the individuals with PD (Nieuwhof et al, 2017). In Gao et al (2017), participants performed the ST and DT (tapping while counting) without any errors during scanning; thus, their DTCs were 0. When comparing the DT with the STs, individuals with PD in this study additionally activated the precuneus.

Al-Yahya et al (2016) reported on two experiments in their article, one of which included both fNIRS and fMRI. In this study, individuals with stroke showed increased activity during DT performance over and above the sum of activation that was revealed during each ST in the bilateral superior frontal gyrus, bilateral inferior temporal gyrus, and left caudate nucleus.

Rasmussen et al (2008) reported increased activation bilaterally in the occipital lobes and medial superior frontal gyrus, in and around the left central sulcus, and in the left cingulate sulcus for individuals with traumatic brain injury (TBI).

Miscellaneous. One of the fMRI studies reported a mix of under-additive, additive, and over-additive activation patterns during dual tasking in individuals with PD (Wu and Hallett, 2008). These authors used a simple motor sequence (4 items) combined with counting as the DT. The bilateral precuneus was additionally activated during DT performance compared with the two STs. In contrast, the sum of the activity of the two STs was greater than the activity found during the DT in the bilateral parietal cortex, PMC, inferior frontal gyrus, SMA, basal ganglia, and cerebellum, indicating under-additive activation.

For two of the fMRI studies, it was not possible to establish the under-, over-, or additive activation pattern because brain activation during one of the tasks (ie, STs or DT) was not measured (Dennis et al, 2011; Maidan et al, 2016b). Maidan et al (2016b) investigated the difference in brain activation patterns between an ST-imagined usual walking task and a DT-imagined navigation task in individuals with PD and found no differences. Dennis et al (2011) investigated the correlation between brain activation patterns during a single visuomotor tracking task and the DT in individuals with stroke. A greater DTC correlated with a higher fMRI signal in the right (contralesional) dorsal premotor cortex, right ventral premotor cortex, and right middle frontal gyrus during the ST (Dennis et al, 2011).

Between-Group Differences in Behavioral Performance and Brain Activation

Of the seven studies that used fMRI as the imaging technique, six compared neurologic patients (PD, stroke, and TBI) with HC (Table 4). Two of the studies reported worse behavioral DT performance during a simulated walking task in individuals with PD compared with HC (Maidan et al, 2016b; Nieuwhof et al, 2017). Maidan and colleagues (2016b) reported higher activation in various brain areas during ST performance, less increase in activation from ST to DT, and lower activation during DT performance in individuals with PD compared with HC (Maidan et al, 2016b). Nieuwhof and colleagues (2017) showed that the ventro-posterior putamen was only recruited by the individuals with PD during the DT, whereas in the HC, greater activation of this area was associated with worse DT performance.

The other four fMRI studies showed no significant differences in behavioral DT performance or DTC between individuals with a neurologic disorder (PD, stroke, and TBI) and HC (Al-Yahya et al, 2016; Gao and colleagues, 2017; Rasmussen et al, 2008; Wu and Hallett, 2008). Wu and Hallett (2008) and Gao et al (2017) both used a tapping task combined with counting as the DT and reported higher activation in various brain areas in individuals with PD compared with HC in both the ST and DT conditions. In Gao and colleagues (2017), while comparing the DT with the STs, individuals with PD additionally activated the precuneus, whereas HC additionally activated the right cerebellar vermis and the left lobule V of the anterior lobe. However, individuals with PD had already shown higher activation in the bilateral cerebellum during the motor ST. Individuals with PD had also already shown increased connectivity compared with HC between the right cerebellar vermis and the left lobule V of the anterior lobe and cognition- and motor-related areas during the cognitive and motor ST, respectively. Individuals with PD had also already shown connections between the right cerebellar vermis and the pre-SMA and PFC during the motor ST. During the DT,

connectivity in these areas was enhanced in individuals with PD compared with HC. Moreover, increased connectivity was found between the precuneus and the right anterior lobe of the cerebellum, right anterior cingulate gyrus, and left superior parietal lobule in individuals with PD compared with HC (Gao et al, 2017).

In contrast, Rasmussen and colleagues (2008) reported generally lower activation of various brain areas during the ST (tapping) and higher activation of various brain areas during the DT (tapping plus a visual search task) in individuals with TBI compared with HC. The individuals with TBI showed a significantly larger increase in activation in the right superior frontal gyrus and the right cingulate gyrus from ST to DT than the HC. Al-Yahya and colleagues (2016) reported no behavioral data of the DT, but compared with HC, individuals with stroke showed a greater increase in activation from STs to DT in frontal areas and increased PFC activation in the DT. In contrast, a lower increase in activation from ST to DT in parietal areas and the cerebellum was reported.

Positron Emission Tomography

PET is an imaging technique that uses radioactive substances to, among other things, visualize metabolic processes. One study (Bracco et al, 2007) used PET to investigate the correlation between the cerebral metabolic rate of glucose consumption (CMRglc) during the resting state and DT performance on a tracking task combined with the digit span forward task in individuals with Alzheimer disease (AD). CMRglc was determined with a PET scan 30 minutes after an injection with fluoro-2-deoxy-D-glucose. Subgroups of mild and very mild AD were analyzed. In the mild AD group compared with the very mild AD group, reductions in CMRglc were reported in the bilateral middle temporal gyrus and the right precuneus. In the very mild AD group, DT performance was significantly related to CMRglc in the left post-central gyrus and middle-superior temporal gyri. In the mild AD group, DT

performance was related to CMRglc in the parietal and (mainly right hemisphere) occipital areas.

Electroencephalography

EEG is a neurophysiological technique that records electrical activity of the brain. Two of the 18 studies we reviewed used EEG to evaluate individuals with PD during an upper limb task while performing either a reaction time task or the phonetic verbal fluency task (Figure 2) (Palmer et al, 2010; Scholten et al, 2016). Spectral EEG was used in these two studies to measure local neural activity and cortico-cortical phase synchronization, which is a correlation between distributed brain areas in specific frequency bands. Both studies analyzed data in the theta (4–8 Hz), alpha (7–12 Hz), and beta (12–30 Hz) bands because these bands are thought to relate to physiological cortical processes that are possibly relevant for dual tasking.

Scholten et al (2016) found reduced performance on the DT for individuals with PD, but they did not analyze Group × Task interactions in behavioral performance or cortical activity between the individuals with PD and the HC. During the DT versus the motor ST, increased cortico-cortical phase synchronization in the beta band in the left prefrontal area and decreased cortical activity in the theta band over the left parietal area was reported in the individuals with PD. In contrast, the HC demonstrated decreased cortical activity in the beta band over the left prefrontal and bilateral parieto-occipital areas and increased cortico-cortical phase synchronization in the theta band in the left prefrontal area. Scholten and colleagues (2016) mentioned that the HC might have had a greater capacity to reduce beta-band activity, which may reflect disinhibition, thereby stabilizing the maintenance and transfer of the motor planning toward motor output despite the higher cortical load under the DT conditions.

Palmer et al (2010) analyzed connectivity within individuals with PD who were off medication (PD-off) after L-dopa medication (PD-on) and HC. The authors found no significant differences in behavioral performance between the individuals with PD and the HC. During the DT versus the motor ST, the PD-off group showed a widespread increase in theta-band connectivity, an increase in beta-band connectivity between the right occipital and temporal areas, and a decrease in beta-band connectivity in the left midline frontal and central areas. The PD-on group showed some increased connectivity in the beta band in the DT and similar connectivity in the theta and alpha bands during the DT and ST.

In addition, Palmer and colleagues (2010) reported significant differences in connectivity and cortical activity between the individuals with PD and the HC. The PD-off group displayed increased theta- and alpha-band connectivity between the frontal and central areas and decreased connectivity between the parietal and occipital areas during the motor ST; these findings were more pronounced in the DT condition. In the beta band, the PD-off group showed frontal and occipital decreases and central and parietal increases during the motor ST. The PD-on group demonstrated fewer differences in connectivity compared with the HC but increased connectivity in the beta band between the left temporal and central/parietal motor areas, and similar differences as found between the HC and the PD-off group in the alpha band. Palmer and colleagues (2010) stated that task-related dopaminergic-sensitive theta and beta changes may represent a marker for the greater recruitment required to accomplish individual tasks, leading to an inability to perform simultaneous tasks without interference.

Correlations Between Brain Activation Patterns and Behavioral Performance

Eight of the fifteen studies using fNIRS or fMRI reported correlations with behavioral DT performances. In individuals with MS, Saleh and colleagues (2018) reported a significant negative correlation between SMA activation and gait speed during dual tasking (left SMA: r

= –0.72; right SMA: r = –0.6). This correlation was not found in the HC, and no correlations with cognitive performance during the DT were found. In individuals with MCI, Doi et al (2013) reported a significant negative correlation between DT brain activation in the left inferior frontal gyrus and executive function (r = –0.663). In individuals with TBI, Rasmussen and colleagues (2008) reported a significant positive correlation between motor DTC and the anterior cingulate cortex, right dorsal superior frontal gyrus, and left occipital lobe.

In a study by Mori et al (2018) significant negative correlations between motor DTC of acceleration magnitude and right PFC activation (r = –0.65) were found for individuals with stroke and not for HC. In contrast, no correlations between cognitive DTC and PFC activation were found for the individuals with stroke, although there was a negative association in the HC. In a study by Al-Yahya and colleagues (2016), increased DT-related behavioral changes were associated with increased DT activation in the bilateral inferior temporal gyrus, left cingulate gyrus, and left frontal pole. And, in a study by Liu and colleagues (2018), bilateral PMC activity was negatively correlated with cadence during DT walking (r > –0.418) and positively correlated with stride time (r > 0.439). In addition, SMA activity of the lesioned hemisphere was negatively correlated with speed (r = –0.464) and stride length (r = –0.429) and positively correlated with spatial asymmetry ratio (r = 0.430).

DISCUSSION

To our knowledge, this is the first review to provide an overview of the neural correlates that are associated with cognitive–motor DT performance in individuals with different neurologic diseases and compared with HC. Some recurrent patterns of brain activation were seen across the individuals with a neurologic disorder. For example, the majority of the studies showed increased activation of the PFC during the DT compared with

the ST, as measured by fNIRS, or over-additive activation of brain areas during the DT, as measured by fMRI. Compared with the HC, the individuals with a neurologic disorder showed higher activations in various brain areas during ST and DT performance in the majority of the studies. However, the various combinations of neuroimaging techniques, DT paradigms, analysis methods, and patient populations hamper direct comparisons between studies and impede drawing a definite picture of which areas of the brain are mostly involved in cognitive–motor dual tasking.

Main Brain Activation Patterns During Cognitive–motor DT in Individuals With Neurologic Issues

Most of the studies that used a DT paradigm with walking showed an increase in PFC activation from ST to DT. Also, in the fMRI studies, widespread increases in various brain areas were reported from ST to DT. Although no neural locus was activated consistently during the performance of a cognitive–motor DT, some specific brain areas that were not activated during ST performance were reported to be particularly involved during DT performance. These areas included the precuneus (Gao et al, 2017; Wu and Hallett, 2008), left cingulate cortex (Rasmussen et al, 2008), frontal gyrus (Rasmussen et al, 2008), and ventro-posterior putamen (Nieuwhof et al, 2017). These findings are in line with Leone et al (2017), who discovered that most of the studies included in their review demonstrated an over-additive activation in the PFC and the precuneus in HC during dual tasking. These results might indicate that these brain areas are involved in DT performance by default.

Activation of the cingulate cortex and the precuneus has been associated with more complex movements, a need for more cognitive control, and directing attention during the execution of movements (Wenderoth et al, 2005). It has been suggested that a core control network providing top–down control regulation exists in the brain, possibly including the

dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, anterior insula, inferior frontal junction, and posterior parietal cortex (Wen et al, 2018). Leone and colleagues (2017) reported an over-additive effect in the cerebellum. In the current review, one study (Gao et al, 2017) examined activation specifically in the cerebellum in individuals with PD but found an already higher activation during performance of the ST compared with the HC and no increase in activation during the DT.

Most of the fNIRS studies we reviewed reported a reduction in behavioral performance from ST to DT combined with an increased or similar PFC activation during the DT compared to the ST, supporting the idea that the dorsolateral PFC has a role in the top–down control of attention during dual tasking (D'Esposito et al, 1995). The higher activation that was already found during ST walking in the individuals with a neurologic disorder compared with HC could explain the difficulty to up-regulate brain activation when task difficulty increases.

The combined findings of greater DTC and altered brain activation (usually increases) could be explained by the capacity-sharing model: Brain capacity may be insufficient to perform the DT successfully. However, only one of the fNIRS studies in our review measured brain activation during both STs (Saleh et al, 2018). Furthermore, a note of caution is that the PFC lends itself very well for assessment with fNIRS; therefore, most studies have investigated this area, and no brain-wide comparisons could be made. Consequently, it is too premature to establish whether overall activation during dual tasking was under-additive, additive, or over-additive. In addition, the task specificity of the required brain areas will be an important determinant of whether brain capacity is a limiting factor.

Differences in Brain Activations Between Individuals With a Neurologic Disorder and HC

Many of the studies we reviewed reported increased brain activity in various brain areas during ST in individuals with neurologic disorders compared with HC. This is in accordance with a recent review on cortical activation in older adults and individuals with PD during walking (Stuart et al, 2018), as well as with a recent study involving individuals with MS (Saleh et al, 2018). This finding of increased brain activity supports a main trend of increased activation in the individuals with a neurologic disorder compared with the HC. The higher activations during usual walking may reflect the need for greater cognitive resources even during relatively more simple tasks and may suggest that individuals with motor and cognitive impairments need a more effortful processing and more top–down control during performance of a DT compared with HC (Al-Yahya et al, 2016; Hernandez et al, 2016; Rasmussen et al, 2008; Wu and Hallett, 2008).

Indeed, in the studies that did not find a greater DTC in individuals with neurologic disorders compared with HC, an increased activation in various brain areas during dual tasking (Gao et al, 2017; Hernandez et al, 2016; Rasmussen et al, 2008; Wu and Hallett, 2008) or an equal activation in the PFC during the ST and DT (Al-Yahya et al, 2016) was reported in the individuals with neurologic disorders compared with HC. Other studies in our review did show a greater DTC in individuals with neurologic disorders compared with HC and found reduced brain activation during the DT (Mori et al, 2018) or higher activation during the ST in the patient population (Chaparro et al, 2017; Maidan et al, 2016a, 2016b). Likely, the higher activation during the STs reduced the possibility to induce even further activation or to maintain this activation during the more complex DT, which would fit the capacity-sharing theory.

In the aging literature, increased activations in various areas of the brain have previously been explained by the compensation-related utilization of neural circuits theory. According to this theory, inefficiencies in neural processing cause the (aging) brain to recruit more neural resources in order to be able to perform equivalently to younger adults. In situations with lower task demands, this compensation is effective, whereas higher task demands may lead to ceiling effects in neural recruitment and decreased performance (Reuter-Lorenz and Cappell, 2008). This phenomenon has also been found in individuals with MS and has previously been described as functional reorganization (Schoonheim et al, 2015). Another model describing the interplay between automatic movements and cognitively controlled processes was developed for individuals with PD (Vandenbossche et al, 2013). In this model, the authors proposed that individuals with PD try to compensate for a lack of automaticity by changing to a more cognitive controlled strategy. However, deficits in executive functioning that are present in individuals with PD may limit this ability, leading to inadequate responses during more challenging conditions.

Methodological Considerations

The type of DT paradigm that is used in DT research is of paramount importance. The most used motor task when analyzed by fNIRS was walking. In fMRI studies, proxy motor tasks for walking (eg, cued ankle movements and imagined walking) were used. Overall, both—real and proxy—walking paradigms resulted in a change in gait parameters from ST to DT. However, conflicting results were reported in the studies we reviewed on whether a greater deterioration in performance was found in the individuals with neurologic disorders compared with the HC.

Upper limb tasks, such as finger-tapping or button-pressing, visuomotor tracking, and isometric hand grip tasks, were also used in the DT paradigms. However, these tasks did not

reveal larger CMI in the individuals with neurologic disorders than in the HC. In fact, one study found no CMI, although this was measured after 1 hour of practice (Gao et al, 2017). It might be that these tasks were too simple and that the increase in brain activity was sufficient to perform the motor task successfully under DT conditions. Only the upper limb task, tracking a trail of boxes, in combination with a digit span forward task resulted in a greater decrease in performance in individuals with AD compared with HC.

The type and complexity of the cognitive task chosen for the DT paradigm is also important (Bayot et al, 2018; McIsaac et al, 2018). Gao and colleagues (2017) and Wu and Hallett (2008) used a counting task that did not result in great CMI, whereas a subtraction or alternating alphabet task did. Cognitive tasks can be classified as reaction time tasks, discrimination and decision-making tasks, mental tracking/working memory tasks, and verbal fluency tasks (Bayot et al, 2018). Multiple cognitive tasks were used in the studies in our review, and these cognitive tasks were combined with different motor tasks in various patient populations. Al-Yahya et al (2011) suggested that internally interfering cognitive tasks (eg, mental tracking or verbal fluency tasks) induce more CMI than externally interfering tasks (eg, discrimination and decision-making or reaction time tasks). Therefore, incorporating multiple DT paradigms with various complexities in a study might be a valuable way of investigating underlying neural mechanisms.

The DT paradigm that is used is also dependent on the neuroimaging technique that is used. fNIRS and mobile EEG allow for real-time, continuous recording during a task, thereby increasing generalizability to real-life tasks as compared with fMRI, where simulated walking tasks such as alternating ankles are used. However, the spatial resolution of fMRI is greater than that of fNIRS, and fNIRS is limited to cortical activity. Both fNIRS and fMRI rely on hemodynamic changes, which are slow and are in need of an analysis where the activation during the DT is compared with a reference like the STs or a baseline rest (Leone et al, 2017).

The technique used to examine neural correlates of cognitive–motor dual tasking therefore depends on the aim of the study, with each technique having different advantages and limitations.

Patient Characteristics

Influences of motor and cognitive functioning have been mentioned previously as determinants of DTC (McIsaac et al, 2018; Wajda and Sosnoff, 2015), and neural changes may (partly) depend on these patient-related factors as well. For example, Hernandez et al (2016) found that individuals with MS with low disability were better able than individuals with higher disability to increase their PFC activation when task demands increased because they displayed lower PFC activation during the ST than individuals with higher disease severity.

Regarding cognitive functioning, Doi and colleagues (2013) found that executive functioning was related to PFC activation during dual tasking in individuals with MCI. In the present review, we included multiple pathologies in order to provide a broad overview of neural correlates associated with CMI over neurologic pathologies where motor and cognitive impairments are prevalent. Half of the included studies were, however, conducted with individuals with PD, who generally have executive dysfunctions, and more than one paper was included only for individuals with PD, MS, or stroke.

Eight of the studies in our review included individuals with PD; of these, two used fNIRS, four used fMRI, and two used EEG. During dual tasking, tapping plus counting did not result in a greater DTC in the individuals with PD compared with the HC (Gao et al, 2017; Wu and Hallett, 2008), but tasks such as (simulated) walking did (Maidan et al, 2016a, 2016b; Nieuwhof et al, 2017). All of the studies that used fNIRS and fMRI reported that the individuals with PD showed already greater recruitment of multiple areas, such as the PFC,

PMC, precuneus, parietal cortex, and cerebellum, during performance of an ST compared with the HC. The studies that showed a reduced DT performance in individuals with PD compared with HC also reported a lower increase in PFC activation from ST to DT (Maidan et al, 2016a), a lower activation during the DT in the frontal and parietal areas (Maidan et al, 2016b), or greater activation of the ventro-posterior putamen during the DT (Nieuwhof et al, 2017). The latter result was explained by the authors as the loss of segregation hypothesis, where cortico-striatal circuits that are normally organized in distinct loops now show dysfunctional overlap. This loss of segregation might be specific for PD pathology. The finding of increased brain activation during ST performance might, however, be a more general mechanism in individuals with a neurologic disorder as described previously with the compensation-related utilization of neural circuits theory.

MS is a chronic, inflammatory, demyelinating, neurodegenerative disease of the CNS (Filippi et al, 2018; Thompson et al, 2018). The course of the disease is heterogeneous because clinical symptoms depend on the location of the damage. However, impairments in both walking and cognitive functions, such as information processing speed, working memory, and attention, are prevalent features of MS. The methodologies used to examine the neural correlates of dual tasking in individuals with MS were quite similar between the studies in our review: All three used fNIRS during walking combined with a mental tracking task (Chaparro et al, 2017; Hernandez et al, 2016; Saleh et al, 2018). The results indicated that, compared with HC, individuals with MS required increased PFC and PMC activation even to perform single motor or cognitive tasks. Complementary to the capacity-sharing model, this increased activation even during ST performance might result in increased DTC when a DT is added.

Individuals with MS did show increased recruitment of the PFC and PMC areas during the DT condition compared with ST walking and ST subtracting, respectively. However, to

establish whether the increased recruitment of the PFC and PMC during DT walking is exclusive to the DT condition, the DT activation needs to be compared to the combined ST activations. Because only one of the three studies we reviewed examined both the motor and cognitive DTC (Saleh et alet al, 2018), we were unable to make those specific comparisons. Further, although all DTs led to decreased performance compared with the STs in individuals with MS, contrasting behavioral results were shown with regard to a difference in CMI compared with HC: Overground walking did not lead to a significantly different motor DTC (Hernandez et al, 2016; Saleh et al, 2018), whereas treadmill walking did result in a higher motor DTC in individuals with MS compared with HC (Chaparro et al, 2017).

Four studies examined the neural correlates of CMI in individuals after stroke (all in chronic phase), of which two used fNIRS and two used fMRI. In the Mori and colleagues (2018) study, individuals with stroke showed similar PFC activation during DT walking compared with ST subtracting 3s. In the Liu and colleagues (2018) study, increased PFC, PMC, and SMA activation was shown during DT walking compared with ST walking, indicating the importance of measuring both STs in order to establish whether activation is due to dual tasking or to an addition of both STs.

Dennis and colleagues (2011) reported that increased recruitment of the contra-lesional dorsal PMC was correlated with a higher motor DTC. On the other hand, Al-Yahya and colleagues (2016) reported over-additive activation in the superior frontal gyrus, inferior temporal gyrus, and left caudate, indicating the need for increased recruitment of brain areas to perform a DT. Only two of these studies made comparisons between individuals with stroke and HC. Mori and colleagues (2018) showed similar PFC activation during the cognitive ST and lower PFC activation during DT performance in individuals with stroke, accompanied by a greater DTC compared with HC. In contrast, Al-Yahya and colleagues

(2016) reported increased recruitment of the PFC during the DT in individuals with stroke compared with HC.

It would be interesting to compare the underlying mechanisms of dual tasking between the various neurologic populations. However, more research in other neurodegenerative and neurologic disorders is indicated to highlight which lesioned systems have the greatest impact on DTC.

Scientific and Clinical Implications

This review showed brain activation during cognitive–motor dual tasking in individuals with neurologic disorders compared with HC, shedding light on the potential neural mechanism underlying CMI. However, as noted in the quality assessment, many of the studies we reviewed did not describe blinding or power. Moreover, many of the studies did not include both STs, making it impossible to establish whether overall activation during the DT was less than, equal to, or more than the sum of the two separate tasks. These methodological concerns limit interpretation.

For future research, it is important to include both motor and cognitive STs in the DT paradigm in order to be able to make all of the comparisons necessary to examine underlying neural mechanisms. Furthermore, incorporating correlational analyses and both simple and more complex motor and cognitive tasks in the study design would be a valuable way to investigate these mechanisms in more depth. More standardized DT paradigms based on behavioral findings—both within pathologies and over multiple pathologies—would provide valid opportunities to compare and investigate specific effects of pathologies as well.

Understanding the neural correlates that underlie dual tasking might eventually result in better patient selection for studies or guide the content of individualized clinical interventions. For example, some of the studies in our review reported increased brain activity during ST

walking (Chaparro et al, 2017; Hernandez et al, 2016; Maidan et al, 2016a), indicating that more cognitive capacity is needed to perform the ST. Someone with high brain activity during ST walking might benefit, at least initially, from ST motor training in order to induce automatization of the tasks and thereby improve DT performance. In contrast, someone who shows a great difference in brain activation during DT compared with ST might benefit more from integrated cognitive–motor DT training. Studies are warranted to investigate these hypotheses.

Limitations

The broad inclusion criteria of our review provided us with the opportunity to present a comprehensive overview of the literature regarding the neural correlates underlying CMI in individuals with neurologic disorders. However, at the same time, the breadth of the criteria led to heterogeneity in paradigms, measurement methods, and patient populations, thereby hampering conclusions. The variety of alterations in the different brain areas among the various pathologies restricts deriving final conclusions and reduces the implications for specific pathologies. However, the review does provide an overview of the current state of the art, being interdisciplinary and showing similarities over pathologies as well. Future reviews might focus on fewer pathologies but directly compare those for which enough research has already been conducted.

Different mechanisms might underlie difficulties with dual tasking depending on the type or location of the pathology. Further, we chose to include only cognitive–motor tasks according to our definition of a task that can be performed independently and measured separately (McIsaac et al, 2015). However, there are also studies including other types of DTs, such as cognitive–cognitive, motor–motor, or tasks that cannot be measured separately but are sometimes regarded as DTs as well (Shine et al, 2013). These studies might provide

valuable information on the underlying mechanisms of dual tasking as well, and future research might focus on the similarities of these type of tasks. Further, although to the best of our knowledge we included all of the papers that met our inclusion criteria, because no backward search was performed, some relevant studies might have been missed. Lastly, the focus of the current review was on functional neuroimaging; structural neuroimaging techniques might also provide valuable information on this topic (Doi et al, 2015; Ruggieri et al, 2018; Vervoort et al, 2016).

CONCLUSION

Despite the heterogeneity in methodologies and patient populations in the included studies, this review did reveal a recurrent pattern of neural correlates in individuals with neurologic diseases. The majority of the studies showed increased activation of the PFC during DT versus ST performance, as measured by fNIRS, or over-additive activation of brain areas during dual tasking, as measured by fMRI, in different patient populations. Further, compared with HC, the individuals with a neurologic disorder showed higher brain activation in STs, perhaps compromising the ability to further adapt brain activation with increasing load during the DT and resulting in reduced behavioral DT performance. These results may direct further research and clinical interventions.

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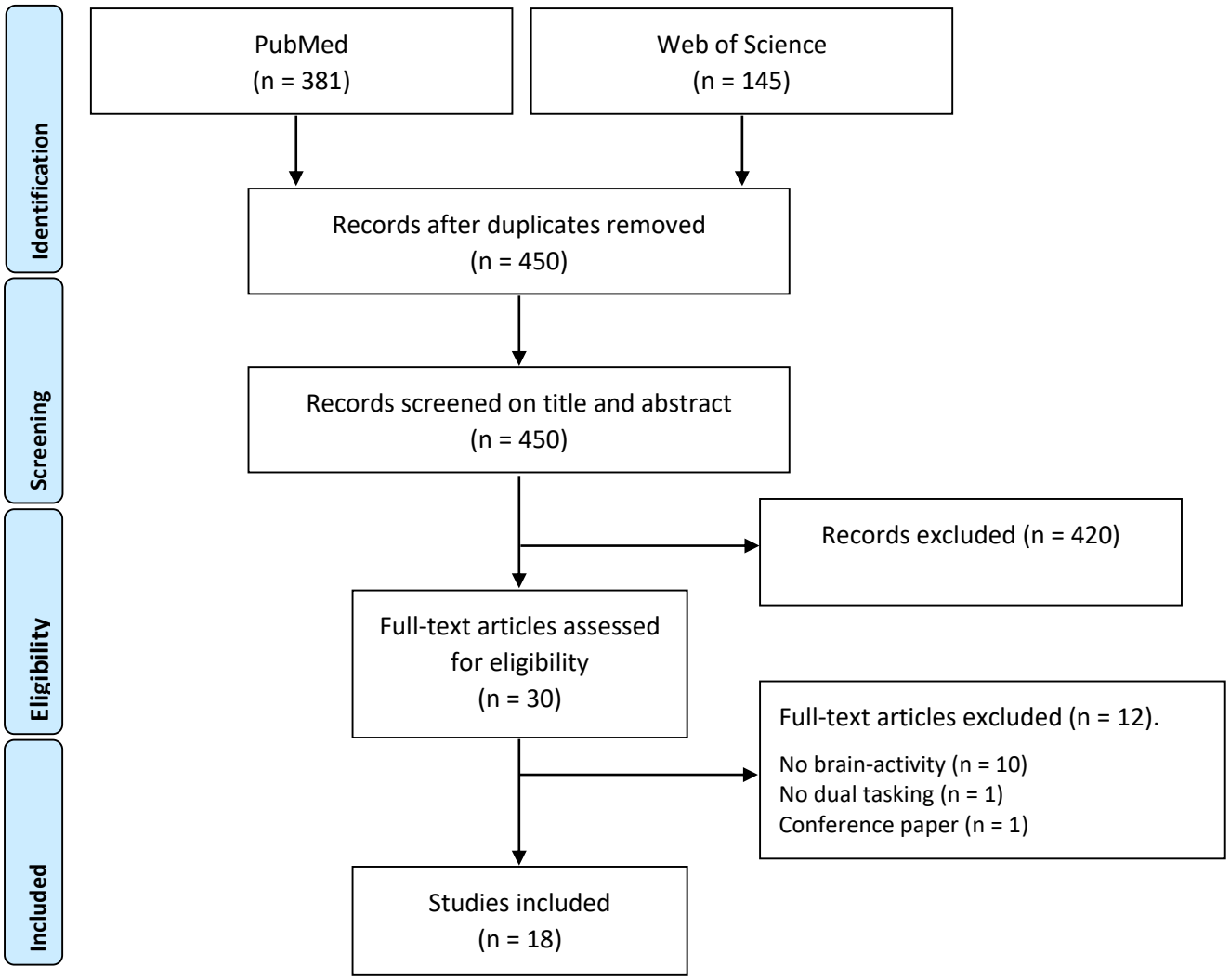
Figure titles

FIGURE 1. Flow diagram of our literature search.

FIGURE 2. Overview of the neuroimaging techniques (fNIRS, FMRI, PET, and EEG) combined with the cognitive–motor dual tasks. From top to bottom: neuroimaging techniques (dark grey) combined with motor tasks (middle grey) combined with cognitive tasks (light grey). The number of studies is shown in parentheses, except when the number is 1. **fNIRS** = functional near infrared spectroscopy. **RT** = reaction time.


Identification
Screening
Eligibility
Included
PubMed
(n = 381)
Web of Science
(n = 145)
Records after duplicates removed
(n = 450)
Records screened on title and abstract
(n = 450)
Records excluded (n = 420)
Full-text articles assessed
for eligibility
(n = 30)
Full-text articles excluded (n = 12).
No brain-activity (n = 10)
No dual tasking (n = 1)
Conference paper (n = 1)
Studies included
(n = 18)

Imaging Technique	**fNIRS (n = 9)**	**fMRI (n = 7)**				**PET (n = 1)**	**EEG (n = 2)**	
Motor Task	Walking (9)	(Cued) ankle movement (2)	Imagined walking	Finger-tapping / button-pressing (3)	Visuomotor tracking	Tracking	Isometric handgrip	Finger-tapping
Cognitive Task	Phonemic fluency Digit span forward Counting Subtracting (6) Alternating alphabet (2)	Subtraction ‘’Inhibition-task’’	Navigation	Counting (2) Visual search	Clock task	Digit span forward	RT task	Phonemic fluency

TABLE 1. Overview of the 18 Studies

Study	Subjects (n) Age (Years)	Motor and Cognitive Tasks	Behavioral Performance	Technical Specifications	Key Findings (●) and Interpretations According to Study Authors
Chaparro et al (2017)	MS (10) 56.2 ± 5.1 HC (12) 63.1 ± 4.4	MT: walking treadmill (self-paced) CT: alternating alphabet	MS vs HC: ↑ DTC–M	fNIRS - 16 channels - PFC	• PFC activation was higher in MS patients than in HC and higher during the DT than the ST, with MS patients showing a larger increase from ST to DT. • During the DT, HC increased PFC activation; MS patients were unable to maintain their PFC activation levels unless provided with PBWS. These findings suggest that due to the physical impairments associated with MS, increases in PFC activation were observed.
Hernandez et al (2016)	MS (8) 57 ± 5 HC (8) 61 ± 4	MT: walking CT: alternating alphabet	MS vs HC: ≈ DTC–M Gait speed ↓ in DT in both groups	fNIRS - 16 channels - Bilateral PFC	• PFC activation was higher in MS patients in ST and DT walking compared with HC. • MS patients showed greater increases in PFC activation from ST walking to DT walking, whereas gait slowed down to the same extent. These findings suggest that individuals with MS might be able to achieve similar levels of DT motor performance as HC through use of increased brain activation.
Saleh et al (2018)	MS (14) 50 ± 8 HC (14) 50 ± 9	MT: walking CT: sub 7	MS vs HC: ↑ DTC–C ≈ DTC–M	fNIRS - 12 channels - rPMC, lPMC, rSMA, & lSMA	• Only MS patients showed reduced cognitive performance during the DT despite no impairments on traditional neuropsychological tests. • MS patients had overall higher lPMC activation compared with HC. HC increased rPMC activation in DT vs ST walking; this was not seen in MS patients. • Activation in the rPMC and SMA increased in the DT vs ST-C. In MS patients, increased rSMA activation during DT correlated with worse motor and cognitive function. These findings suggest that the rPMC plays an important role in maintaining cognitive performance during DT and that individuals with MS with lower baseline gait speed and worse processing speed show maladaptive recruitment of the rSMA.

Maidan et al (2016a)	PD-on (68) 71.6 ± 0.9 HC (38) 70.4 ± 0.9	MT: walking CT: sub 3	PD vs HC: ↑ DTC–M	fNIRS - 6 channels - Bilateral PFC	• PD patients had a higher PFC activation in ST walking compared with HC. • Only HC increased their PFC activation from ST walking to DT walking. These findings reflect the need for the use of cognitive resources even in a relatively "simple" task.
Nieuwhof et al (2016)	PD-on (12) 70.1 ± 5.4	MT: walking CT: 1. counting: +1 2. sub 3 and 7 3. titrated digit span	DT. 3 vs DT. 2: ↓ stride length DT. 3 vs DT. 1: ↓ stride length & ↑ stride length variability	fNIRS - 6 channels - rPFC & lPFC	• PFC activation was higher during DT walking while serially subtracting and while reciting digits compared with rest. These findings suggest that PFC activation increases during DT walking in individuals with PD and is feasible to measure with fNIRS.
Mori et al (2018)	Stroke (14) 61.1 ± 9.3 HC (14) 66.3 ± 13.3	MT: walking CT: sub 3	Stroke vs HC: ↑ DTC–M acceleration magnitude ↑ DTC–C mistake rate ≈ DTC–C correct rate	fNIRS - 16 channels - rPFC, lPFC, & middle PFC	• PFC activation correlated with cognitive performance in HC and with physical performance in stroke patients. The PFC in HC prioritizes cognitive demands, whereas the PFC in stroke patients prioritizes their motor demands. • DTC-M and DTC-C were higher in stroke patients compared with HC. • PFC activation during the DT was lower in stroke patients compared with HC. The low PFC activity in stroke patients may induce a deficit of attentional resources. However, the insufficient DT itself or the lesions might also affect low PFC activation in stroke patients.
Liu et al (2018)	Stroke (23) 51.5, 28–66	MT: walking CT: sub 3	DT < ST for gait speed, cadence, and stride length DT > ST for stride time	fNIRS - 14 channels - Bilateral PFC, PMC, & SMA	• Increased activation during DT vs ST walking was found in the bilateral PMC and the PFC of the lesioned hemisphere and in the SMA of the non-lesioned hemisphere. • Gait performance correlated with bilateral PMCs and lesioned SMA. Gait performance deteriorated during DT walking. The SMA and PMC seem to play important roles in DT walking after stroke.
Doi et al (2013)	MCI (16) 75.4 ± 7.2	MT: walking CT: verbal fluency	DT < ST for gait speed	fNIRS - 16 channels - PFC ROIs: RIFG & LIFG	• PFC activation was higher during DT vs ST walking. DT walking involves PFC activation among older adults with MCI, and the PFC activation during DT, but not ST, walking is correlated with executive function.

Wu & Hallett (2008)	PD-off (12) 61.2, 53–77 HC (12) age-matched	MT: sequence tapping CT: visual letter counting	PD vs HC ↑ errors during DT	fMRI - Whole brain, including cerebellum	• During the DT vs ST, the bilateral precuneus was additionally activated in both groups and showed higher activation in PD patients compared with HC. • PD patients required greater activations at extensive regions to perform simple DTs than HC. Difficulties with dual tasking in individuals with PD might be due to limited attentional resources, defective central executive functioning, and/or less automaticity.
Gao et al (2017)	PD-off (18) 62.5 ± 7.0 HC (18) 62.3 ± 6.8	MT: self-paced tapping CT: visual number counting	No significant difference in performance between and within two groups after practice	fMRI - Whole brain, including Cerebellum ROIs: RVM, LCV, & precuneus	• During the DT, the RVM, LCV, and precuneus were additionally activated in HC; in PD patients, only the precuneus was additionally activated. Individuals with PD have limited cerebellar resources that are already used for STs and, for DTs, cannot augment as necessary in order to integrate motor and cognitive networks.
Maidan et al (2016b)	PD-on (20) 72.9 ± 1.6 HC (20) 69.7 ± 1.3	MT: imagined usual walking CT: imagined navigation walk	Navigation correct responses: PD: 61 ± 6% HC: 90 ± 5%	fMRI - Whole brain, including cerebellum	• PD patients showed greater activation during imagined walking compared with HC. • During the DT, HC had higher activation in left parietal (precuneus) and right premotor area. • PD patients had no increased brain activation from ST to DT. The increased activation during the ST may reduce the functional reserve needed during more demanding tasks such as navigation, perhaps contributing to the high prevalence of falls and DT difficulties among PD patients.
Nieuwhof et al (2017)	PD (19) 70.7 ± 6.1 HC (26) 71.2 ± 5.3	MT: ankle movements (auditory-cued) CT: ''inhibition task''	PD made more motor and cognitive errors during the DT and showed a relatively larger DT effect compared with HC.	fMRI - Whole brain, including cerebellum ROI: putamen	• During the DT, PD patients recruited the ventro-posterior putamen, which was not engaged during the STs, and was not recruited by HC in whom higher activity in that area was associated with worse DT performance. These findings suggest that DT deficits in individuals with PD are related to reduced spatial focusing of striatal activity, which might be explained by a loss of functional segregation between striatal territories during DT.
Rasmussen et al (2008)	TBI (10) 25, 18–36 HC (11) age-matched	MT: button pressing CT: visual search	No Group × Task interaction	fMRI - Whole brain, without cerebellum	• During the DT, TBI patients and HC displayed increased activation of the basic networks subserving each component task.

					• During the DT, TBI patients recruited a left lateralized anterior prefrontal (midline) parietal network compared with HC. These findings suggest substitution, functional reorganization within the primary network subserving the task after TBI, and more effortful processing. Thus, in individuals with severe TBI, low-level DT performance depends on increased attentional and executive guidance.
Al-Yahya et al (2016)	Exp. 1 Stroke (19) 59.6 ± 15.0 HC (20) 54.4 ± 9.4 Exp. 2 Stroke (9) 66.2 ± 8.3 HC (10) 56.2 ± 9.5	MT: Exp. 1: treadmill walking Exp. 2: reciprocal foot movements CT: Exp. 1: sub 7 Exp. 2: sub 3	Main effects of task and group on counting rate Main effects of task and group on stride length and cadence	Exp. 1 + 2: fNIRS - 8 channels - rPFC & lPFC Exp. 2: fMRI - Whole brain, including cerebellum	• fNIRS revealed higher PFC activation in DT vs ST walking (exp. 1) and in stroke patients compared with HC (exp. 2). • In stroke patients vs HC, fMRI showed increased activity during the DT vs ST in the inferior temporal gyri, superior frontal gyri, cingulate gyri, and right precentral gyrus. • DT-related increase in fMRI activity correlated with DT-related behavioral change in stroke patients in the bilateral inferior temporal gyrus, left cingulate gyrus, and left frontal pole. These findings suggest a greater dependence on top–down control for walking after stroke.
Dennis et al (2011)	Stroke (8) 63.5, 44–85	MT: tracking task CT: “clock faces”	Tendency errors DT > ST	fMRI - Whole brain, including cerebellum	• The DTC-M correlated to ST-M brain activations in the right (contra-lesional) dorsal PMC, right ventral PMC, and right middle frontal gyrus. These findings suggest that variations in the interference of a cognitive task with performance of a concurrent motor task explains a substantial proportion of the variations in movement-related brain activity after stroke.
Bracco et al (2007)	AD (50) very mild (22) mild (28) 73.6 ± 7.1 HC (13) 70.5 ± 6.3	MT: tracking task CT: digit span forward task	Very mild AD group performed better than mild AD group, and HC performed better than very mild AD group.	PET - Whole brain	• Performance on the DT is mainly related to glucose metabolism in the parieto-temporo-occipital and posterior cingulate cortices. • The mild AD patients displayed more numerous and widely distributed associations than the very mild AD patients. These findings suggest that a large cortical network is implicated in executive dysfunction in individuals with AD, and it varies according to disease severity. When structures cannot meet the functional demands of the task, other portions of the network for more automatic, sensation-dependent mechanisms come into play.

Palmer et al (2010)	PD (7) 63.7 ± 7.1 HC (6) 60.5 ± 11.3	MT: isometric handgrip CT: visual-motor reaction task	No significant difference in tracking errors between groups	EEG - 19 scalp electrodes - Freq. bands: 5–8 Hz 8–12 Hz 12–30 Hz	• PD-off medication demonstrated enhanced fronto-central and decreased occipital synchronization within theta and alpha bands, as well as widespread increased beta-band synchronization, compared with HC. • During the DT vs ST, PD-off showed synchronization changes within theta and beta bands, with alpha connectivity largely unchanged. These findings suggest that downstream influences of basal ganglia dysfunction on cortico-cortical connectivity may result in difficulties with DT performance in individuals with PD. Task-related dopaminergic-sensitive theta and beta changes may represent a marker for the greater recruitment required to accomplish individual tasks, leading to the inability to perform simultaneous tasks without interference.
Scholten et al (2016)	PD-dbs (14) 60.6 ± 11.6 HC (13) 63.1 ± 10.1	MT: continuous finger tapping CT: verbal fluency	↑ freezing episodes during DT in PD ↑ tapping irregularity in DT	EEG - 36-channel surface EEG - Freq. bands: 4–7 Hz 7–11 Hz 13–30 Hz	• Dual tasking increased susceptibility to upper limb freezing in PD patients, which was associated with increased cortico-cortical phase synchronization in the beta band over the left prefrontal area. • PD patients lacked the increase of frontal synchronization in the theta band and decrease in the beta band in the left prefrontal and bilateral parieto-occipital areas, which were observed in HC. These findings suggest that HC have greater capacity than individuals with PD to modulate cortical function and are able to decrease beta-band activity, thereby decreasing inhibition of associated areas, and to promote neural communication between long-range distance cortical processors.

Values are presented as M ± SD unless noted otherwise.

↑ = increase, ↓ = decrease. ≈ = similar/not significantly different. **AD** = Alzheimer disease. **CT** = cognitive task. **DT** = dual task. **DTC-C** = cognitive dual task cost. **DTC-M** = motor dual task cost. **fNIRS** = functional near-infrared spectroscopy. **freq.** = frequency. **HC** = healthy controls. **l** = left. **LCV** = left lobule V of the cerebellar anterior lobe. **LIFG** = left inferior frontal gyrus. **MCI** = mild cognitive impairment. **MS** = multiple sclerosis. **MT** = motor task. **PBWS** = partial bodyweight support. **PD** = Parkinson disease. **PD-dbs** = PD on subthalamic nucleus deep brain stimulation. **PD-off** = PD off medication. **PD-on** = PD on medication. **PFC** = prefrontal cortex. **PMC** = premotor cortex. **r** = right. **RIFG** = right inferior frontal gyrus. **ROI** = region of interest. **RVM** = right cerebellar vermis. **SMA** = supplementary motor area. **ST** = single task. **ST-C** = cognitive single task. **ST-M** = motor single task. **sub** = subtracting. **TBI** = traumatic brain injury.

TABLE 2. Quality Assessment Results of the 18 Studies According to the Modified Downs and Black (1998) Checklist

	Reporting									Validity								Other		
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**Total**
Chaparro et al (2017)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	16
Hernandez et al (2016)	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	14
Saleh et al (2018)	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	Y	13
Maidan et al (2016a)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	N	N	Y	N	Y	14
Nieuwhof et al (2016)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	N	NA	N	N	N	12
Mori et al (2018)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	N	Y	14
Liu et al (2018)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	NA	N	N	Y	13
Doi et al (2013)	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	NA	Y	N	N	12
Wu and Hallett, 2008)	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	N	Y	Y	N	N	N	Y	11
Gao et al (2017)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	Y	Y	N	N	N	N	Y	11
Maidan et al (2016b)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	N	N	N	Y	13
Nieuwhof et al (2017)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y	14
Rasmussen et al (2008)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	16
Al-Yahya et al (2016)	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	N	Y	N	Y	14
Dennis et al (2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	NA	Y	N	Y	14
Palmer et al (2010)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	Y	Y	N	Y	N	N	13
Scholten et al (2016)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	N	N	N	Y	13
Bracco et al (2007)	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	13
Total NOs per item	0	0	1	1	1	0	0	13	5	14	7	16	1	0	3	9	7	18	4	

N = no (0 points); NA = not applicable; Y = yes (1 point).

Reporting: clear description of (1) aim and hypothesis, (2) main outcomes, (3) characteristics of participants, (4) interventions of interests, (5) principal confounders, (6) main findings, (7) estimates of random variability, (8) adverse events, (9) characteristics of patients lost to follow-up. **Validity:** *external validity:* (10–11) representative sample? *Internal validity – bias:* (12) blinding, (13) data dredging described, (14) appropriate statistical tests, (15) appropriate outcome measures, *Interval validity – confounding:* (16) participants from similar population, (17) adequate adjustment for confounders. **Other:** (18) sufficient power and (19) correction for multiple comparisons.

TABLE 3. Brain Activity in Various Areas During Cognitive–motor Dual Tasking Compared With Single Tasking in the Patient Populations

Article	Task	Population	Clinical Outcome	DT vs ST	Frontal					Parietal		Other							
					PFC	PMC	SMA	Frontal gyrus	Central sulcus	Parietal cortex	Precuneus	Occipital cortex	Temporal gyrus	Cingulate sulcus	Basal ganglia	Caudate	Putamen	Cerebellum	Whole brain
Chaparro et al (2017)	fNIRS walk + alphabet	MS	Cognitive ST > DT DTC-M unclear	DT vs ST-M	↑														
Hernandez et al (2016)	fNIRS walk + alphabet	MS	Gait speed ST > DT	DT vs ST-M	↑														
Saleh et al (2018)	fNIRS walk + sub 7	MS	Gait & Cognitive ST > DT	DT vs ST-M DT vs ST-C		≈ ↑ R	≈ ↑												
Maidan et al (2016a)	fNIRS walk + sub 3	PD	DTC is present	DT vs ST-M	≈														
Nieuwhof et al (2016)	fNIRS walk + count/sub/ds	PD	No comparison with ST walk	DT vs Rest	↑														
Mori et al (2018)	fNIRS walk + sub 3	Stroke	DTC is present	DT vs ST-C	≈														
Al-Yahya et al (2016)	fNIRS walk + sub 7	Stroke	Gait & Cognitive ST > DT	DT vs ST-M	↑														
Liu et al (2018)	fNIRS walk + sub 3	Stroke	Gait Speed ST > DT	DT vs ST-M	↑	↑	↑												
Doi et al (2013)	fNIRS walk + fluency	MCI	Gait Speed ST > DT	DT vs ST-M	↑														
Wu & Hallett (2008)	fMRI tap seq. + count	PD	Errors ST < DT	DT vs STs		↓	↓	↓ I		↓	↑				↓			↓	
Gao et al (2017)	fMRI tap + count	PD	No errors DTC = 0	DT vs STs							↑								
Maidan et al (2016b)	fMRI navigation walk	PD	No comparison with STs	DT vs ST-M															≈
Nieuwhof et al (2017)	fMRI ankle + inhibition	PD	Errors ST < DT	DT vs STs													↑		
Al-Yahya et al (2016)	fMRI ankle + sub 3	Stroke	Not reported	DT vs STs				↑ S					↑ I			↑ L			
Rasmussen et al (2008)	fMRI tap + visual search	TBI	Motor rhythm speed ST > DT	DT vs STs				↑ S	↑ L			↑		↑ L					

Green/up arrow (↑) means higher activation, red/down arrow (↓) means lower activation, blue/approximately-equal-to-sign (≈) means approximately equal activation, in the DT compared with the ST(s).

ankle = alternating ankle movements. **count** = counting. **ds** = digit span. **DT** = dual task. **DTC** = dual task cost. **DTC-M** = motor dual task cost. **fNRIS** = functional near-infrared spectroscopy. **I** = inferior. **L** = left. **MCI** = mild cognitive impairment. **MS** = multiple sclerosis. **PD** = Parkinson disease. **PFC** = prefrontal cortex. **PMC** = premotor cortex. **R** = right. **seq.** = sequence. **SMA** = supplementary motor area. **ST** = single task. **ST-C** = single cognitive task. **ST-M** = single motor task. **sub** = subtracting. **S** = superior. **tap** = finger-tapping. **TBI** = traumatic brain injury.

TABLE 4. Brain Activity in Various Areas During Single and Cognitive–motor Dual Tasking in the Patient Populations Compared With HC

Article	Task	Population	Clinical Outcome	ST-DT	Frontal					Parietal				Other								
					PFC	PMC	SMA	Frontal gyrus	Precentral gyrus/sulcus	Postcentral gyrus/sulcus	Parietal cortex	Precuneus	Angular gyrus	Occipital cortex	Temporal lobule/gyrus	Lateral sulcus	Cingulate gyrus/sulcus	Lingual gyrus	Thalamus	Putamen	Insula	Cerebellum
Chaparro et al (2017)	fNIRS walk + alphabet	MS HC	DTC-M MS > HC	ST	↑																	
				DT	↑																	
				ST vs DT	↑																	
Hernandez et al (2016)	fNIRS walk + alphabet	MS HC	DTC-M MS ≈ HC	ST	↑																	
				DT	↑																	
				ST vs DT	↑																	
Saleh et al (2018)	fNIRS walk + sub 7	MS HC	DTC-M MS ≈ HC DTC-C MS > HC	ST		↑L	≈															
				DT		↑L	≈															
				ST vs DT		↓R	≈															
Maidan et al (2016a)	fNIRS walk + sub 3	PD HC	DTC-M PD > HC	ST	↑																	
				DT	≈																	
				ST vs DT	↓																	
Mori et al (2018)	fNIRS walk + sub 3	Stroke HC	DTC-M Str > HC DTC-Cmr Str > HC DTC-Ccr Str ≈ HC	ST	≈																	
				DT	↓																	
				ST vs DT																		
Al-Yahya et al (2016)	fNIRS walk + sub 7	Stroke HC	No Task x Group interaction	ST	≈																	
				DT	≈																	
				ST vs DT	≈																	
Wu & Hallett (2008)	fMRI tap + counting	PD HC	Simple DT errors PD ≈ HC	ST	↑	↑					↑	↑										↑
				DT	↑	↑		↑			↑	↑		↑	↑		↑		↑			↑
				ST vs DT																		
Gao et al (2017)	fMRI tap + counting	PD HC	No errors DTC = 0	ST		↑R			↑L		↑L											↑
				DT	↑R	↑R					↑	↑										↑R
				ST vs DT																		↓
Maidan et al (2016b)	fMRI walk + navigation	PD HC	Correct response navigation PD < HC	ST	↑			↑			↑	↑		↑	↑							
				DT		↓R					↓L	↓L										
				ST vs DT							↓R	↓R		↓								
Nieuwhof et al (2017)	fMRI ankle + inhibition	PD HC	Motor &Cognitive errors PD > HC	ST																		
				DT																↑VP		
				ST vs DT																↑VP		
Al-Yahya et al (2016)	fMRI, fNIRS ankle + sub 3	Stroke HC	Not reported	ST																		
				DT	↑																	
				ST vs DT	↑			↑S	↑R	↓L		↓R	↓R		↑ I		↑	↓				↓
Rasmussen et al (2008)	fMRI tap + search	TBI HC	No Task x Group interaction	ST										↓			↓		↓ VL	↓L		
				DT				↑	↑R	↑L		↑L		↑LI	↑ LS	↑R	↑L			↑R	↑R	
				ST vs DT				↑R.S									↑R					

Green/Up-arrow (↑) means higher activation in the patient-population than in HC, red/down-arrow (↓) means lower activation in the patient-population compared to HC, blue/approximately-equal-to-sign (≈) means approximately equal activation in the patient-population and HC.

ankle = alternating ankle movements. **Ccr** = correct rate. **Cmr** = mistake rate. **DT** = dual task. **DTC-C** = cognitive dual task cost. **DTC-M** = motor dual task cost. **DTC** = dual task cost. **I** = inferior. **L** = left. **MS** = multiple sclerosis. **PD** = Parkinson disease. **PFC** = prefrontal cortex. **PMC** = premotor cortex. **R** = right. **S** = superior. **Str** = stroke. **SMA** = supplementary motor area. **ST** = single task. **sub** = subtracting. **tap** = finger-tapping. **TBI** = traumatic brain injury. **vis.** = visual. **VL** = ventrolateral. **VP** = ventro-posterior.