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"The Link between Executive Functions and Mobility in Aging and Advanced Parkinson's Disease – Chances and Limits of Individualized Multimodal Early Geriatric Rehabilitation"

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Content

1 General introduction

“In the 2040s, the number of people aged 80 or over will increase, as will probably the need for long-term care” (Destatis-Statistisches Bundesamt, 2022). This forecast is based on data for the German population at the end of the year 2021 - the highest population level ever recorded. It has been clear for several years now that, particularly in the course of demographic change in Germany and other industrialized countries, the age pyramid is shifting into the shape of an urn. However, the current estimate for Germany of nearly 20 million people who will be 67 or older in about 10 years (that is 4 million more than today) once again highlights the upcoming challenges to the healthcare system and politics that come with the necessity of caring for an increasingly aging and longer-living society (BARMER, 2017; Destatis-Statistisches Bundesamt, 2022). With the extended average human lifespan and increasing chronological age, aspects of biological human aging will need to be increasingly considered in health care management. The complex biological process of aging describes a reduction of reparative and regenerative potential at various levels in the human organism (Khan et al., 2017). As a result, the physiological stress resistance and functional reserves of the organism decrease. Thus, aging is one of the primary risk factors for chronic diseases, such as neurodegenerative disorders (Dong et al., 2016; Hou et al., 2019). Older adults are more likely to suffer from age-related functional impairments and multimorbidity (Anderson & Hussey, 2000; Synofzik & Maetzler, 2015). Against this background, the growing relevance of ensuring evidence-based and effective medical care of older adults becomes quite clear, and the continuing regional disparities and partially limited accessibility of specific geriatric treatment services appear problematic (Achterberg et al., 2019; BARMER, 2017). Geriatrics is a rapidly developing field of medicine that has been taking a holistic approach to the health of older adults since the late 1940s, focusing on diagnostic and therapeutic aspects of their medical condition (Jacobs et al., 2020; Maetzler, Grond, et al., 2016). Following this approach, the geriatric setting includes a Comprehensive Geriatric Assessment (CGA) in which the domains of mobility, cognition, mood, and independent living capabilities are assessed. These domains are derived from the most common impairments in geriatric patients (here defined as aged over 70 years suffering from multimorbidity (Sieber, 2007)), which are associated with reductions in functionality and everyday life management (Ellis et al., 2017). Especially, mobility and cognitive performance play an important role in the self-determined lifestyle of older adults (Davis et al., 2015; Royall et al., 2004). Impairments in both areas can increase with age (Soldan et al., 2017; Verghese et al., 2002, 2006), lead to falls (Herman et al., 2010; Nevitt et al., 1991; Rubenstein, 2006; Stolze et al., 2004) and, as a result, to injuries, hospitalization, need for nursing care and death (Rubenstein, 2006; Snijders et al., 2007). One group that is particularly affected by impaired mobility and cognition are patients suffering from neurodegenerative diseases such as idiopathic Parkinson's Disease (PD). There is a growing research interest in the link between motor and cognitive functions in patients with PD and its impact on treatment outcome. For example, there is evidence that executive functions (EF) and attentional processes in particular are associated with walking performance ((Yogev-Seligmann et al., 2008), see Chapter 2). However, there is still a lack of evidence on the extent to which exactly deficits in EF and specific aspects of walking performance are related to each other. It remains also unclear how this link between EF and walking performance may possibly affect the outcome of individualized treatment in the acute geriatric rehabilitation. This treatment is carried out by a multi-professional team and the content is individually adapted to the patient's needs. Although this patient-oriented approach to multimodal individualized treatment is a well-established component of geriatric rehabilitation, there is a lack of both efficacy studies and sufficient knowledge about specific quantitative prognostic markers that may influence treatment outcome (Nonnekes & Nieuwboer, 2018).

2 Theoretical background

Quantification of mobility impairment in aging and PD

Mobility is broadly defined as the ability to move oneself within community environments that expand from one's home (Webber et al., 2010; World Health Organisation, 2001). This ability is an important brick for independent living, active participation and thus the preservation of quality of life, especially for older adults (Davis et al., 2015; Shafrin et al., 2017). The term mobility encompasses a broad concept. In this dissertation, mobility is understood as function of autonomous human body movement associated with physical or sensory abilities (Sammer et al., 2012). Mobility impairments can occur in different domains, such as balance, transfer behavior and gait. Gait disorders are the most common mobility impairment in older adults with a prevalence of 35% in 70 year-olds, increasing with age (Verghese et al., 2006). Gait disorders can manifest themselves as, impaired walking performance (Mirelman et al., 2018) and are associated with increased risk of falls in people over 65 years of age (of whom about one-third fall at least once a year, (Hausdorff et al., 2001)). The consequences are severe injuries, delayed recovery due to complications, hospitalization and long-term morbidity (Nevitt et al., 1991; Rubenstein, 2006; Rubenstein & Josephson, 2006; Snijders et al., 2007; Suzuki et al., 2002; M. E. Tinetti et al., 1995).

Walking performance can be described in terms of spatio-temporal properties (distance and time) of lower limb movement, where the movement of each limb can be divided into stance phase (the foot touches the ground) and swing phase (the foot is lifted and moves forward) in the so-called gait cycle (Jordan et al., 2007; Mirelman et al., 2018; Sampath Dakshina Murthy et al., 2020). The beginning and end of these phases are defined by the events of heel strike and toe off of each foot that can be used for step detection in walking patterns (Del Din et al., 2016; Pham, Elshehabi, Haertner, Del Din, et al., 2017). In the last 20 years, many efforts have been made to quantify walking performance using wearable sensor technology (so-called inertial measurement units, IMUs), and to implement these approaches in clinical routine (Austen, 2015; Dorsey et al., 2018; Gravitz, 2016; Maetzler, Klucken, et al., 2016). This continuously developing technology allows an examiner-independent, accurate and time- as well as cost-saving evaluation of walking parameters to detect age-related walking patterns (Bernhard et al., 2018; Herssens et al., 2018; Maetzler, Klucken, et al., 2016). Sensor-based spatio-temporal walking parameters can map changes in walking performance over the lifespan. For example, parameters such as gait speed decreases with age (over 60 years), and step time, stance time, and double limb support time (DLS) increase concomitantly (Herssens et al., 2018). In addition, spatio-temporal walking parameters can be useful to distinguish healthy older adults from patients with neurodegenerative diseases like PD already at an early disease stage (Del Din et al., 2019) as well as to identify and classify the progression of PD (Alberto et al., 2021; Hobert, Nussbaum, et al., 2019; Maetzler, Klucken, et al., 2016; Polhemus et al., 2021; Schlachetzki et al., 2017), see Chapter 5 and 6).

PD is the second most common neurodegenerative disease (Hou et al., 2019) with a prevalence of 797 to 916 per 100 000 among people over 50 years of age in Germany (Nerius et al., 2017) . PD is caused by the progressive loss of primarily dopaminergic neurons in different brain areas (Dickson, 2018). PD is a clinical diagnosis and is characterized by several non-motor as well as specific motor symptoms, such as bradykinesia (general slowness of movement), rigidity, postural instability and tremor (Postuma et al., 2015). In the course of the disease, motor fluctuations, dyskinesia (involuntary, random movements) and freezing of gait (FOG, episodic inability to generate steps despite the intention to walk) may also occur (Goetz et al., 2007, 2014). The execution of sequential movements is disturbed in PD by impaired motor automaticity (Mirelman et al., 2019). Reduced walking performance is one of the most common consequences. Disease duration and severity of motor symptoms often serve as anchors for assessing disease severity and determining disease stage (Hass et al., 2012; Titova et al., 2017). For example, disease stages can be differentiated as mild to moderate PD with less severe motor symptoms (associated with a disease duration of less than 10 years) and advanced PD with severe motor symptoms ((associated with a disease duration of about 10 or more years, (Titova et al., 2017)). Individuals with advanced PD represent the largest group among patients with PD who required inpatient treatment in Germany in 2015, accounting for about two-thirds of the total (Tönges et al., 2019). These patients are particularly vulnerable to age- and PD-related impairments of walking performance, falls and related consequences.

Several sensor-based spatio-temporal walking parameters have already been investigated that seem promising for the characterization of walking patterns in PD (Alberto et al., 2021; Hobert, Nussbaum, et al., 2019; Maetzler, Klucken, et al., 2016; Micó-Amigo et al., 2019; Polhemus et al., 2021; Schlachetzki et al., 2017). The walking parameters considered in this dissertation (Hansen et al., 2022; Pham, Elshehabi, Haertner, Del Din, et al., 2017) are described in Table 2.1. and will be defined in more detail in Chapter 5 and 6.

Table 2.1 Description of sensor-based spatio-temporal walking parameters used in this dissertation.

Spatio-temporal walking parameter	Description
Number of steps	Number of steps required for a certain distance
Gait speed	Speed at which a certain distance is walked
Step time	Time needed for one step
Stride time	Time required for two successive steps, each with one foot
Stance time	Time during which a foot touches the ground
Swing time	Time during which a foot is lifted from the ground
Double limb support (DLS)	Time during which both feet touch the ground
Double limb support variability (DLSV)	Time variance between all DLS over a certain distance
Step time asymmetry (ASYM)	Difference of step time between both feet over a certain distance
Step time variability (STV)	Variance of step time per foot over a certain distance

A systematic review summarizes the results of 64 studies in individuals with PD and healthy controls in which spatio-temporal walking parameters were measured using IMUs (Bouça-Machado, Jalles, et al., 2020). This among other work illustrates that individuals with PD differ from healthy individuals in several aspects of walking (Mirelman et al., 2019; Vila et al., 2021; Zanardi et al., 2021)). For example, individuals with PD tend to walk more slowly and asymmetrically (e.g. with higher step time asymmetry, ASYM), with delayed rhythm (e.g. with higher step and stride time as well as with higher gait variability (e.g. higher step time variability, STV, and higher double limb support variability, DLSV, (Mirelman et al., 2019; Vila et al., 2021; Zanardi et al., 2021)). Another recently published work reviewed, among other things, convergent and predictive validity for clinical outcomes (such as falls or disease progression) as well as responsiveness to interventions of various spatio-temporal walking parameters in individuals with PD and other conditions (Polhemus et al., 2021). The authors highlighted that some parameters (e.g. gait speed, step time, stance time, double limb support or asymmetry measures) showed consistent evidence in different disease conditions. In contrast, for several other parameters, evidence was inconsistent or lacking in terms to the examined quality criteria. In addition, walking performance in the late stage of the disease has hardly been investigated with spatio-temporal walking parameters and, accordingly, there is no sufficient knowledge about the walking pattern of patients with advanced PD (Bouça-Machado, Jalles, et al., 2020; Mirelman et al., 2019; Polhemus et al., 2021), see Chapter 5 and 6). This gap is particularly problematic because these patients are often older and increasingly suffer from the disorder-specific complications described above.

The role of executive functions in aging and PD

The term EF encompasses a set of higher-level cognitive control processes that humans need to focus their attention, to act in a planned and goal-oriented manner, and to adapt to the changing demands of everyday life (Cristofori et al., 2019; Diamond, 2013). EFs are used whenever automated, instinctive or intuitive behavior is inappropriate, ineffective or impossible (Diamond, 2020). They enable us to develop and adapt problem-solving strategies and to reason, think ahead and plan in complex situations with new requirements. EF also serve as a means of self-control in everyday social situations in order to avoid impulsive, thoughtless behavior. Based on a well-established model, EF can be subdivided into the three components “Inhibition”, the ability to withhold inappropriate prepotent or automatic responses, “Updating”, the ability to evaluate and process incoming information (working memory), and “Shifting”, the ability to switch attention between tasks (cognitive flexibility, (Miyake et al., 2000)). These three components form the basis for a complex network for the control and management of further cognitive functions such as memory and attention (reviewed in (Cristofori et al., 2019)). This three-component model was shown to be most consistent in studies across lifespan (Adrover-Roig et al., 2012; Fisk & Sharp, 2004). However, EF using is effortful, i.e. it requires more mental capacity than automated cognitive processes (Diamond, 2013). Some evidence points to a possible mechanism of dedifferentiation between these three components as a consequence of cognitive aging (Adrover-Roig et al., 2012). Furthermore, cognitive processing speed mediates the effect of age on EF (Gilsoul et al., 2019). EF show a significant performance decline with age and older adults (aged 51 years and older) have poorer performance in EF associated tasks compared to younger adults (aged between 17 and 30 years, (Andrés & Van der Linden, 2000; Fisk & Sharp, 2004; Keys & White, 2000)).

Traditionally, EF are associated with brain areas in the frontal cortex (Diamond, 2020; Moscovitch & Winour, 1995; West, 1996). Age-related differences in EF performance were found on task-dependent dorsolateral prefrontal dysfunction (MacPherson et al., 2002). Over the years, imaging studies have shown that EF require a complex neural network that is not restricted to frontal brain areas (reviewed in (Collette et al., 2006)). However, poorer EF performance appears to be related to an age-related decline in dopaminergic activity in the frontal cortex (reviewed in (Bäckman et al., 2006; Burke & Barnes, 2006)). The clinical pattern of cognitive impairment in patients with PD can also be attributed to the primary neuropathology of dopaminergic neuronal loss that affects the fronto-striatal circuitry (Owen, 2004; E. Ziegler et al., 2014). Deficits in EF and divided attention, as well as in the ability to maintain attentional focus, are evident early in the course of the disease (Dirnberger & Jahanshahi, 2013; Koerts et al., 2009). Thus, they are also considered an early-onset non-motor symptom in patients with PD ((Chaudhuri et al., 2006), see Chapter 5 and 6). With disease progression, an average of 27% develop Mild Cognitive Impairment (MCI), which can include deficits in EF and attention as well as impairments in language, visuospatial, and mnemonic domains (reviewed in (Dirnberger & Jahanshahi, 2013)). Up to 80% of patients with PD suffer from dementia in the advanced stage of the disease (Aarsland et al., 2003). Cognitive impairment and dementia are associated with an increased risk of falls (Lauretani et al., 2016) and reduced quality of life (J. M. Domingos et al., 2015).While severity of motor symptoms and disease duration has been largely described as anchors for advanced stage of PD, it is now thought that non-motor symptoms such as cognitive deficits may also be markers for this stage of the disease (Titova et al., 2017). These deficits may already occur when motor symptoms are not yet pronounced, and therefore concepts of non-motor subtypes of PD are currently discussed, as is a comprehensive definition (including cognitive impairment and dementia) of advanced PD.

The link between executive functions and walking performance in aging and PD

Walking is not a merely automated process (Yogev-Seligmann et al., 2008). In everyday situations, the ability to manage additional demands and tasks simultaneously is constantly required in addition to performing the basic movements of walking. Traditionally, two parallel age-related decline processes of walking and cognition have been assumed (Montero-Odasso et al., 2012). According to this model, falls and their consequences result from mobility impairments with reduced walking performance (characterized by decreased gait speed), whereas age-related cognitive impairments would lead to MCI and later to dementia. Recently, however, it is theorized, that cognitive and mobility impairments develop in a concurrent manner, and that these processes are linked (Montero-Odasso et al., 2012; Yogev-Seligmann et al., 2008). Several studies have investigated this link using both ST (walking without an additional task) and DT (walking with an additional attention demanding task) paradigms (Herman et al., 2010; Hobert et al., 2017; Rubenstein & Josephson, 2006; Salkovic et al., 2017; Verghese et al., 2002). Under DT, the concurrent additional task interferes with the walking task, resulting in a performance loss in one or both tasks. This loss can be represented in terms of DTC for each task ((Fino et al., 2018; O'Shea et al., 2002; Rochester et al., 2004), see Chapter 5) and is known to substantially increase risk of falls and reduce mobility in older adults (Plummer et al., 2015). Older adults with poorer EF performance seem to prioritize the cognitive task at the expense of gait speed, indicating a change in prioritization that is mediated by EF performance (Hobert et al., 2011). Furthermore, walking abnormalities in older adults have been described as a risk factor for developing dementia (Verghese et al., 2002). According to a meta-analysis in older adults, poorer cognitive performance is also associated with reduced gait speed (Al-Yahya et al., 2011). Furthermore, deficits in EF and divided attention showed predictive value for increasing mobility impairments, falls and increased mortality (Gothe et al., 2014; Herman et al., 2010; Vazzana et al., 2010). Overall, under more demanding DT walking conditions, healthy older adults appear to strategically adjust their behavior, e.g. in form of slower walking or longer processing time for cognitive tasks, but do not show strong changes in walking performance compared to ST walking conditions (Yogev-Seligmann et al., 2008).

In contrast, patients with PD seem to have more difficulties to cope with increasing task complexity. They require a higher amount of executive control and attention to manage activities such as walking (Dirnberger & Jahanshahi, 2013; Koerts et al., 2011; Plotnik et al., 2011; Rochester et al., 2004; Yogev-Seligmann et al., 2008). Several studies have shown that deficits in EF in patients with PD may affect gait speed, stride length, and gait variability, especially under DT conditions ((Hillel et al., 2019; Hobert et al., 2017; Johansson et al., 2021; Lord et al., 2010, 2011; Maidan et al., 2016; Mirelman et al., 2018; Nieuwhof et al., 2017; Plotnik et al., 2011; Rochester et al., 2014, 2008; Salazar et al., 2017; Salkovic et al., 2017; Smulders et al., 2013; Stegemöller et al., 2014; Varalta et al., 2015; Wild et al., 2013; Yogev-Seligmann et al., 2008; Yogev et al., 2005), see Chapter 5 and 6). Also, patients with PD have high DTC while walking, which evidently shows the complexity of these walking situations (Kelly et al., 2012; Plotnik et al., 2011; Rochester et al., 2008; Warmerdam et al., 2021). Furthermore, it could be shown that additional tasks with higher complexity have a greater effect on walking performance in PD. It is not clear whether an additional motor or cognitive task influences the walking performance more strongly (Kelly et al., 2012). However, these studies could not identify the distinct predictive value of EF and divided attention on individual walking parameters such as gait speed (Plotnik et al., 2011; Rochester et al., 2008; Stegemöller et al., 2014).

However, the underlying mechanisms for these two concurrently developing processes are not well understood and neuropathological studies come to different conclusions for healthy adults and individuals with PD, respectively. For example, a recent diffusion tensor imaging study in middle-aged and older adults (55 to 81 years of age) found a link between widespread white matter lesions in frontal cortex regions and declined walking performance under DT walking conditions (Alzaid et al., 2022). However, this effect did not seem to be mediated by EF performance of these subjects. One study identified an age-related relationship between DTC of gait speed and variability in older adults (66 to 86 years) with brain atrophy in several brain regions, including the frontal cortex (Hupfeld et al., 2022). This relationship was not shown in the younger cohort (18 to 34 years). In another comparative study, activity in the prefrontal cortex during walking was investigated in both healthy young and older adults and in patients with PD using mobile functional near infra-red spectroscopy (fNIRS, (Stuart et al., 2019)). Individuals with PD had significantly higher activation in the prefrontal cortex during walking than both healthy control groups. Furthermore, prefrontal activation patterns (also examined using fNIRS during walking) differed between patients with PD and healthy older adults under both ST and DT conditions (Maidan et al., 2016). In contrast to the healthy control group, the PD group showed prefrontal activation even under ST, and the level of activation in the PD group under DT appeared to be dependent on the nature of the secondary task (cognitive vs. visual-motor). In addition, impairments in DT performance in PD are thought to result from a loss of segregation between striatal regions and a resulting overlap of otherwise parallel cognitive and motor processes (Nieuwhof et al., 2017). Looking at the above-mentioned neuroanatomical structures and processes involved in both walking and EF, the assumption of a link between EF and walking performance seems reasonable but further investigation of this link and its effect on treatment outcome for PD is needed.

Non-pharmacological treatment options to improve walking performance in aging and PD

With reference to the results presented above on the link between EF and walking performance the question of the role EF performance in treatment of impairments in walking performance arises (both for older adults in general and patients with PD in particular, (Milman et al., 2014; Mirelman et al., 2018)). Deficits in EF performance even affects physical intervention outcomes. For example, one study has shown that baseline EF performance can predict mobility performance after 12-month physical training in older adults (Gothe et al., 2014). Cognitive training to improve or remediate cognitive impairment (e.g., deficits in EF performance) has been widely studied in the past years (reviewed in (Meulenberg et al., 2022)). As technology advances, computer-based cognitive training approaches (CCT, e.g., virtual reality or so-called exergames) are increasingly used in both clinical and domestic settings (de Bruin et al., 2013; Meulenberg et al., 2022). In 2023, a position paper was published on possible transfer effects of cognitive training (defined here as the generalization of required skills across multiple cognitive domains) on cognitive outcome parameters (Gobet & Sala, 2023). Based on the results of meta-analyses and single intervention studies of the last 20 years, the authors postulate that there is no sufficient evidence of transfer effects, particularly for distantly related cognitive domains. In distinction to this, an effect of cognitive training on mobility is referred to as carryover effect in the following (Milman et al., 2014). While a positive effect of regular physical training on various aspects of mobility such as walking performance has been consistently demonstrated, fewer studies have also investigated which forms of cognitive and combined cognitive and physical rehabilitation intervention approaches are suited to improve mobility outcomes such as walking performance (reviewed in (Pichierri et al., 2011; Yogev-Seligmann et al., 2008)). However, the current evidence does not allow a clear statement about which training method has the greatest effect on mobility in older adults. On the one hand, this can be explained by the small number of studies and the heterogeneity of the study designs (type of training, duration and intensity) as well as the mobility outcomes investigated (see Chapter 3). On the other hand, the previous studies show either low statistical power or do not investigate specific spatio-temporal walking parameters, whose association with specific brain structures as well as with specific cognitive functions such as EF and divided attention is already described (Pichierri et al., 2011).

In contrast, for the treatment of impaired walking performance in patients with PD, there is a large body of research and guidelines for both pharmacological and non-pharmacological treatment options that are already being implemented in the therapeutic context (Bouça-Machado, Rosário, et al., 2020;

Debû et al., 2018; J. Domingos et al., 2018; Ni et al., 2018; Radder et al., 2020; Smulders et al., 2016; Zeuner et al., 2019). In the early stages of the disease pharmacological treatment with oral dopaminergic medication is considered the established most effective therapy, when motor symptoms and problems in walking performance already occur (Zeuner et al., 2019). However, this effect diminishes as the disease progresses, and in the later stages of PD pharmacological treatment effects become increasingly insufficient (Debû et al., 2018; Dietrichs & Odin, 2017). Accordingly, additive non-pharmacological approaches of rehabilitation and physical training programs play a crucial complementary role in improving motor symptoms, impaired walking performance and functional mobility (Bloem et al., 2015; Bouça-Machado, Rosário, et al., 2020; J. Domingos et al., 2018; Witt et al., 2017). Physical rehabilitation guidelines include various forms of intervention for different aspects of mobility impairment depending on the severity of motor symptoms (e.g. gait re-education and functional strategy-training for compensation, treadmill training, lower limb muscle strength and balance training, (J. Domingos et al., 2018; Nonnekes & Nieuwboer, 2018)). In addition, recent studies of patients with PD with mild to moderate motor impairment demonstrated that the use of spatio-temporal walking parameters can be helpful in gaining a more detailed understanding of specific aspects of walking performance that can be improved by physical and multimodal rehabilitation (Frenkel-Toledo et al., 2005; Hartelt et al., 2020; Scherbaum et al., 2020; Serrao et al., 2019). However, the gap of knowledge with regard to responsiveness to treatment has already been mentioned above. For instance, gait speed could be identified as consistently responsive (which is the most commonly used parameter in treatment efficacy studies focusing on walking impairment), while the evidence of responsiveness is inconsistent or lacking for other gait parameters (Polhemus et al., 2021; Scherbaum et al., 2020; Serrao et al., 2019).

In conjunction with the above findings on patients with PDs' difficulties in DT situations in everyday life, DT interventions for PD have been evaluated in recent years. Mainly one multi-center randomized control trial with 121 patients with PD provided promising results (Geroin et al., 2018; Strouwen et al., 2017, 2019). In this study, consecutive (separate training of walking and cognition) and integrative training (simultaneous training of walking and cognition) were compared with respect to their effect on the change in walking performance (using spatio-temporal walking parameters) under both ST and DT conditions. The authors found similar effects for both intervention approaches in terms of improvement of gait speed, step length and cadence, but no changes in gait variability, under ST and DT. In addition, the patients with PD who benefited most from the intervention were those who had low gait speed under DT and good cognitive performance at baseline. It has been discussed that DT training therefore might be inappropriate (in terms of increasing the risk of falls) for some patients with PD due to a compromised transfer of learning for complex tasks and a possible attentional overload (Nonnekes & Nieuwboer, 2018; Strouwen et al., 2017). These findings can be taken as further evidence that, in addition to the severity of motor symptoms, non-motor symptoms such as deficits in cognitive performance need to be considered when developing intervention programs for improving walking performance in PD. Other interventions also seem to be influenced by patients' cognitive performance with regard to their effectiveness, for example, strategy training to compensate for existing deficits is most effective for patients with advanced PD with severe motor deficits and less cognitive decline (Nieuwboer et al., 2002; Nonnekes & Nieuwboer, 2018).

Thus it becomes apparent that a "one-size-fits-all" treatment approach may not mirror the complexity of PD adequately (Ginis et al., 2017; Nonnekes & Nieuwboer, 2018; Serrao et al., 2019; Swanson & Robinson, 2020; Witt et al., 2017). Rather, individualized, goal-directed, multimodal treatment approaches are needed to meet the needs of older patients with advanced PD and to maximize functional preservation. One clinical field in which such concepts are implemented in a multiprofessional therapeutic team is geriatrics ((Jacobs et al., 2020; Swanson & Robinson, 2020), see Chapter 6). The geriatric treatment setting combines both skilled (i.e., goal-driven, provided by professional therapists to treat acute illness) and maintenance (self-directed by patients/caregivers to maintain optimal functionality over time and beyond hospitalization) rehabilitation. Thus, the geriatric setting offers an appropriate treatment concept for the multidimensional impairments and risks for patients with advanced PD elaborated above, for which a neurological expertise in the geriatric team remains essential ((Jacobs et al., 2020; Synofzik & Maetzler, 2015) , see Chapters 1; 3 and 6). Only in recent years have such individualized multimodal treatment approaches received increased attention in intervention research for advanced PD. Possible reasons for this are, on the one hand, the already described increasing complexity of the disease and potentially arising interferences of the individual symptoms, whereby treatment effects can no longer be clearly delineated (Witt et al., 2017). Problems in evaluating the efficacy of individualized treatment are, for example, the lack of possibility of blinding or comparison with an (inactive) control group, as well as aspects of the therapeutic relationship and interaction. On the other hand, the above-mentioned effects of standardized operationalized training are not per se transferable to individualized multimodal concepts and the underlying mechanisms are more difficult to identify, since, among other things, a uniform comparison with a control group in this intervention design is complicated. However, as multimodal, multiprofessional complex treatments are already established as common practice in clinical treatment, the need for studies on their efficacy is inevitable. For example, a study of 47 patients with PD across different stages of disease showed improvement in motor symptoms and complications as well as health-related quality of life and depression after two weeks of multimodal complex therapy (Hartelt et al., 2020; Scherbaum et al., 2020). Patients with moderate motor impairments benefited the most. The authors and others also point out that a differentiated selection of patient characteristics and their condition is not yet sufficiently done to predict which influencing factors (such as higher age or deficits in EF and divided attention) contribute to or impede the best possible benefit of individualized treatment (Dietrichs & Odin, 2017; Nonnekes & Nieuwboer, 2018; Scherbaum et al., 2020).

Aim and outline of this dissertation

The aim of this dissertation is to better understand the link between cognition (particularly EF and divided attention) and mobility in both healthy older adults and patients with advanced PD as well as how this link is associated with the effects of CCT and individualized early geriatric rehabilitative treatment (ERGCT). Therefore, the following three main scientific questions will be addressed.

1. Can an effect of CCT on mobility outcomes in healthy older adults be supported based on the current literature?
2. Are EF and divided attention associated with straight walking performance and DTC for walking under ST and DT straight walking conditions in patients with advanced PD?
3. Is performance in global cognition, EF and divided attention associated with change in straight walking performance after individualized early rehabilitation under ST and DT straight walking conditions in patients with advanced PD?

To answer the first research question, an overview of the influence of CCT on mobility in healthy older adults by means of a systematic literature review is provided (Chapter 3). It is hypothesized that improvements in different domains of mobility can be found after application of CCT in terms of a carryover effect in selected interventional studies. Here, the results of CCT studies in healthy older adults published up to and including June 2017 with primary outcome parameters for mobility were summarized. Study quality was categorized using the criteria of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM).

To give an overview of the methods used in this dissertation, the study protocol of the exploratory, observational, multi-center study “Cognitive and Motor interactions in the Older population” (ComOn) is presented (Chapter 4). The ComOn study forms the framework of this dissertation and was designed to integrate advanced assessment tools into a routine clinical geriatric setting and to map the benefits of ERGCT for different geriatric patient groups. In this study, geriatric patients were assessed before and after two weeks of inpatient individualized early geriatric rehabilitation using a comprehensive assessment. It includes a quantitative sensor-based movement analysis, a detailed neuropsychological examination (focusing on global cognitive performance as well as executive and attentional functions) in addition to other behavioral and health-related aspects.

To answer the second and third research questions, ComOn study data from a subcohort of patients with advanced PD were analyzed (Chapter 5 and 6). The association between EF and divided attention and straight walking performance under ST and DT conditions as well as the DTC for walking were examined using baseline data at admission for the inpatient stay (Chapter 5). The straight walking performance was measured under two ST (fast or normal pace) and DT (secondary motor or cognitive task) walking conditions using spatio-temporal walking parameters extracted from the raw data of a wearable sensor worn on the lower back. In addition, the DTC while walking for both DT conditions were calculated for each walking parameter. It is hypothesized that reduced performance in EF and divided attention is associated with reduced straight walking performance in acutely hospitalized patients with advanced PD under both ST and DT walking. In addition, it is hypothesized that performance in EF and divided attention is associated with the occurrence of DTC while walking. The association of global cognitive performance, EF, and divided attention and the change in straight walking performance was examined using baseline data at admission (for the cognitive parameters) and the calculated difference of each spatio-temporal walking parameter between admission and discharge measurements after two weeks of treatment (Chapter 6). It is hypothesized that reduced performance in global cognition and EF and divided attention limits the change in walking performance in terms of improvement after two weeks of ERGCT.

Finally, the main findings are summarized and discussed in the light of other studies, and suggestions for further research questions and optimization of individualized geriatric treatment are given (Chapter 7).

3 Influence of computer-based cognitive training on mobility in healthy older adults. A systematic review

This chapter addresses the first research question stated in the introduction. Here, an overview of the results of studies that have examined the effect of CCT on mobility in healthy older adults as well as a categorization of the study quality is provided. The content of this chapter has been translated into English for this dissertation for the purpose of consistency and has been published in German as a systematic review article in *Zeitschrift für Gerontologie und Geriatrie (ZGG)*:

Geritz, J., Maetzler, W., & Schlenstedt, C. (2018). Einfluss von computerbasiertem kognitivem Training auf Mobilität bei gesunden Älteren: Ein systematischer Review. In Zeitschrift für Gerontologie und Geriatrie (Vol. 51, Issue 2, pp. 184–192). https://doi.org/10.1007/s00391-018-1369-9

Abstract

Background: Mobility is important and often affected in older adults. Mobility is related to cognitive function, which is associated with age-related decline. Computer-based cognitive training (CCT) is increasingly used to treat such cognitive deficits. Whether CCT also has an effect on mobility is not yet clear.

Objective: The aim of this systematic review was to identify and evaluate available intervention studies investigating the effect of CCT on mobility-related outcome parameters in healthy older adults.

Methods: Studies with CCT interventions with mobility outcome parameters (gait, balance, transfer) as primary outcomes and published up to June 2017 were categorized based on the criteria of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) and then systematically evaluated.

Results: Out of 305 identified studies, 11 CCT studies met the inclusion criteria. The quality of these studies was generally high but definitions and effects of mobility outcome parameters were heterogeneous. The most promising mobility outcome parameters that may be influenced by CCT are step length under dual task conditions and gait initiation.

Conclusion: The use of CCT may have positive effects on mobility parameters. Further studies focusing on this hypothesis as the primary outcome parameter are needed.

Keywords: Aging, Balance, Cognitive therapy, Gait, Motor cognitive risk syndrome

Introduction

Mobility and cognitive function play an important role in older peoples' lives. The prevalence of gait disorders is 35% for people over 70 years, and significantly higher for people over 80 years (Verghese et al., 2006). Research in older adults suggests a link between cognitive deficits (particularly regarding deficits in executive functions, EF, and attention) and mobility (e.g., through increased risk of falls, (Herman et al., 2010; Hsu et al., 2012; Tabbarah et al., 2002). A link between cognition and motor function was also found in studies that focused on compensatory strategies for motor deficits (Maetzler et al., 2013) as well as in studies that focused on so-called dual task (DT) effects (Hobert et al., 2011). These findings raise the question whether cognitive training can improve motor skills or mobility. In other words, is a carryover effect on motor skills during cognitive training possible, although the latter have not been trained explicitly.

This systematic review provides an overview of the effects of computer-based cognitive training (CCT) on mobility in healthy older adults.

Methods

Study inclusion

Studies in healthy older adults (>65 years) were screened, which were published in English and German in the databases Pubmed, Web of Science and PsychInfo until the end of November 2017. Only papers that focused on the influence of CCT on mobility parameters (walking, balance and transfer behavior) were included. CCT describes computer-based procedures for specific training of cognitive functions. Studies in which the primary training content was based on motor aspects with additional cognitive tasks were excluded, as well as studies in which only the effect on cognitive performance was investigated. In addition, no studies with patient cohorts were included. The following search criteria were used in each database:

> ((((aged OR elderly OR old*)) AND (computeri* cognitive training OR computeri* cognitive exercise OR computeri* cognitive rehabilitation OR computer-based cognitive training OR computer-based cognitive exercise OR computer-based cognitive rehabilitation OR computer-assisted cognitive training OR computer-assisted cognitive exercise OR computer-assisted cognitive rehabilitation)) AND (gait OR balance OR mobility OR motor* OR motor function OR motor performance OR motor capacity OR physic* OR physical function OR physical examination OR physical performance OR physical capacity)) NOT (child OR children OR adolescent OR youth OR young))).

First, keywords were entered separately, then keywords were combined. The database search was performed using the search fields "All Fields" (Pubmed, PsychInfo) or "Topic" (Web of Science). From 305 search results, 193 studies were excluded after title screening. Abstracts of the remaining 112 articles were screened according to the following criteria: Target population (healthy older adults, 65 years or older), performance of a CCT, investigation of influence on mobility parameters (i.e., gait, balance, transfer). Based on this evaluation, 31 publications remained for subsequent full-text evaluation. Twenty of these 31 studies were excluded post-hoc. Five studies examined a different target group, three examined cognitive functions only, two examined mobility only, and two studies examined the relationship between cognition and mobility inverse to the research question of this review. Two studies did not use a CCT method, and one study examined neuroplasticity. One study was a validation study, three studies were study protocols, and one publication was a review. Figure 3.1 provides an overview of the systematic literature search.

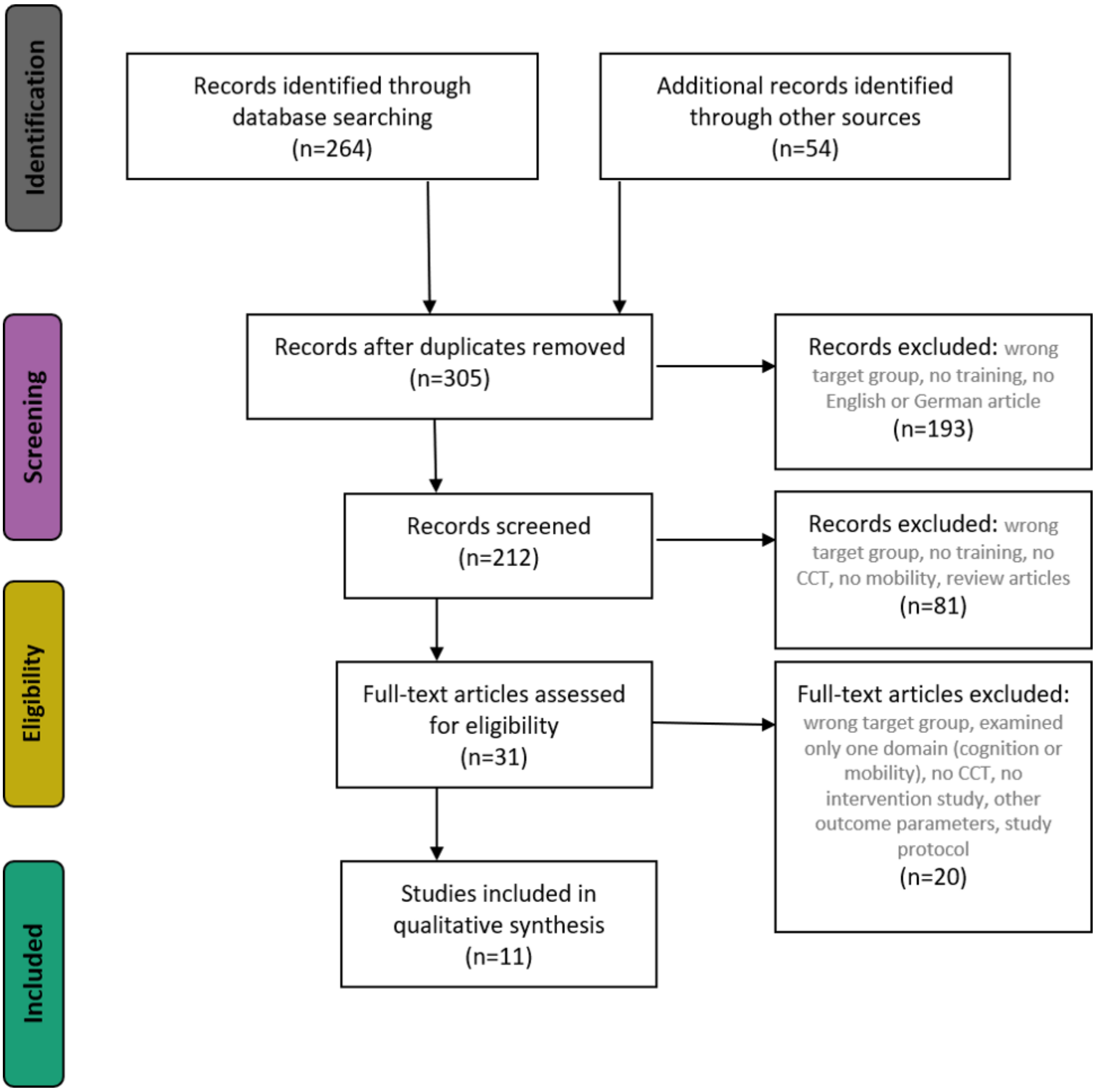

Figure 3.1: Phases of systematic study selection and evaluation. (adapted version of the recommendation of the PRISMA group ((Moher D, Liberati A, 2009)).

Evaluation of Study Quality

The eleven included studies were categorized according to the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) level of evidence for group design intervention studies (Darrah et al., 2008). According to this classification, studies are assigned level I to V based on their design. These levels indicate the extent to which the observed effects are attributable to the study intervention and not to other aspects. In this context, studies with level I (randomized control studies with n>100) suggest the highest degree, and level V studies (e.g. single case reports, expert opinions) the lowest degree of causality between intervention and effect.

Results

The descriptive evaluation of the included studies with regard to the investigated sample characteristics (e.g., age, gender), methodology (study design and duration, control groups, training type), and objectives (functional correlations, training effects), as well as the respective results relevant here (pre-post evaluation of mobility parameters), as well as the AACPDM classification, are described in Table 3.1. Walking parameters were evaluated in nine studies (Blackwood et al., 2015; de Bruin et al., 2013; Fraser et al., 2017; Middleton et al., 2017; Pichierri et al., 2012; Schoene et al., 2013; Smith-Ray et al., 2014, 2015; van het Reve & de Bruin, 2014). Effects on balance were assessed as primary outcome in two studies (Y. M. Lee et al., 2013; Padala et al., 2017) and as a secondary outcome in four studies (Fraser et al., 2017; Schoene et al., 2013; Smith-Ray et al., 2014; van het Reve & de Bruin, 2014). Transfer behavior was assessed in four studies (Blackwood et al., 2015; Fraser et al., 2017; Middleton et al., 2017; Schoene et al., 2013). In addition, two studies assessed the rate of falls (Blackwood et al., 2015; van het Reve & de Bruin, 2014) and six studies assessed the fear of falling (de Bruin et al., 2013; Fraser et al., 2017; Padala et al., 2017; Pichierri et al., 2012; Schoene et al., 2013; van het Reve & de Bruin, 2014), which are reported here for the purpose of detailed study description. The individual aspects of the studies are presented in more detail below.

Participant characteristics

The group sizes of the individual studies ranged from n=16 (de Bruin et al., 2013) to n=182 (van het Reve & de Bruin, 2014). All studies recruited healthy older adults. Six studies included nursing home residents (Blackwood et al., 2015; de Bruin et al., 2013; Padala et al., 2017; Pichierri et al., 2012; Smith-Ray et al., 2014; van het Reve & de Bruin, 2014), one study also recruited people living independently in the immediate vicinity of the facility (van het Reve & de Bruin, 2014), two studies examined self-supporting residents in housing units designed for senior citizens (Schoene et al., 2013; Smith-Ray et al., 2015), three studies did not provide precise information (Fraser et al., 2017; Y. M. Lee et al., 2013; Middleton et al., 2017). The proportion of female subjects ranged from 13% to 100%; one study did not provide any information on gender (Schoene et al., 2013). The drop-out rate ranged from zero to 32%. In six studies, the criterion "ability to walk independently" was defined more precisely as an inclusion criterion: without a walking aid (Blackwood et al., 2015; Padala et al., 2017), with or without a walking aid for at least 8 meters (Pichierri et al., 2012), without walking aid for at least 20 meters (de Bruin et al., 2013), with or without walking aid for at least 20 meters (Schoene et al., 2013; van het Reve & de Bruin, 2014). In two studies, the inclusion criterion was "≥1 fall in the past 2 years or subjective balance problems" (Smith-Ray et al., 2015) or "the inability to stand on one leg for > 3 seconds"(Smith-Ray et al., 2014). For one study, the ability to stand independently on soft ground ("step pad") was (Schoene et al., 2013) an inclusion criterion, another study looked at people who did less than 150 minutes of physical activity a week (Fraser et al., 2017). All eleven studies reported including only healthy study participants "without pre-existing cognitive impairment" (i.e., no clinically diagnosed deficit). The definition here for each study was as follows: Montreal Cognitive Assessment (MoCA) ≥26 points (Blackwood et al., 2015), Mini-Mental State Examination (MMSE) ≥26 points (Smith-Ray et al., 2014, 2015), ≥25 points (de Bruin et al., 2013), ≥24 points (Padala et al., 2017; Schoene et al., 2013) and ≥22 points (Pichierri et al., 2012; van het Reve & de Bruin, 2014), or no history of clinically diagnosed dementia or other neurological disease (no cut-off values, (Fraser et al., 2017; Y. M. Lee et al., 2013; Middleton et al., 2017)). One study examined individuals with "subjective cognitive difficulties" without a history of clinically relevant cognitive deficits (Fraser et al., 2017). A comprehensive neuropsychological assessment of EF and attention was conducted in four studies (Blackwood et al., 2015; Fraser et al., 2017; Schoene et al., 2013; van het Reve & de Bruin, 2014).

Duration, intervals and content of the interventions

In two studies, the intervention were designed as individual training sessions (Blackwood et al., 2015; de Bruin et al., 2013) while the other studies conducted group training. One study conducted parts of the intervention in both individual and group training sessions (Middleton et al., 2017). The duration for intervention protocols were about six (Blackwood et al., 2015; Y. M. Lee et al., 2013), eight (Padala et al., 2017; Schoene et al., 2013), ten (Smith-Ray et al., 2014, 2015) or twelve weeks (de Bruin et al., 2013; Fraser et al., 2017; Middleton et al., 2017; Pichierri et al., 2012; van het Reve & de Bruin, 2014). Training intervals for CCT were once (Fraser et al., 2017), twice (Pichierri et al., 2012), two to three times (Schoene et al., 2013), three times (Blackwood et al., 2015; Y. M. Lee et al., 2013; Middleton et al., 2017; Padala et al., 2017; Smith-Ray et al., 2014, 2015; van het Reve & de Bruin, 2014) and three to five time per week (de Bruin et al., 2013). The duration for each CCT session varied between ten (de Bruin et al., 2013; van het Reve & de Bruin, 2014), ten to fifteen (Pichierri et al., 2012), 15 to 20 minutes (Schoene et al., 2013), 23 minutes (Blackwood et al., 2015), 30 minutes (Y. M. Lee et al., 2013), 45 minutes (Padala et al., 2017) und 60 minutes (Fraser et al., 2017; Middleton et al., 2017; Smith-Ray et al., 2014, 2015). In five studies CCT was performed in the intervention group, whereas the control group did not perform any type of training (inactive control group, (Blackwood et al., 2015; Y. M. Lee et al., 2013; Schoene et al., 2013; Smith-Ray et al., 2014, 2015)). In three studies, the intervention group performed both CCT and physical exercises for motor strength, endurance and balance (de Bruin et al., 2013; Pichierri et al., 2012; van het Reve & de Bruin, 2014) while an active control group performed the same physical exercises (de Bruin et al., 2013) or other endurance and balance tasks (Pichierri et al., 2012; van het Reve & de Bruin, 2014). The training sessions always took place in the same locations for both groups in all studies. In one study, the intervention group performed computer-based balance training and the control group performed CCT (Padala et al., 2017). Two studies each examined four active groups (Fraser et al., 2017; Middleton et al., 2017), with training combinations of CCT and intensive aerobic training, CCT and stretching exercises, computerized learning (CL, no specific CCT) and intensive aerobic training, CL and stretching exercises. As CCT programs „Cogniplus“ (de Bruin et al., 2013; van het Reve & de Bruin, 2014), „Lumosity“ (Blackwood et al., 2015), „Stepmania“ (Pichierri et al., 2012; Schoene et al., 2013), „RehaCom” (Y. M. Lee et al., 2013), „Brain-Fitness “und „Wii-Fit“ (Padala et al., 2017) were used as well as variants of the combined programs „ACTIVE“ und „IMPACT“ (Smith-Ray et al., 2014, 2015). Two studies did not mention which CCT program was used (Fraser et al., 2017; Middleton et al., 2017).

Table 3.1. Overview of included studies.

First Author (Year)	participants		methods				main results	AACPDM level
	n_{total}, n, f (%), drop-out rate	Mean age [years], (SD)	Design, pre-post interval	Parameters, assessments	Intervention interval, frequency	Intervention type, environment		
Blackwood, J. et.al. (2015)	n_{total}=44 TG: n=19, f:73.7%, CG: n=25, f:72%; Drop-out:5 (11.4%)	M=74.6 (n.a.) TG: M=73.8 (4.4) CG: M=75.9 (6.9)	NRCT 7 weeks	Global cognitive performance (MoCA-Test), EF and divided attention pre-post intervention (TMT); walking/mobility (gait speed over 3m, FTST, TUG) rate of falls, ADL, IADL	6 weeks TG: 3x/week, 23min (±2min) CG: inactive	TG: independent, domestic environment, nursing home CCT (program "Lumosity")	Gait speed in the TG significantly higher than in the CG. No group differences regarding other walking parameters.	III
Bruin, E. D. de et al. (2012)	n_{total}=16 TG: n=8, f:62.5%, CG: n=8, f:75%; Drop-out:3 (18.75%)	TG: M=79.8 (6.8) CG: M=75 (8.3)	RCT 12 weeks	Rate of recruitment, attrition and adherence, global cognitive performance (MMS), reaction time (Hand and Foot), walking/mobility (ETGUG under ST and DT with lower back wearable sensor "Dynaport"), fear of falling (FES-I)	12 weeks TG: 1x/week, 45-60min + 3-5x/week, 10min (ab week 3) CG: 1x/week, 45-60min	Guided, single, nursing home TG: strength and balance training + CCT (program "Cogniplus") CG: strength and balance training	Significant training effects in both groups. No significant group differences in walking parameters. Significantly reduced fear of falling in the TG than in the CG,	II
Fraser, S. et al. (2017)	n_{total}= 125, f: 70.8% TG1: n= 21, TG2: n= 17, TG3: n= 18, CG: n= 16 Drop-out: 53 (42.4%)	TG1: M=71.9 (6.8) TG2: M=70.5 (7.4) TG3: M=72.3 (5.9) CG: M=71.1 (5.4)	RCT (block) 12,5 weeks	Global cognitive performance (comprehensive neuropsychological assessment), working memory (n-back-task under ST and DT combined with balance and walking), balance (several mediolateral sway measures), walking parameters (6MWT, TUG, SPPB, number of steps and gait speed over 37m), fear of falling (ABC-Scale)	12 weeks All 4 groups: 1x/week, 60min + 3x/week, 60min	Independent, group (4 - 8 people), TG1: CCT (2 DT) + aerobics, TG2: CL (Word, Excel, internet) + aerobics, TG3: CCT + stretching exercises, CG: CL + stretching exercises	Training effects in all groups for both physical and cognitive training. Increased walking speed and improvement in balance after treatment in all 4 groups. Significant reduction in dual-task cost in CCT training groups (TG1 and TG3). Overall, no group differences in working memory accuracy, walking, and balance. No significant group differences with respect to physical training and fear of falling.	II
Lee, Y. et al. (2013	n_{total}= 30, f:56.6% TG: n= 15, f: 60%, CG: n= 15, f: 53.8% Drop-out: 0 (%)	TG: M=72.8 (3.8) CG: M=71.7 (5.6)	RCT 6 weeks	Global cognitive performance (MMSE), Balance (measurement system “BioRescue AP 153”)	6 weeks TG: 3x/week, 30min, CG: inactive	TG: Independent, group, CCT (program "RehaCom", tasks for visuo-spacial and attentional functions)	Significant training effects on MMSE score and balance in the TG. Significant group difference in favor of TG.	II
Middleton, L. et al. (2017)	n_{total}= 126, f:62.7%, TG1: n= 31, f:62.5%, TG2: n= 32, f: 67.7%, TG3: n= 32, f: 58.1%, CG: n= 31, f: 62.5% Drop-out: 26 (20.6%)	M=72.47 (6.3) TG: M=73.26 (7.15) CG: M=71.46 (5.39)	RCT (block) 12 weeks	Global cognitive performance (3MS), mobility (senior fitness test: body strength, flexibility, endurance, TUG), health-related quality of life (Short Form 12 healthy survey), physical activity (CHAMPS), depressive symptoms (GDS)	12 weeks all 4 groups: 3x/week, 60min+ 3x/week, 60min	Physical training: guided, group (12 people); CCT+CL: independent, TG1: CCT (visual/auditive processing speed) + aerobics, strength- u. stretching exercises, TG2: CCT + stretching exercises, TG3: CL (learning sessions of art, history and science) + aerobics, strength- and stretching exercises, CG: CL + stretching exercises)	Significant training effects in physical fitness (except in TUG) across all 4 groups. Associations between increased physical activity and physical strength and endurance parameters. No significant group differences in physical fitness parameters.	I
Padala, K. et al. (2017)	n_{total}= 30, f:13.3% TG: n= 15, f:13.3%, CG: n= 15, f: 13.3% Drop-out: 3 (10%)	M=68 (6.7) TG: M=67.5 (8.1)	RCT 8 weeks	Global cognitive performance (MMSE, 3MS), balance (BBS), fear of falling (ABC-Scale), physical activity	8 weeks TG + CG: 3x/week, 45 min	Independent, group, TG: combined physical + CCT (program "Wii-Fit", yoga, balance, strength,	Significant training effect in balance in the TG and significant group difference in favor of the TG. No other significant group differences. Reduced fear of falling in the TG.	III

		CG: M=69 (3.8)		enjoyment (PACES), health-related quality of life (SF-36)		aerobics, complex DT), CG: CCT (program Brain-Fitness)		
Pichierri, G. et al. (2012)	n_{total}=31 TG: n=15, f:53.3%, CG: n=16, f:62.5%; Drop-out:5 (16,2%)	M=86.2 (4.6) TG: M=86.9 (5.1) CG: M=85.6 (4.2)	RCT 14 weeks	Global cognitive performance (MMSE), fall risk (PPA), viewing direction (ASL Mobile Eye), walking (ST and DT, using walking mat "GAITRite", FPA), fear of falling (FES I)	12 weeks TG: 2x/week, 40min (incl. 10-15min CCT) CG: 2x/week, 40min	Guided, group (2 – 3 people) nursing home TG: endurance and balance training + CCT (program "StepMania"), CG: endurance and balance training	Significant training effects in TG for most of the walking parameters in all walking conditions. Significantly higher walking speed and shorter single stance phase in TG than in CG under DT condition. No group differences with respect to other walking parameters in any of the conditions. Reduced fear of falling in both groups after treatment.	II
Reve, E. van (2014)	n_{total}=182 TG: n=98, f:71%, CG: n=84, f:68.4%, Drop-out:26 (14.3%)	M=81.5 (7.3) TG: M=81.1 (8.3) CG: M=81.9 (6.3)	RCT (parallelized, multi-center) 12 weeks	Global cognitive performance (MMSE), EF and divided attention (TMT, *Wiener Testsystem*), reaction time, walking/balance/mobility (ST and DT, using walking mat "GAITRite", SPPB, ETGUG), fear of falling (FES I), rate of falls (pre-, inter-, post intervention)	12 weeks TG: 2x/ week, 40min + 3x/week, 10min CG: 2x/week, 40min	Guided, group (4 – 6 people) domestic environment and nursing home TG: endurance and balance training + CCT (program "Cogniplus"), CG: endurance and balance training	Significant interaction effects for gait initiation in ETUG and step length under DT condition. Significant training effects in both groups for various gait parameters as well as a reduced fall rate during the intervention and after 1 year.	I
Schoene, D. (2013)	n_{total}= 37, f: n.a. TG: n= 15, CG: n= 17 Drop-out: 5 (13.5%)	TG: M=77.5 (4.5) CG: M=78.4 (4.5)	RCT (block) 9 weeks	Global cognitive performance, EF and divided attention (MMSE, TMT), reaction time, mobility (CSRT, AST, TUG ST and DT, FTST, static balance), fall risk (PPA), fear of falling (icon-FES)	8 weeks TG: 2-3x/week, 15-20min CG: inactive	TG: independent group (2 – 4 people), CCT (program "Stepmania")	Significant group difference and training effect in favor of TG for step reaction time, step mobility, static balance and TUG performance under DT condition. No significant results regarding other parameters.	II
Smith-Ray, R. L. et al. (2015)	n_{total}=53, f:76.5% TG: n=27, f:77.8%; CG: n=24, f:75%; Drop-out:4 (7.5%)	M=81.5 (6.4) TG: M=82.7 (6.0) CG: M=81.1 (6.8)	RCT 10 weeks	Global cognitive performance (MMSE), walking (gait speed over 10m, ST and DT), mobility (TUG), IADL, depressive symptoms (GDS)	10 weeks TG: 3x/week, 60min CG: inactive	TG: independent group, nursing home, CCT (2 programs "IMPACT" and "ACTIVE")	Significant interaction effect for TUG performance (with deterioration of both groups after treatment). Post-hoc analysis with subgroup "slow walkers" (pre >9 sec. for 10m): significant interaction effects TUG performance and walking speed under DT condition.	II
Smith-Ray, R. L. et al. (2014)	n_{total}=45 f:91.1% TG: n=23, f:82.6%, CG: n= 22, f:100%, Drop-out:9 (20%)	M=72.5 (6.3) TG: M=73.3 (7.2) CG: M=71.5 (5.4)	RCT 10 weeks	Global cognitive performance (MMSE), IADL, walking (gait speed over 10m, ST and DT), balance (BBS),	10 weeks TG: 3x/week, 60min CG: inactive	TG: independent group, nursing home, CCT (2 programs "IMPACT" and "ACTIVE", modified)	Significant interaction effects in the TG for balance and walking speed when walking under ST condition.	II

The studies are listed in alphabetical order according to the respective first author. ABC-Scale, Activities-Specific Balance Confidence Scale; (I) ADL, (Instrumented) Activities of Daily Living; AST, Alternate Step Test; BBS, Berg Balance Scale; CHAMPS, Community Healthy Activities Model Program for Seniors; CCT, computer-based cognitive training; CL, computer-based learning program; CSRT, choice stepping reaction time; DT, dual task; EF, executive functions; ETUG, expanded timed get-up-and-go-test; FES-I, Falls Efficacy Scale International; FPA, Foot Placement Accuracy Test; FTST, Five Times Stand Test; GDS, Geriatric Depression Scale; IADL, Instrumented Activities of Daily Life; icon-FES; Iconographic Falls Efficacy Scale; CG, Control group; m, meter; M, mean; min, minutes; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; n_{total}, sample size; n, subsample size; n.a., information not available; NRCT, non-randomized controlled trial; PACES, Physical Activity Enjoyment Scale; PPA, Physiological Profile Assessment; SF-36, Rand Short Form 36; RCT, randomized controlled trial; s, seconds; SD, standard deviation; SPPB, Short Physical Performance Battery; ST, single task; TG, training group, TMT, Trail-Making test; TUG, Timed Up and Go Test; f, percentage of females; 3MS, Modified Mini Mental State Exam; 6MWT, Six-Minute-Walk-Test.

Study quality

Two studies (Middleton et al., 2017; van het Reve & de Bruin, 2014) achieved the highest level of evidence (I) according to the AACPDM classification used here (Darrah et al., 2008). Seven studies achieved level II (de Bruin et al., 2013; Fraser et al., 2017; Y. M. Lee et al., 2013; Pichierri et al., 2012; Schoene et al., 2013; Smith-Ray et al., 2014, 2015) and two studies level III (Blackwood et al., 2015; Padala et al., 2017). Reasons for qualitative limitations were missing or unreported blinding (de Bruin et al., 2013; Fraser et al., 2017; Y. M. Lee et al., 2013; Middleton et al., 2017; Padala et al., 2017; Pichierri et al., 2012; Smith-Ray et al., 2014, 2015), an inactive control group (Y. M. Lee et al., 2013; Schoene et al., 2013; Smith-Ray et al., 2014, 2015), small sample size (e.g. n=16) (de Bruin et al., 2013), and missing information regarding inclusion and exclusion criteria (Y. M. Lee et al., 2013). Two studies reported partial blinding of the investigators with respect to parameters collected at baseline (Blackwood et al., 2015) or in recruitment of participant (Schoene et al., 2013).

CCT effects on primary mobility parameters

Walking

Nine studies investigated walking parameters during straight walking (Blackwood et al., 2015; de Bruin et al., 2013; Fraser et al., 2017; Middleton et al., 2017; Pichierri et al., 2012; Schoene et al., 2013; Smith-Ray et al., 2014, 2015; van het Reve & de Bruin, 2014). Four studies used gait speed. Four studies collected the parameter gait speed by time measurement over a walking distance of 3 meters (Blackwood et al., 2015), 10 meters (Smith-Ray et al., 2014, 2015) or 37 meters (Fraser et al., 2017). Two studies used „GAITRite“ (Pichierri et al., 2012; van het Reve & de Bruin, 2014), one studie used the wearble lower back sensor „Dynaport“ (de Bruin et al., 2013) for collection of walking parameters. Walking was investigated under single task (ST) condition in two studies (Blackwood et al., 2015; Middleton et al., 2017), and under both ST and dual task (DT) walking conditions in the other seven studies (de Bruin et al., 2013; Fraser et al., 2017; Pichierri et al., 2012; Schoene et al., 2013; Smith-Ray et al., 2014, 2015; van het Reve & de Bruin, 2014).

Seven studies (Blackwood et al., 2015; de Bruin et al., 2013; Fraser et al., 2017; Pichierri et al., 2012; Smith-Ray et al., 2014, 2015; van het Reve & de Bruin, 2014) investigated the effect of CCT on gait speed, one of them only under ST walking condition (Blackwood et al., 2015). In two studies (Blackwood et al., 2015; Smith-Ray et al., 2014), participants in the intervention group increased their gait speed to a significantly greater extent than the control group under ST, and in two other studies (Pichierri et al., 2012; Smith-Ray et al., 2015) this effect was shown under DT. In the three remaining studies (de Bruin et al., 2013; Fraser et al., 2017; van het Reve & de Bruin, 2014) no significant group differences were found under ST nor DT with regard to gait speed.

One study investigated the stepping behavior on a stepping pad (Schoene et al., 2013) and found a significant reduction in step time and increase in step amplitude in the CCT group compared with the inactive control group. Step length was assessed in three studies (all with active control groups) (de Bruin et al., 2013; Pichierri et al., 2012; van het Reve & de Bruin, 2014). In the study with the highest quality, step length improved significantly more in the intervention group than in the control group under DT (van het Reve & de Bruin, 2014). In the other studies no significant effects were found (de Bruin et al., 2013; Pichierri et al., 2012). The same three studies investigated single and double stance support phase under ST and DT. None of them found a significant effect under ST (de Bruin et al., 2013; Pichierri et al., 2012; van het Reve & de Bruin, 2014). One study found a significant reduction in single stance phase in the CCT group compared to the control group under DT (Pichierri et al., 2012). The other two studies did not find a significant difference between their groups (de Bruin et al., 2013; van het Reve & de Bruin, 2014). In one of the studies with four active groups, dual-task walking costs decreased significantly in both CCT groups (Fraser et al., 2017).

Balance

Balance parameters were assessed in six studies (Fraser et al., 2017; Y. M. Lee et al., 2013; Padala et al., 2017; Schoene et al., 2013; Smith-Ray et al., 2014; van het Reve & de Bruin, 2014). Out of these six, two studies used the *Berg Balance Scale* (BBS) (Padala et al., 2017; Smith-Ray et al., 2014), and in one of these studies a significantly higher positive effect on Balance was detected for the CCT-group compared to the control group (Smith-Ray et al., 2014). Two other studies used the *Short Physical Performance Battery* (SPPB) (Fraser et al., 2017; van het Reve & de Bruin, 2014). No significant group effects for CCT were found neither in the study with one active control group (van het Reve & de Bruin, 2014) nor in the one that measured postural instability under both ST and DT conditions in four active training groups (Fraser et al., 2017). Two studies (with inactive control groups) investigated static balance (Y. M. Lee et al., 2013; Schoene et al., 2013), one of these used the measurement system BioRescue AP 153 (Tab. 1). Both studies found a significant effect in favor of the CCT group.

Transfer and other mobility parameters

Two studies measured transfer parameters using the five-times sit-to-stand test (FTST) (Blackwood et al., 2015; Schoene et al., 2013), and did not find a significant effect of CCT. In seven studies the total performance time of the *Timed-Up-and-Go-Test* (TUG) or its extended version (ETUG, with longer walking distance over 24 meters) was measured (Blackwood et al., 2015; de Bruin et al., 2013; Fraser et al., 2017; Middleton et al., 2017; Schoene et al., 2013; Smith-Ray et al., 2015; van het Reve & de Bruin, 2014). One of these studies detected a significantly increased gait initiation speed after the intervention in the CCT group compared to the control group (van het Reve & de Bruin, 2014). In one study total TUG performance time was significantly shorter after the intervention compared with the control group, with both groups walking more slowly after the intervention than before (Smith-Ray et al., 2015). One other study showed a significant effect in favor of the CCT group under DT condition (Schoene et al., 2013), while the other four studies did not find any effects of CCT (Blackwood et al., 2015; de Bruin et al., 2013; Fraser et al., 2017; Middleton et al., 2017). One of the two studies with four active groups also used the Senior Fitness Test to assess endurance, strength, and motor flexibility, but also found no CCT-specific effects (Middleton et al., 2017).

Secondary outcome parameters (rate of falls and fear of falling)

One study assessed rate of falls at, prior to, immediately after, and six months after intervention (van het Reve & de Bruin, 2014). Here, no significant difference between CCT group and control group was found, but a significant reduction in fall rate occurred after the intervention in both groups. In another study, the fall rate was assessed only prior to the intervention (Blackwood et al., 2015). In nine studies, the fall rate was not included as outcome parameter.

Six studies examined the effect of CCT on fear of falling (de Bruin et al., 2013; Fraser et al., 2017; Padala et al., 2017; Pichierri et al., 2012; Schoene et al., 2013; van het Reve & de Bruin, 2014). Three studies used the Falls Efficacy Scale - International Version (FES-I, (de Bruin et al., 2013; Pichierri et al., 2012; van het Reve & de Bruin, 2014)), one study used its short version Iconographic Falls Efficacy Scale (icon-FESI, (Schoene et al., 2013)), and two studies used the Activities-Specific Balance Confidence Scale ((ABC Scale, (Fraser et al., 2017; Padala et al., 2017)). One study showed a significantly higher reduction in fear of falling in the CCT group than in the control group (de Bruin et al., 2013), another, however, found the same effect in the group that that did not receive plain CCT (Padala et al., 2017). Four studies showed no CCT-related reduction in fear of falling (Fraser et al., 2017; Pichierri et al., 2012; Schoene et al., 2013; van het Reve & de Bruin, 2014).

Discussion

CCT provides a training option that can be effective for older adults who have deficient cognitive functions (Lampit et al., 2014). The link between cognition and mobility as well as a possible mutual benefit of both domains (e.g., in terms of compensation strategies) is also described in the literature (Hsu et al., 2012; Maetzler et al., 2013; Muir et al., 2012). To our knowledge, at the present time there is no review that has evaluated the relationship between CCT and improvement of mobility-associated parameters. This systematic review shows that there are already studies with decent quality that have taken up the topic, at least as a secondary target criterion.

Overall, the study results do not suggest that CCT has a specific effect on mobility under ST conditions: Sporadically found, positive effects on walking speed (Blackwood et al., 2015; Smith-Ray et al., 2015) as well as on balance capacity (Y. M. Lee et al., 2013; Schoene et al., 2013; Smith-Ray et al., 2014) have been reported by studies with inactive control groups, but could not be confirmed by any of the studies with active control groups (Fraser et al., 2017; Padala et al., 2017; van het Reve & de Bruin, 2014).

Under DT conditions, CCT had a significant effect on stride length and stride initiation, which was demonstrated by a study with a large number of cases and active control group (van het Reve & de Bruin, 2014). Another study confirmed CCT-specific effects under dual-task conditions compared with active controls (Pichierri et al., 2012). On the one hand, these effects are credibly associated with effective CCT in terms of pathophysiology, and on the other hand, they are relevant to everyday life (van het Reve & de Bruin, 2014). These results suggest that a combination of CCT and effective physical fitness training may have a therapeutic effect in coping with demands appearing in DT situations. According to current studies, all other mobility-associated parameters have little evidence of improvement under CCT. A convincing CCT-specific effect was also not found on the parameter "fear of falling", which was investigated quite frequently.

Conclusion for practice

Overall, the effects are heterogeneous, and a clear conclusion (e.g., by a quantitative meta-analysis) can therefore not be derived at present. Further, more thorough investigations of a possible carryover effect are needed. Future studies should be conducted on larger cohorts with and without cognitive or motor impairment, in randomized design, and with active control groups. In addition, attention should be paid to outcome parameters specifically from the EF domain. According to current knowledge, EF are the main domain of cognition that can be associated with an improvement in mobility (Hobert et al., 2011; Maetzler et al., 2013).

4 Motor, cognitive and mobility deficits in 1000 geriatric patients: protocol of a quantitative observational study before and after routine clinical geriatric treatment – The ComOn-Study

This chapter presents the methodology of the exploratory, observational, multi-center ComOn study that started in 2017. The ComOn study represents the main part of the dissertation project on which this dissertation is based. Both studies presented in Chapters 5 and 6 are subprojects of the ComOn study, in which selected data from the subcohort of patients with advanced PD were used for the analyses. This chapter has been formally adapted to the style of the dissertation for consistency. The content corresponds to the publication as Study Protocol in the journal BMC Geriatrics:

Geritz, J.[†]*, Maetzold, S.*[†]*, Steffen, M.*[†]*, Pilotto, A., Corrà, M. F. M. F., Moscovich, M., Rizzetti, M. C. M. C., Borroni, B., Padovani, A., Alpes, A., Bang, C., Barcellos, I., Baron, R., Bartsch, T., Becktepe, J. S. J. S., Berg, D., Bergeest, L. M. L. M., Bergmann, P., Bouça-Machado, R., … Maetzler, W. (2020). Motor, cognitive and mobility deficits in 1000 geriatric patients: protocol of a quantitative observational study before and after routine clinical geriatric treatment - The ComOn-study. BMC Geriatrics, 20(1), 1–13. https://doi.org/10.1186/s12877-020-1445-z*

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Abstract

Background: Motor and cognitive deficits and consequently mobility problems are common in geriatric patients. The currently available methods for diagnosis and for the evaluation of treatment in this vulnerable cohort are limited. The aims of the ComOn (Cognitive and Motor interactions in the Older populatioN) study are (i) to define quantitative markers with clinical relevance for motor and cognitive deficits, (ii) to investigate the interaction between both motor and cognitive deficits and (iii) to assess health status as well as treatment outcome of 1000 geriatric inpatients in hospitals of Kiel (Germany), Brescia (Italy), Porto (Portugal), Curitiba (Brazil) and Bochum (Germany).

Methods: This is a prospective, explorative observational multi-center study. In addition to the comprehensive geriatric assessment, quantitative measures of reduced mobility and motor and cognitive deficits are performed before and after a two week's inpatient stay. Components of the assessment are mobile technology-based assessments of gait, balance and transfer performance, neuropsychological tests, frailty, sarcopenia, autonomic dysfunction and sensation, and questionnaires to assess behavioral deficits, activities of daily living, quality of life, fear of falling and dysphagia. Structural MRI and an unsupervised 24/7 home assessment of mobility are performed in a subgroup of participants. The study will also investigate the minimal clinically relevant change of the investigated parameters.

Discussion: This study will help form a better understanding of symptoms and their complex interactions and treatment effects in a large geriatric cohort.

Keywords: Balance, body-worn sensors, wearables, comprehensive geriatric assessment, executive function, gait, older adults, quantitative assessment.

Background

The demographic changes associated with increased life-expectancy have led to a substantial increase in older people suffering from multimorbidity with age-related neurological diseases and functional impairment (Anderson & Hussey, 2000; Lehnert et al., 2011; Synofzik & Maetzler, 2015). A target-oriented and specific geriatric treatment designed by a multiprofessional and –disciplinary team including neurological expertise, addressing both the clinical relevant functional deficits and the individual needs of the patients, is urgently needed (Kane et al., 2016; M. Tinetti, 2016). Impaired gait, balance, cognitive functions and, consequently, reduced mobility and falls are among the most relevant age-related functional impairments associated with multimorbidity. At 70 years, the prevalence of gait disorders is about 35% and increases further with age (Verghese et al., 2006). About one third of people aged 65 years or above fall at least once a year (World Health Organization, 2007). Interestingly, the prevalence of falls among neurological patients is nearly twice as high as in the general population (Stolze et al., 2004). Of these patients, 5-10% develop serious injuries, e.g. fractures and head trauma (Nevitt et al., 1991; M. E. Tinetti et al., 1995). Delayed recovery from fall-related injury in geriatric patients often requires long-lasting inpatient stays with high resource costs (Bergman & Papendick, 2014; Rubenstein, 2006; Snijders et al., 2007) and the possibility of complications such as pneumonia. Moreover, long-term morbidity associated with fear of falling affect quality of life and mobility (Friedman et al., 2002; Rubenstein & Josephson, 2006; Suzuki et al., 2002).

Cognition, particularly executive functions, are also often affected in older adults (Royall et al., 2004; Yogev-Seligmann et al., 2008) and can interfere with daily life activities and influence mortality rates. In an 8-year follow-up study (Vu et al., 2013), people with deficits in executive functions had a higher mortality rate than those without. One reason may be the reduced ability to manage multiple medical conditions (Vu et al., 2013). Executive dysfunctions even affect intervention outcomes. For example, a recent study showed that baseline executive function performance predicted performance on the mobility tests after training in older adults (Gothe et al., 2014).

A growing amount of epidemiological and pathophysiological studies suggests that motor and cognitive deficits interact and amplify each other (Herman et al., 2010; Rubenstein & Josephson, 2006; Verghese et al., 2002; Yogev-Seligmann et al., 2008). The interaction is not surprising as: (i) recent neuroimaging studies indicate a strong involvement of, e.g. the thalamus, basal ganglia, cerebellum, mesiotemporal areas and the frontal cortex in gait and balance performance (Jahn et al., 2004; Sahyoun et al., 2004), and (ii) lesions in these areas are associated with falls, e.g. for Parkinson patients (Ciliz et al., 2018; Ebersbach et al., 2002; ten Harmsen et al., 2018).

Physical activity may depend on brain integrity and influences geriatric conditions, such as frailty. A recent study indicates that physical activity interventions can reduce the prevalence and severity of frailty in elderly people (Cesari et al., 2015). A post-mortem study showed that white matter lesions of the brain explained 4% of the variance of physical frailty in 165 participants with a mean age at death of 88 years (Buchman et al., 2008). However, the interaction between physical activity and age-associated functional impairment, such as motor and cognitive deficits and frailty, remain largely unexplained and need further investigation. Research and clinical routine commonly use qualitative measures for the assessment of mobility, and motor and cognitive deficits, and these tools improved our understanding of these symptoms. However, these tools have numerous disadvantages, such as inaccuracy, high time expenditure and investigator dependency (Maetzler, Klucken, et al., 2016). Due to the dynamic development in the fields of life sciences and technology, quantitative measures to evaluate impairment of gait, balance, cognitive functions and mobility –including mobile technology, so-called “wearables”- are increasingly available also for medical purposes. This technology can generate highly accurate outcome parameters for clinical studies and is even close to be implemented in the clinical routines (Austen, 2015; Dorsey et al., 2018; Gravitz, 2016; Maetzler, Klucken, et al., 2016).

The first major aim of this prospective, explorative observational multi-center study is therefore to explore quantitative markers of gait, balance and cognitive deficits in relation to routine clinical and specific geriatric parameters –as assessed with the comprehensive geriatric assessment (CGA)- in a large cohort of geriatric patients with predominantly chronic neurologic conditions. Detailed information beyond usual CGA parameters, e.g. gait variability, step characteristics, postural control and (semi-)quantitative cognitive parameters could substantially improve our understanding of geriatric conditions (Maetzler, Klucken, et al., 2016). We will also determine the minimal detectable and clinically relevant change of many of the parameters investigated.

The second major aim of the study is to examine the association between executive and attentional deficits and the identified quantitative motor parameters in this vulnerable clinical cohort. We hypothesize that these cognitive deficits have predictive value for certain gait and balance deficits. The third major main aim is to evaluate the efficacy of an individualized geriatric inpatient treatment. The large dimension and multifaceted construction of the dataset will also allow many additional hypotheses to be tested.

Novel aspects of this study are (i) the recruitment of a prospective and large geriatric cohort, (ii) the coverage of a broad range of clinically relevant parameters, (iii) the identification of stabile quantitative parameters with clinical relevance, (iv) the evaluation of treatment response, (v) the definition of the minimal clinically relevant change (MCRC) of the investigated parameters, (vi) the inclusion of newest mobile technology for the assessment of mobility, motor functions and balance aspects using validated algorithms, and (vii) the assessment of this vulnerable cohort at places beyond the clinical environment.

Methods

Ethics

Ethical approvals have been obtained from the ethical committees of Kiel, Brescia, Porto, Curitiba and Bochum. The centres have submitted their proposals according to the principles of the Declaration of Helsinki. All participants will receive detailed oral and written information about the content and procedure of the study.

Participants

The study will include geriatric patients aged 70 years and older, with and without neurological conditions (Johnston et al., 2019; Maetzler, Grond, et al., 2016; Sieber, 2007). Patients aged between 50 and 69 years will also be considered if they suffer from at least two chronic conditions (Sieber, 2007). Additional inclusion criteria are the ability to stand without personal aid for at least ten seconds and to walk at least three meters (walking aids permitted). Exclusion criteria are severe deficits in consciousness (clinical diagnosis), more than two falls during the previous week (fall risk during the assessment too high), five points or less in the Montreal Cognitive Assessment (MoCA) test (Lawton et al., 2016; Nasreddine et al., 2005), history of or current drug abuse (except nicotine) and (corrected) visual acuity below 60% (assessed using a Sloan Letter Chart for three meter distance (Ashmore et al., 2013)). Magnetic Resonance Imaging (MRI) will be performed in a subset of patients having a clinical indication for this examination. Participants suffering from claustrophobia, or having pacemakers, defibrillators, targeted drug delivery systems, deep brain stimulation, vena cava filters, cochlear implants or any kind of ferromagnetic material within the body will not be considered. The cohort will include inpatients treated in University and General hospitals and geriatric rehabilitation centres.

Procedure

This is a prospective, explorative observational multi-center study. Most of the participants will be recruited at admission. A subsample (n=100) with a planned hospital stay (e.g. to evaluate new treatment options or to improve medication plans in severely affected patients that are at risk of losing functional independency) will be contacted via telephone, to ask them whether they would be interested to participate in a one-week home-based assessment with wearables before and after the treatment phase. All participants will be assessed within the first two days (T1) and during the last two days before discharge (T2) of their inpatient stay. To determine the Minimal Detectable Change, an additional subgroup (n= 100) will undergo a visit (T0) 24 hours before or after T1. Inpatient's stay will be approximately 14-20 days. All participants will receive multidisciplinary care with an individually adapted set of therapeutic options depending on their needs during their inpatient treatment. Data obtained from T1 will be used to evaluate cross-sectional aspects of the study. The response to treatment will be evaluated by calculating the change between T1 and T2 after an approximately 14-20 days multidisciplinary treatment. Figure 4.1 illustrates the detailed study design.

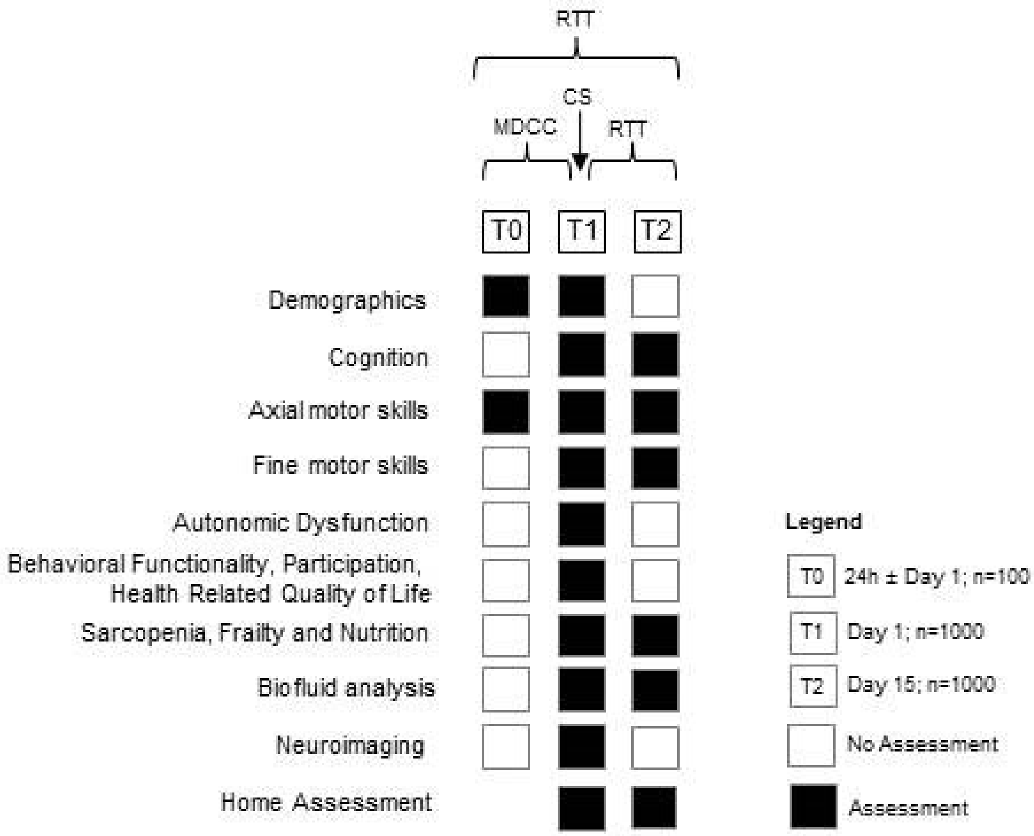

Figure 4.1: Study flowchart. Overview of the study including visits and relevant assessments. CS: Cross-sectional, MCRC: Minimal clinically relevant change, RTT: Response to treatment, T1: Baseline assessment (before / at admission), T2: Follow-up assessment (at / after discharge), T0: Time of assessment 0, for reliability / MCIC evaluation (24h before or after T1).

Measures

All participants will undergo an extensive and quantitatively oriented CGA, i.e. an assessment that collects information about all five relevant components of the International Classification of Functioning, Disability and Health (ICF) model (World Health Organisation, 2001). Furthermore, a detailed evaluation of mobility, and specific motor and cognitive function will be conducted. For measurements of motor and cognitive parameters, translated and validated test versions will be used as far as available. Clinical and demographical data and questionnaires will also be assessed in the required languages.

Clinical and demographic data

Clinical and demographic data –including age, gender, diagnosis, initial and current symptoms, concomitant diseases, activities of daily living (ADL, (Katz, S., Ford, A.B., Maskowitz, 1963)), instrumental ADL (iADL, (Lawton, M.P., Brody, 1969)), nutritional aspects and medication– will be collected from clinical records and also with a semi-standardized clinical interview. Neurological routine assessment will include evaluation of strength (grip force), muscular proprioceptive reflexes, pallaesthesia, signs of ataxia, and frontal lobe dysfunction. We will use the *Geriatrie-Check,* which is a screening tool for the identification of geriatric patients (Bellmann et al., 2013; Hobert, Bernhard, et al., 2019) and assesses aspects of dementia, level of care, frailty, and the premorbid level. It has recently been validated (Hobert, Bernhard, et al., 2019). We will also use the geriatric screening according to Lachs et al. (Lachs et al., 1990) to evaluate the functional aspects of vision, hearing, and urinary incontinence. Self-care and mobility skills (e.g. toilet use, eating, dressing, climbing stairs) will be appraised by the commonly used and reliable (kappa = 0.93) Barthel Index (Heuschmann et al., 2005; Lübke et al., 2004). Subjective improvement will be assessed using the Clinical Global Impression - Global Improvement - Scale (CGI-I, (Busner & Targum, 2007)).

Diagnoses and medication will be extracted from the medical reports. Extent of treatment and rehabilitation -as a covariate- will be evaluated using number and duration of therapeutic sessions as well as (change of) medication and medical aids.

Cognition

Cognitive functions will be measured with standardized neuropsychological screening tools and tests. We will use the MoCA for the evaluation of global cognitive performance. The MoCA has been shown to be internally consistent (Cronbach's alpha = 0.83) and highly sensitive in detecting Mild Cognitive Impairment (MCI, 90%) and Alzheimer's Disease (100%). Normative and validation data are available for Brazilian, Italian, German and Portuguese populations (Freitas et al., 2011; Nasreddine et al., 2005; Pinto et al., 2018; Santangelo et al., 2015). For the assessment of frontal-executive dysfunctions the required version of the Frontal Assessment Battery (FAB) will be used (Appollonio et al., 2005; Beato et al., 2007; Benke et al., 2013). The FAB consists of six items, testing aspects of conceptualization, lexical fluency, motor programming, sensitivity to interference, inhibitory control and environmental autonomy.

The Trail Making Test (TMT, (Strauss, E., Sherman, E. & Spreen, 2006)) assesses visual scanning and processing speed (TMT part A) as well as mental flexibility and divided attention ((TMT part B, B-A). Construct validity of the TMT is good (Sánchez-Cubillo et al., 2009) and there are normative data available stratified by age and education for the required languages (Amodio et al., 2002; Cavaco et al., 2013; Hamdan & Hamdan, 2009; Tombaugh, 2004).

In order to gain the second study aim in more detail regarding specific cognitive functions, the Kiel centre will perform a detailed neuropsychological testing in this subcohort, including the following tests:

- The *Testbatterie zur Aufmerksamkeitsprüfung* (*TAP,* (Zimmermann & Fimm, 2012)) is a computer-based assessment battery for attention. We will use the subtest "Alertness" to measure reaction time to a visual stimulus and the capability to inhibit reactions to a pre-stimulus.
- The standardized *Alters-Konzentration-Test* (*AKT*, (Gatterer, 2007)) provides information about vigilance, concentration and focused attention (the capacity to focus on a stimulus while suppressing imposed distractors). Retest-reliability is high (r=0.75-0.89, (Morgenstern et al., 2017)).
- The Five-Point Test (FPT, (Goebel et al., 2009)) is a standardized paper-pencil test for figural fluency and strategic thinking. The test consists of five-dot boxes in six rows on each sheet where participants produce as many different figures as possible by connecting the dots in each box within a defined time period. The FPT is a valid test that has excellent inter-rater (ICC=0.99) and good test-retest reliability (ICC=0.72-0.84, (Goebel et al., 2009)).
- The *Regensburger Wortflüssigkeitstest (RWT,* (Aschenbrenner, A., Tucha, O., Lange, 2000)) assesses verbal fluency and flexibility. Subjects have to name as many words as possible within two minutes that (i) belong to a certain category, (ii) have a defined starting letter, (iii) belong to two different categories (alternating naming) and (iv) have two defined starting letters (again alternating naming). Inter-rater reliability of the test is excellent (ICC=0.99) and test-retest reliability good (r_{tt}=0.72 – r_{tt}=0.89, (Aschenbrenner, A., Tucha, O., Lange, 2000)).
- The *Nürnberger-Alters-Inventar (NAI,* (Oswald & Fleischmann, 1997)), normed for people aged between 57 and 96 (Oswald & Fleischmann, 1997), provides information about cognitive and behavioural aspects. We will use the subtest *Farb-Wort-Interferenz-Test (FWIT)*, based on the widely used Stroop-Test, to assess attention and cognitive flexibility during provision of conflicting stimuli.

To avoid learning effects in T2, parallel versions of the MoCA, the AKT and RWT will be provided.

Axial motor function

Gait, balance and transfer aspects will be measured in a supervised environment (e.g., the ward, Figure 4.2) using a set of well-established tests (summarized in Table 4.1), which will all be instrumented with CE-certified wearable devices (Rehagait®, Hasomed GmbH, Magdeburg, Germany; sensors at the feet and on the lower back).

Table 4.1 Tests of axial motor functions

Test	Task
Short Physical Performance Battery	Tandem, semi-tandem, side-by-side stand Two 4-meters-walks with comfortable speed 5-Chair rise test, as fast as possible
Timed-up-and-Go test	Rise from a chair, 3-meters-walk, turning, walk back
Straight walk	Standing position, 3-meters-walk, no turning
Straight walk	Standing position, 20-meter-walk under single and dual task conditions
Circular walk	Walk around a 1.20 m circle under single and dual task conditions

The protocol will include the Short Physical Performance Battery (SPPB, (Guralnik et al., 1994; Paz et al., 2018; Vasunilashorn et al., 2009)). The SPPB measures balance (tandem, semi-tandem, and side-by-side stand), gait speed (walking twice four meters at a comfortable speed) and chair rise performance (5-Chair rise test, as fast as possible) which has been shown to be reliable in older adults (ICC=0.83-0.89, (Freire et al., 2012)). Participants will also perform the above-mentioned balance tasks on a foam pad (Airex balance pad, 50x41x6 cm). This test has already been performed under instrumented conditions with test-retest reliability (ICC) between 0.41 and 0.81 (Lin et al., 2015).

Moreover, the Timed-up-and-Go test (TUG) will be used to assess mobility aspects and turning. Recent studies suggest that instrumentation of the TUG with wearable devices can provide useful additional and complementary information to the generally used total time (Al-Jawad et al., 2012; Paz et al., 2018; Varalta et al., 2015; Weiss et al., 2010).

Participants will also perform straight walks (out of a standing position) over three meters and 20 meters and circular walks around a 1.20 m circle (360°). Single task performance will be assessed during both walking conditions with self-selected and as-fast-as-possible pace, except for circular walking (self-selected pace starting with the right leg and then with left leg). Dual task performance (checking boxes and subtracting serial 7s) will be assessed during circular walks in self-selected pace condition, straight walking dual-task performance in fast pace condition (Hobert et al., 2011, 2017; Salkovic et al., 2017).

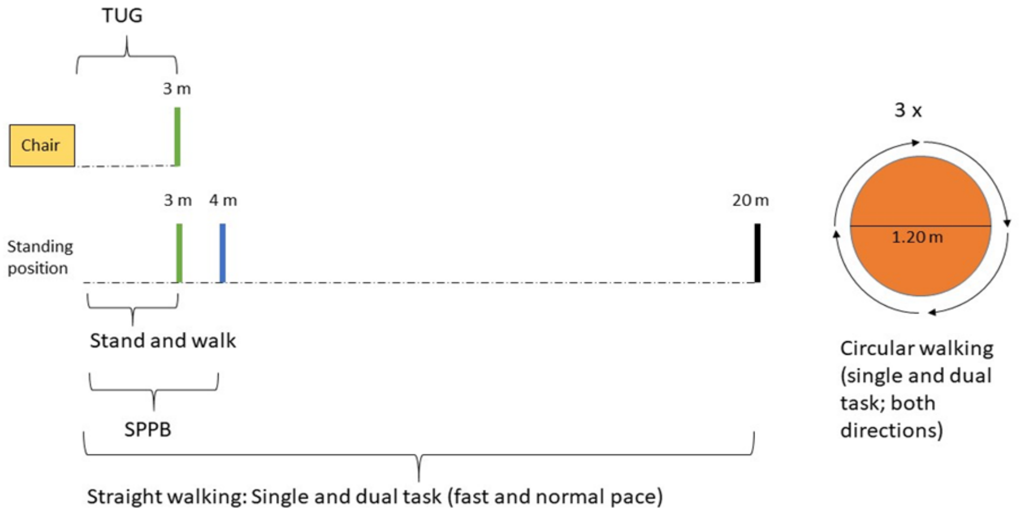

Figure 4.2: Assessment of axial motor function. Simplified illustration of the standardized motor tasks. SPPB, Short Physical Performance Battery, TUG, Timed-up-and-Go Test.

The functional reach (FR) test measures balance at the limits of stability in the anterior direction. It can identify fall risk and balance impairment in geriatric patients (Duncan et al., 1990; Hasmann et al., 2014). We have recently published an instrumented version of the test (Hasmann et al., 2014). Participants will stand upright next to a wall with a yardstick and put their right arm in a stretched-out position. Then they will reach forward as far as they are able to, and then be asked to keep this position for 15 seconds.

Part III of the revised version of the Unified Parkinson's Disease Rating Scale (MDS UPDRS-III, (Goetz et al., 2008)) will be used to assess axial deficits (e.g., via the postural instability and gait (PIGD) subscore) and parkinsonian signs. The Hoehn & Yahr scale will be used in patients with Parkinson’s disease (PD) to define disease severity (Hoehn & Yahr, 2001).

The Falls Efficacy Scale (FES-I, (Delbaere et al., 2010)) consists of 16 questions about concerns regarding falling in specific activities of daily living (e.g., when getting dressed, when taking a shower or when shopping). The FES-I is a reliable instrument (Cronbach’s alpha = 0.79) and a strong association with previous as well as future falls has been found (Delbaere et al., 2010).

Fine motor function

The Functional Dexterity Test (FDT, pegboard test) is a reliable and valid instrument to measure finger and thumb movement (Aaron & Stegink Jansen, 2003). Participants will turn 16 pegs in a zigzag manner as fast as possible on a wooden board with holes, first with the dominant, then with the non-dominant hand.

The 20-Cents test assesses fine motor skills under daily life conditions and is validated for geriatric patients (Krupp et al., 2015). Twenty 1-cent coins, spread over a white sheet of paper, will be picked up with each hand (first the dominant one, then the non-dominant one) and put into a box as fast as possible.

Health-Related Quality of Life, Behavior, Social Participation, Physical Activity and Pain

Health-Related Quality of Life (HrQoL, (Deuschl et al., 2006; Wood-Dauphinee, 1999)) is one of the most important factors regarding treatment decisions and outcome of treatment. Main dimensions of HrQoL are physical, mental, social and role functioning. The EuroQol questionnaire with five dimensions (EQ-5D-5L, (Herdman et al., 2011)) consists of a descriptive part and the EQ Visual Analogue Scale. For the descriptive part, participants rate the impact of mobility and its deficits, self-care, usual activities, pain/ discomfort and anxiety/ depression on HrQoL. The EQ Visual Analogue Scale allows the participant to rate today's overall HrQoL on a scale of 0 (worst health they can imagine) to 100 (best health).

The *Depression im Alter* scale (DIA-S, (Heidenblut & Zank, 2010)) assesses specific aspects of depression and consists of ten items. The test person is asked to focus on the previous 14 days. The DIA-S is reliable (Cronbach's alpha=0.84) and has been validated in geriatric patients (Montgomery & Asberg, 1979).

Apathy, a common symptom in neurological and psychiatric diseases, will be assessed with the German version of the Apathy Evaluation Scale (AES-D, (Lueken et al., 2006)). The AES-D includes cognitive and emotional aspects of goal-directed behaviour. A total of 18 items are rated on a four-point Likert scale by the participant (AES-D-S, self-rated) and by a relative (AES-D-I, informant). The AES-D is reliable (Cronbach's alpha=0.91-0.94) and has been shown to be valid in patients with diverse diseases and in healthy adults (Lueken et al., 2006).

The reliable (ICC=0.70-0.94) and valid *Nürnberger-Alters-Alltagsaktivitäten-Skala (NAA)*, part of the *NAI* (Oswald & Fleischmann, 1997), is a 20-item questionnaire for the assessment of independency and participation in activities of daily living.

Physical activity (PA) will be assessed with the self-administered short version of the International Physical Activity Questionnaire (IPAQ, (Craig et al., 2003)). The participants are asked to estimate how much time in days per week and in hours per weekday they spend doing: (i) vigorous physical activities, (ii) moderate physical activities, (iii) walking, and (iv) sitting. Detailed information about reliability and validity are available for all versions from over twelve countries (Craig et al., 2003).

Pain will be assessed via the painDETECT Questionnaire (PD-Q), which is a reliable screening tool with high sensitivity, specificity and positive predictive accuracy (Freynhagen et al., 2006).

Sarcopenia, Frailty and Malnutrition

The Jamar hydraulic hand dynamometer (AFH, Lügde, Germany) will be used to measure grip force (Roberts et al., 2011). Lean body / muscle mass and total body water and fat will be quantitatively assessed with the validated bioelectrical impedance analysis (BIA, Akern Bia 101, SMT medical GmbH & Co. KG, Würzburg, Germany, (Drey et al., 2017; Janssen et al., 2000)). The BIA will be applied as instructed in the manual with four electrodes (two at the right foot, two on the right hand) in a lying position after a rest phase of about ten minutes (Reimers et al., 2005). *For the definition of sarcopenia we will follow the definition of the European consensus on definition and diagnosis for sarcopenia* (Cruz-Jentoft et al., 2019; Maetzler et al., 2015).

Frailty will be assessed with the FRAIL-scale, a five-item questionnaire asking for fatigue, resistance, ambulation, illness and weight loss during the last three months. Usefulness for detecting frailty in elderly people has been proven (Díaz de León González et al., 2016; Theou et al., 2013; Woo et al., 2015).

The Swallowing Disturbance Questionnaire for Detecting Dysphagia (SDQ, (Manor et al., 2007)) is a 15-item questionnaire to detect dysphagia. The SDQ has been shown to be reliable (Cronbach's alpha=0.89) and useful to assess swallowing in PD.

Different aspects of malnutrition will be measured via interview using the Mini Nutritional Assessment (MNA, (Vellas et al., 1999)), Malnutrition Universal Screening (MUST, (Eia, 2003)) and Subjective Global Assessment (SGA, (Detsky et al., 1987)). The instruments assess nutritional status based on objective data (e.g. weight, height, Body-Mass-Index), physical examination and the participant's self-report.

Autonomic dysfunction

At the location of Kiel, heart rate variability (HRV) will be examined using computer-assisted equipment (ProSciCard III, MediSyst GmbH, Germany) during rest and controlled deep breathing (six respiratory cycles per minute). Coefficient of variation, root mean square of successive differences, mean circular resultant, expiration-inspiration difference and E/I-ratio as well as a spectral analysis of HRV will be quantified and compared to age-related normal ranges of 120 healthy subjects (D. Ziegler et al., 1992).

Blood pressure (BP) and heart rate (HR) during orthostatic exposition will be monitored after ten minutes of supine rest on a tilt table. Patients will then be moved to the erect position (65°) and BP and HR changes recorded at one, three, and five minutes of head-up tilt. A decrease of systolic BP >20 mmHg and diastolic BP >10 mmHg within three minutes of tilting is regarded as orthostatic hypotension (Schatz et al., 1996).

Residual urine volume will be determined with the BladderScan BVI6100 (Verathon Medical BV, The Netherlands, (Y. H. Park et al., 2011)). Moreover, the reliable and validated Qualiveen (P. Costa et al.,

2001) questionnaire will be used for the evaluation of HrQoL in patients with urinary disorders. It covers frequency and intensity of different aspects (limitations, constraints, fears, feelings) of urinary dysfunction.

The German version of the Female Sexual Function Index (FSFI-d, (Berner et al., 2004)) is a 19-item questionnaire for the assessment of six different domains of female sexuality: desire, arousal, lubrication, orgasm, satisfaction, and pain. Its internal consistency (Cronbach's alpha=0.75-0.95) is good to very good. The International Index of Erectile Function (IIEF, (Rosen et al., 1997)) is a self-administered questionnaire for males and includes aspects of erectile function, orgasm function, sexual desire, intercourse satisfaction and overall satisfaction. The original version (Cronbach's alpha>0.9, (Rosen et al., 1997)) and the German translation have been shown to be reliable (Cronbach's alpha=0.95, (Wiltink et al., 2003)). As sexual function is a sensible topic also in older adults, participants will be informed again explicitly that answering this questionnaire is voluntarily.

Biofluid analysis

Participants will be asked to provide blood and stool samples for our established biobank (G. Richter et al., 2018). Material will be collected from the wards and directly brought to the technicians responsible for the pre-processing and storage of the material, to ensure highest quality standards of the bio samples. Blood samples will be used for blood counts and DNA isolation, whereas stool samples will be used for gut microbiome analysis.

Neuroimaging

We will analyse gradient echo T1-weighted sequences, as well as T2-weighted flair sequences, susceptibility-weighted imaging and DTI datasets collected with a standardized protocol on a 3-tesla MRI. In addition, participants will be asked to provide any existing MRI data for semi-quantitative analysis (Fazekas et al., 1987).

Home Assessment

Those patients, who will undergo a planned inpatient stay from a former clinical contact, will be contacted by phone in advance. Patients interested in joining the home assessment will be visited at their homes by staff and introduced into this part of the study. During the home assessment, participants will wear three wearables (inertial measurement units IMUs, GaitUp SA, Lausanne, Switzerland) fixed at the lower back and at the more affected ankle and wrist (if both sides are equally affected they wear the sensors on the right). They will also be asked to keep a structured diary about their activities to ensure comparability of subjective evaluation with IMU-based data. Participants will be assessed 24 hours per day over seven days before and after the inpatient stay. In case patients may have difficulties with the handling of the sensor system, relatives will be asked to support the measurement process.

Database and Statistics

Study data will be collected and managed using REDCap electronic data capture tools hosted at Kiel University (Harris et al., 2009). Statistical analysis will be performed using established statistical programs (e.g. R version 3.5.0, The R Foundation; SPSS 24, SPSS Corp, Chicago IL, USA). We abstained from providing a detailed analysis plan and power analyses as the analysis plans will be substantially influenced by the type of research question, and power analyses depend on both, concrete study hypotheses (which are given here only to a certain extent) and at least preliminary effect sizes that are, to our best knowledge, not yet available for most of the Parameters collected in this specific cohort. The use of z-scores will ensure comparability between data sets of different centres and countries. Common descriptive and inferential statistics and equivalent nonparametric statistics will be used for baseline data analysis. Logistic regression will be used to evaluate confounding factors (e.g. age, gender). A pre-post comparison with correction for multiple testing will be conducted to evaluate changes in mobility, motor function and cognition between T2 and T1. To assess reliability and responsiveness of the assessments (T1 to T0), we will use t-test and Cohen's d after testing for normal distribution, and extract Intra-Class-Correlation (ICC), Standard Error of Measurement (SEM) and Minimal Detectable Change (Weir, 2005). An explorative comparison of sensor-based data with clinical data and quantitative imaging parameters will be conducted by common descriptive and inferential statistics, (non-) parametric statistics and logistic regression.

Discussion

This study will include 1000 geriatric patients, and this number may be increased in the course of the ongoing recruitment due to the exploratory, prospective, modular, and observational study design. We are not aware of a comparable endeavor in this research field. Due to the large number of participants, data obtained from this study will also allow sub-analyses focusing on, e.g., presence and absence of geriatric and non-geriatric conditions and comparisons across centers.

We will collect data covering many aspects of body structure and function, but will –in line with the CGA- go beyond this usually well-assessed ICF component and collect data of all five components of this WHO-designed and most widely accepted model of health and dysfunction (World Health Organisation, 2001). The main asset of this study is in our view that as many as possible parameters of disability and symptomatology, from biofluid and neuroimaging, over quantitative geriatric syndrome assessment and parameters of autonomic and mobility dysfunctions will be collected on a quantitative level.

This study will also evaluate treatment response. The broad range of parameters will allow the use of novel analysis approaches and testing of hypotheses that can serve as an ideal starting point for the initiation of hypothesis-driven studies in the field of geriatrics through repeated assessment at the beginning and the end of multidisciplinary geriatric care programs. The programs will be comparable in the majority of participants and will encompass individual allied health training of at least 20 sessions, and re-evaluation and adaptation of medication (in the frame of, e.g., the *early rehabilitation in geriatric medicine* concept as applied in Germany (Kolb et al., 2014; Swoboda, W.; Sieber, 2010)). This approach will allow the definition of effective versus non-effective response-to-treatment parameters as well as the definition of predictive parameters for defined treatment approaches. This aspect is relevant especially at times when value-based healthcare (Elf et al., 2017; Porter, 2009), precision medicine (Mirnezami et al., 2012) and shared decision making (Barry & Edgman-Levitan, 2012) become increasingly important.

Moreover, we will evaluate test-retest reliability and minimal clinically relevant change through an additional T0 assessment. This approach is relevant in the light of the large number of assessments and inclusion of novel parameters in this study, to provide first evidence for the clinical meaningfulness of these parameters but also to provide information about the extent of noise that these parameters have during repeated assessments.

We will also use modern technology for the assessment of movement deficits, including but not limited to gait, balance, transfers, sleep and mobility. We will only apply algorithms that are validated for these populations for the extraction and appraisal of movement episodes and mobility patterns (e.g., (Del Din et al., 2016; Pham, Elshehabi, Haertner, Del Din, et al., 2017; Pham, Elshehabi, Haertner, Heger, et al., 2017; Ramsperger et al., 2016)). It is expected that yet unknown symptoms will be detected that are not visible with the usual “clinical eye” (Maetzler, Klucken, et al., 2016). We will evaluate our participants not only in the hospitals but will collect daily-life data during a 24/7 assessment before and after the inpatient stay in a subgroup. This approach will give us access to an entirely new field of research, i.e. mobility, movement, and behavioral aspects in the natural environment of the participants. These measures will provide complementary aspects to the supervised assessments in the clinic, where measures mainly reflect functional capacity (“How well can you perform?”), as parameters collected in the usual environment rather reflect functional activity (“How do you regularly perform?”) [4,55]. We have recently learned that “identical” behaviors and movements can substantially differ depending on whether they are collected in the clinical or the home environment (Haertner et al., 2018). The home-based dataset will also allow evaluation of fluctuation in performance.

Limitations

This study’s limitations include: firstly, the cohort includes old and frail people, and the assessment is somewhat exhaustive. Thus, it is possible that some participants lose motivation during the first assessment or between the first and second assessment. We will therefore split the respective assessments into parts and will allow adequate breaks (e.g. over lunch). This is possible as participants are investigated during an inpatient stay, and assessment times can be flexibly organized. Second, although the treatment is highly standardized at least in the German centers, this treatment is not comparable to standardized treatments as they are typically performed in clinical trials. Still, we feel that our approach is of value as this treatment reflects the “real life situation” in the participating centers and the high number of participants will most probably allow analyses in similarly treated subgroups. Third, the home assessment requires some technical understanding, which may not always be given in all participants. We will address this issue by asking spouses and other related people to help with the charging of the sensors, and by providing telephone contact in case technical issues occur. Fourth, use of novel technology always includes the risk of technical problems and potential data loss. We are confident that this is a little risk as we have long-lasting experience with the companies providing the sensors and constant communication and support is ensured by the manufacturers. Finally, our multi-center design requires an intense and regular interaction between respective principle investigators and study personnel, and highly standardized protocols. We address these aspects by providing all relevant documents in English, by performing personal visits at all cites to personally train the assessments and to solve any upcoming issues, and by regularly and randomly performed internal quality checks of the data.

This exploratory study investigates a large sample of geriatric patients. It uses a comprehensive, mainly quantitative and novel technology-oriented assessment protocol that is performed in the clinic and at home and thus goes beyond the already established CGA. This study design will allow evaluation of treatment effects. Taken together, this study has the potential to enhance our understanding of geriatric deficits and the intra-individual interaction of neurological age-related diseases. The dataset will also allow drawing new conclusions and hypotheses about disease and treatment effects in this vulnerable population.

5 Does executive function influence walking in acutely hospitalized patients with advanced Parkinson's disease: a quantitative analysis

This chapter addresses the second research question of this dissertation stated in the introduction and highlights the relationship between EF and divided attention and walking performance and DTC while walking under ST and DT straight walking conditions in patients with advanced PD. The findings presented here result from the analysis of data from the sub-cohort of the ComOn study introduced in Chapter 4. The chapter has been formally adapted to the style of the dissertation for consistency. The content was published in Frontiers in Neurology as an original research article:

Geritz, J., Welzel, J., Hansen, C., Maetzler, C., Hobert, M. A., Elshehabi, M., Sobczak, A., Kudelka, J., Stiel, C., Hieke, J., Alpes, A., Bunzeck, N., & Maetzler, W. (2022). Does Executive Function Influence Walking in Acutely Hospitalized Patients With Advanced Parkinson's Disease: A Quantitative Analysis. Frontiers in Neurology, 13(852725), 1–15. https://doi.org/10.3389/fneur.2022.852725

Abstract

Introduction: It is well known that, in Parkinson's disease (PD), executive function (EF) and motor deficits lead to reduced walking performance. As previous studies investigated mainly patients during compensated phases of the disease, the aim of this study was to investigate the above associations in acutely hospitalized patients with PD.

Methods: Seventy-four acutely hospitalized patients with PD were assessed with the delta Trail Making Test (ΔTMT, TMT-B minus TMT-A) and the Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III). Walking performance was assessed with wearable sensors under single (ST; fast and normal pace) and dual task (DT; walking and checking boxes as motor secondary task, walking and subtracting serial 7s as cognitive secondary task) conditions over 20 meters. Multiple linear regression and Bayes factor BF_{10} were performed for each walking parameter and their dual task costs while walking (DTC) as dependent variables, and also included ΔTMT, MDS-UPDRS III, age and gender.

Results: Under ST, significant negative effects of the use of a walking aid and MDS-UPDRS III on gait speed and for fast pace on number of steps were observed. Moreover, depending on the pace, the use of a walking aid, age and gender affected step time variability. Under walking-cognitive DT, a resolved variance of 23% was observed in the overall model for step time variability DTC, driven mainly by age ($\beta=0.26$, $p=0.09$). Under DT, no other significant effects could be observed. ΔTMT showed no significant associations with any of the walking conditions.

Discussion: The results of this study suggest that in acutely hospitalized patients with PD reduced walking performance is mainly explained by use of a walking aid, motor symptoms, age and gender, and EF deficits surprisingly do not seem to play a significant role. However, these patients with PD should avoid walking-cognitive DT situations, as under this condition especially step time variability -a parameter associated with risk of falling in PD- worsens.

Keywords: Parkinson’s disease, straight walking, wearable sensors, executive functions, dual task, aged

Introduction

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder characterized by specific motor symptoms, such as bradykinesia and rigidity, and several non-motor symptoms, such as cognitive impairment and depression (Chaudhuri et al., 2006; Moustafa, Chakravarthy, Phillips, Gupta, et al., 2016). The progression of these symptoms and the associated limitations – particularly deteriorated walking performance - can lead to reduced quality of life (Qin et al., 2009). Due to this progressive aggravation of both motor and non-motor symptoms accompanied with effects of age as well as history or risk of falls, patients with advanced PD may increasingly require inpatient medical treatment (Fasano et al., 2017). However, these vulnerable patients are often not included in studies (J. M. Domingos et al., 2015; Mirelman et al., 2019). Furthermore, the association between specific non-motor symptoms and walking performance in patients with PD is not fully understood. Hence, an important open question is how motor and specific non-motor symptoms are related in the advanced stage of the disease in acutely hospitalized patients.

Typical motor symptoms can be accompanied by reduced walking performance, i.e. decreased gait speed, increased asymmetry and impaired rhythmicity and stability of gait (Mirelman et al., 2019). These symptoms lead to daily life-relevant limitations especially concerning mobility. As motor impairments progress, the risk of falls increases and patients become more dependent (for example, being in need of using walking aids). Both factors are associated with reduced quality of life (Bettecken et al., 2017; Fasano et al., 2017). To detect motor impairment in PD, wearable devices have been increasingly used in recent years as a flexible and cost-effective option in clinical settings (Bernhard et al., 2018; Bettecken et al., 2017; Del Din et al., 2019; Maetzler, Klucken, et al., 2016).

Among the non-motor symptoms in patients with PD, cognitive impairment, namely deficits in cognitive flexibility, set shifting and working memory (so-called fronto-striatal associated executive functions, EF), as well as in divided attention and keeping attentional focus play an important role (reviewed in (Dirnberger & Jahanshahi, 2013; Owen, 2004)). Even in the early stages of the disease and also in patients with PD without dementia, deficits in internal attentional control, cognitive flexibility, and planning actions have been reported (Koerts et al., 2009). Cognitive impairment and dementia in PD are associated with an increased risk of falls (Lauretani et al., 2016) and reduced quality of life (J. M. Domingos et al., 2015).

In everyday situations, walking is not merely a simple task, but rather requires the ability to manage multiple tasks simultaneously. This complex process requires a high degree of cognitive flexibility and integration of movement sequences and external stimuli, depending on environmental demands. In light of this, recent studies have investigated a possible link between limited walking performance and deficits in EF and attention both in older healthy individuals and patients with PD (Hillel et al., 2019; Hobert et al., 2017; Johansson et al., 2021; Lord et al., 2010; Maidan et al., 2016; Mirelman et al., 2018; Nieuwhof et al., 2017; Rochester et al., 2008, 2014; Salazar et al., 2017; Salkovic et al., 2017; Smulders et al., 2013; Stegemöller et al., 2014; Wild et al., 2013; Yogev-Seligmann et al., 2008; Yogev et al., 2005). These studies typically examined walking under both single task (ST) and dual task (DT) conditions, with different methods, paradigms and outcome parameters. A meta-analysis showed negative associations between age and cognitive status, as well as age and gait speed under DT in healthy older adults (Al-Yahya et al., 2011). In addition, in a longitudinal study over six years with healthy older adults (n=583, aged 65 and older), reduced cognitive flexibility (measured by the Trail Making Test, TMT (Reitan, R. M., & Wolfson, 1985)) was identified as a predictor for increasing mobility impairment and mortality (Vazzana et al., 2010). Another study found associations between poor TMT performance and changes in DT prioritization during walking at the expense of gait speed in older adults (Hobert et al., 2011). Overall, the existing evidence suggests that healthy older adults under DT strategically adapt to increased demands, e.g., by reducing gait speed or requiring increased reaction time during cognitive tasks, but do not exhibit extensive changes in walking performance (Yogev-Seligmann et al., 2008). In contrast, patients with PD appear to need higher levels of attention, executive control, and cognitive flexibility for actions such as walking. During the course of the disease, coping with increasing task complexity becomes more difficult for patients with PD (Dirnberger & Jahanshahi, 2013; Koerts et al., 2011; Plotnik et al., 2011; Rochester et al., 2004; Yogev-Seligmann et al., 2008). Comparative studies have shown that EF performance and associated walking impairment (primarily reduced gait speed and increased gait variability) is worse in patients with PD than in healthy controls, especially under DT conditions (Salazar et al., 2017; Yogev et al., 2005). In addition, studies in patients with PD have shown that spatio-temporal walking parameters, such as gait speed and stride length, gait variability, as well as postural control may be differently affected by impaired EF (Lord et al., 2011; Plotnik et al., 2011; Rochester et al., 2008; Stegemöller et al., 2014; Varalta et al., 2015). These findings suggest that deficits in EF and divided attention in PD are associated with impaired walking performance and altered task prioritization as cognitive demands increase. The complexity of the (gait) situation is particularly evident with regard to higher dual task costs (DTC) while walking (Plotnik et al., 2011; Rochester et al., 2008; Warmerdam et al., 2021).

However, the studies mentioned above could not identify EF and divided attention as a relevant predictor for specific walking parameters and mainly focused on single walking parameters or used group comparisons or simple correlations (Plotnik et al., 2011; Rochester et al., 2008; Stegemöller et al., 2014). Cognitive impairment, advanced disease stage, severe motor symptoms and needing a walking aid were exclusion criteria (either combined or single) in most of the studies. Also, acutely hospitalized patients were often not included. However, these aspects are highly relevant for treatment indications, risks as well as quality of life and patients' ability to cope with everyday life (Bettecken et al., 2017; J. M. Domingos et al., 2015; Mirelman et al., 2019). Thus, it remains unclear to what extent EF and divided attention have an influence on specific aspects of gait for patients with advanced PD in acute need of inpatient care. Furthermore, many studies are conducted under lab conditions, which means that the results are not necessarily transferable to clinical diagnostics or home environment (Warmerdam et al., 2020). Further investigation is important focusing on the understanding and clinical considerations that follow from these findings. Therefore, the aim of this study was to investigate the association between EF, divided attention and walking performance under ST and DT conditions in acutely hospitalized patients with advanced PD. We also included patients with severe symptoms (e.g. cognitive impairment and reduced walking performance). In doing so, different requirements under ST as well as under DT with both congruent (i.e., predominantly motor) and divergent (i.e., cognitive) additional demands during straight walking were investigated. Walking performance was assessed using spatio-temporal walking parameters in order to identify those associated with EF and divided attention in PD. Outcomes were measured with assessments integrated into the clinical routine on a neurogeriatric ward.

Methods

This study is part of the exploratory, observational multi-center study "COgnitive and Motor interaction in the Older populatioN" (ComOn). In the ComOn study, participants aged 50 years and older with at least one chronic disease are included. The main aim of the study is to gain better understanding of the multifaceted symptoms of this cohort and their complex interactions using quantitative and digital parameters. Therefore, a comprehensive examination protocol to assess cognitive, motor, behavioral and other clinical parameters was conducted. For the full examination protocol, we refer to publication (Geritz et al., 2020). The focus of these analyses is on the influence of EF and divided attention on straight walking performance in patients with advanced PD.

The data presented here were collected between October 2017 and November 2020 at the Department of Neurology, University Hospital Schleswig-Holstein Campus Kiel (Germany). Informed oral and written consent was obtained from all participants and, if necessary, their legal representative or assistance (e.g. due to cognitive impairment or dementia). The study was reviewed by the ethics committee of the Medical Faculty of the University of Kiel (Ethics application number D 427/17).

Participants

The study included geriatric inpatients diagnosed with PD (n=119) according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria (Gibb & Lees, 1988) and the Movement Disorder Society (MDS) clinical diagnostic criteria for PD (Marsili et al., 2018; Postuma et al., 2015). All participants fulfilled the inclusion criteria of the ComOn study protocol (Geritz et al., 2020). Briefly summarized, participants were included if they were 50 years or older, able to walk at least three meters independently with or without walking aid, and had sufficient hearing and visual acuity as well as sufficient speech comprehension as judged by the investigator. Main reasons for inpatient admission were deterioration in mobility and walking ability or general condition, recent falls or medication adjustment due to reduced drug effects. Patients with severe motor symptoms measured by the MDS-revised motor part of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III, (Goetz et al., 2008)) as well as patients with previously described mild cognitive impairment (MCI) or mild to moderate dementia were included (see section 2.3.1). Patients were excluded if they scored <5 points in the Montreal Cognitive Assessment (MoCA, (Nasreddine et al., 2005)) as a cut-off value for severe dementia in PD (Lawton et al., 2016). Patients with more than two falls in the past week were excluded due to safety reasons in the motor assessment.

Procedure

Assessments took place in a clinical setting within the first two days after admission to the neurogeriatric ward. On the day of admission, a detailed medical history was conducted and participants were given self-reporting questionnaires on various behavioral and clinical aspects. On the first day of treatment, a detailed neuropsychological examination was carried out, followed by a comprehensive movement analysis using inertial measurement units (IMUs, see 2.3.4). The duration of the two latter assessments was about 60 to 90 minutes each. Between the assessments, participants had a break of at least 60 minutes. The movement analysis was carried out on the ward corridor (>3 meters broad, well-lit) in a designated area for this purpose. For this study, the data for straight walking over 20 meters in ST and DT conditions were considered. In order to examine the patients in their best mobility condition possible, the medication was to be administered with a suitable time interval prior to the measurement after consulting with the medical staff.

Measures

Demographical and clinical parameters

Age, gender, years of education (total number of years in school plus standard time period for any completed professional education (Thomann et al., 2018)) and current disabilities (e.g. care level, frailty, vision and hearing impairments and urinary incontinence) were collected via interview using geriatric screening tools which are described in detail in the ComOn study protocol (Bellmann et al., 2013; Geritz et al., 2020; Lachs et al., 1990). From the medical records, PD duration and aspects of previously described cognitive deficits were extracted. In addition, the MoCA was performed to assess global cognitive performance (Nasreddine et al., 2005). Depressive symptoms were assessed using the screening questionnaire *Depression im Alter* Scale (DIA-S,(Heidenblut & Zank, 2010)). Based on the medication schedule at admission, the levodopa equivalent daily dose (LEDD (Tomlinson et al., 2010)) was determined.

The MDS-UPDRS III (Goetz et al., 2008) was used to evaluate severity of motor symptoms. We scored values below 30 as mild, between 30 and 60 as moderate, and values above 60 as severe PD motor stage (adapted from (Martínez-Martín et al., 2015)). Moreover, the modified Hoehn & Yahr Scale (Goetz et al., 2008) was assessed. Furthermore, the occurrence of dyskinesia (according to the MDS-UPDRS definition involuntary, random movements) during the examination as well as their impact on the rating of the MDS-UPDRS III, and occurrence of freezing of gait (FOG) were recorded using the three related items of the MDS-UPDRS III (Goetz et al., 2007, 2014).

Executive functions and divided attention

EF and divided attention were measured by the Trail Making Test (Reitan, R. M., & Wolfson, 1985). The TMT is a widely used neuropsychological paper-pencil test consisting of two parts, TMT A and TMT B (Strauss, E., Sherman, E. & Spreen, 2006). Both tasks capture components of perceptual tracking as well as processing speed. The TMT B also captures more complex executive functions such as alternating sequencing and set shifting (as part of cognitive flexibility) and divided attention (Lamberty & Axelrod, 2012; Lezak et al., 2012; Strauss, E., Sherman, E. & Spreen, 2006). In TMT A, circles with the numbers "1" to "25" must be connected as quickly as possible in ascending order. In TMT B, circles with the numbers "1" to "13" and the letters "A" to "L" must be connected alternately, again as quickly as possible. For both tasks, a test run with eight items was carried out in advance. The required time to complete each task was measured in seconds. Errors were corrected in a standardized way while time continued to run (Strauss, E., Sherman, E. & Spreen, 2006). In this paper the difference index ΔTMT (TMT B minus TMT A) was calculated. Several authors recommend using this derived score as it corrects for processing speed and therefore provides a better index of EF (Axelrod et al., 2000; Hester et al., 2005; Hobert et al., 2011; Lamberty et al., 1994; Lamberty & Axelrod, 2012; Vazzana et al., 2010).

Straight walking performance

Walking conditions

For the gait analysis, the participants were asked to walk a marked straight distance of 20 meters for four times. A different condition was set for each walk with increasing motor difficulty. During all four walks participants wore an IMU system. It was documented whether patients completed the task with or without a walking aid. In condition one, *ST normal pace*, the distance was to be covered at a self-selected comfortable gait speed. In condition two, *ST fast pace*, participants were asked to walk as fast as possible without running. In condition three, *DT walking-cognitive*, participants were asked to subtract seven consecutively from a given three-digit number as fast as possible while walking at fast pace. In condition four, *DT walking-motor*, predetermined boxes on a sheet of paper were to be crossed as quickly as possible with a pen while walking at fast pace. Condition four was only possible for patients without walking aid. Walking conditions were performed in the following order if patients had the capacity: ST fast pace, ST normal pace, DT walking-motor, DT walking-cognitive.

IMU system

Velcro straps were used to attach the RehaGait® IMU (Hasomed, Magdeburg, Germany (Byrnes et al., 2018)) to the patient's lower back at the level of the fifth lumbar vertebra before the gait assessment. The IMU is CE-certified and includes a triaxial accelerometer (±16 g) and a triaxial gyroscope (±2000/s). Data was collected at a sampling frequency of 100 Hertz and transmitted during the measurement via Bluetooth to a tablet with the RehaGait® application modified for the ComOn study in cooperation with the manufacturer.

Extraction and analysis of walking parameters

Walking performance data were analyzed by an algorithm that has been validated for step detection in PD (Pham, Elshehabi, Haertner, Del Din, et al., 2017). From the raw data, the spatio-temporal parameters number of steps and gait speed (m/s), double limb support time (DLS, s), mean step time asymmetry (ASYM, s; difference between mean step time difference between both feet) and step time variability (STV, s; square rooted sum of variance of step time for each foot divided by two) were calculated. A linear correction of DLS, ASYM and STV to normalize for gait speed (to 1m/s) was applied, as recommended in previous biomechanical studies on sensor-based walking parameters (Warmerdam et al., 2021).

For the two DT conditions, the DTC for walking ($DTC_{Walking}$) were calculated for each of the parameters according to the formula $DTC = (ST - DT)/ST \times 100$ (Fino et al., 2018), with positive DTC indicating deterioration of gait performance under DT compared to ST (Rochester et al., 2014).

Statistics

To address the question to which extent EF and divided attention are associated with quantitative walking parameters in PD, both multiple linear regression models and Bayesian regression models were calculated in all four walking conditions for each of the five walking parameters (number of steps, gait speed, DLS, ASYM and STV) as well as their $DTC_{Walking}$ in both DT conditions as outcome variables. Each model included ΔTMT as predictor and MDS-UPDRS III, use of a walking aid (except for DT walking-motor), age and gender as covariates (using the forced entry method). Outliers, defined as ±3SD, were excluded. In detail, ΔTMT scores of two patients and $DTC_{Walking}$ parameters of two patients (one in each of the two DT walking conditions) were excluded (Tab. 1). Model assumptions multicollinearity (with

Variance Inflation Factor and Tolerance), homoscedasticity, linearity and normality of residuals (with Q-Q-Plots) and independence of residuals (with Durbin-Watson) where checked (Goss-Sampson, 2018). For the multiple linear regression models, the goodness of fit of each overall model using the R^2_{adj} (adjusted for sample size n and multiple predictors using McNemar (Goss-Sampson, 2018)) and the standardized regression weights β were determined and tested for significance (level of significance $\alpha<0.05$). Post hoc, Spearman's rho (ρ) correlation coefficient was calculated. For each Bayesian regression model, the Bayes factor BF_{10}, as a measure for strength of evidence in favor of one of two competing scientific theories (here, influence vs. no influence of EF and divided attention on walking performance) provided by the data (Kass & Raftery, 1995; Wagenmakers et al., 2016), was estimated using the Bayesian Information Criterion (BIC, (Glen, 2018). BF_{10} was classified according to Lee and Wagenmakers (2013) with BF_{10} above ten (for H1, here: EF are associated with walking parameters) respectively below 0.03 (for H0, here: EF are not associated with walking parameters) as "strong evidence", BF_{10} between three and ten (H1) respectively 0.10 and 0.03 (H0) as "moderate evidence", BF_{10} between one and three (H1) respectively 0.33 and 0.10 as "anecdotal evidence" (for H0), and $BF_{10}=1$ as no evidence (M. D. Lee & Wagenmakers, 2013). Differences between the four walking conditions were calculated for ΔTMT, MDS-UPDRS III, age (using Kruskal-Wallis H test) and gender (using χ^2 test, (Goss-Sampson, 2018)). As an additional explorative analysis, differences in ΔTMT, MDS-UPDRS III, age, and gender between patients with and without walking aid were calculated for the ST normal pace, ST fast pace, and DT walking-cognitive conditions (using Mann-Whitney U test for continuous variables and fisher's exact test for gender as dichotomous (Goss-Sampson, 2018)).

Data were preprocessed using MATLAB (version 2020b, (*MATLAB*, 2020)) and Python (version 3.9.1., (Van Rossum G & Drake FL., 2009)) Statistical analysis were conducted using JASP (version 0.14.1, (JASP Team, 2020)).

Results

Descriptive characteristics

Out of n=119 patients with PD who participated in the ComOn study and performed the TMT, a total of n=74 participants with complete IMU-based data were included for this analysis (n=45 did not perform the 20m walking tasks due to lack of capacity or motivation). In this overall group, the mean age was 72 years (SD=8), 34% (n=25) of participants were female, and the mean period of education was 10 years (SD=2). Mean disease duration was 10 years (SD=7), median Hoehn & Yahr stage was 3 (IQR=1), mean MDS-UPDRS III was 30 points (SD=15), and mean LEDD was 748mg (SD=371). According to medical records cognitive impairment was previously reported in 17.7% of the cohort, of which 8.8% were diagnosed with dementia. The mean MoCA score was 23 points (SD= 3.2) and thus was below the diagnostic cut-off for MCI in PD (26 points, (Dalrymple-Alford et al., 2010)). The mean score of the DIA-S was 3 points (SD=2.3) and thus below the cut-off for suspected depressive mood (≥4 points, (Heidenblut & Zank, 2010)), with 23% of the patients showing depressive mood.

Complete data on IMU-based walking measurement were available from n=74 participants for ST normal pace, n=60 for ST fast pace, n=45 for DT walking-cognitive, and n=34 for DT walking-motor. The decrease in sample size is due to the fact that not all subjects were capable to participate in every condition which can be explained by the increasing demands per condition and the prioritized order of the tasks (e.g., due to reduced physical capacity not necessarily all subjects who passed the ST normal pace condition could also perform ST fast pace, etc.). In general, over all four walking conditions participants were comparable with respect to age (H=0.72 (3), p=0.87, Tab. 5.1), gender (χ^2=2.13 (3), p=0.55 Tab. 5.1), and ΔTMT performance (H=2.18 (3), p=0.54, Tab. 5.1). A walking aid was used by one quarter (DT walking-cognitive) to one third (ST normal pace) of the participants. Dyskinesia occurred during the measurement in 13% (DT walking-cognitive) to 21% (ST normal pace) and had an impact on the MDS-UPDRS III ratings in 0% (DT walking-motor) to 7% (ST normal pace). FOG occurred in 27% (DT walking-motor) to 42% (ST fast pace) of the participants during the MDS-UPDRS III examination. DT walking-motor was only feasible for participants who did not require a walking aid, as the checking boxes task while walking required the use of both arms. This group also had a lower MDS-UPDRS III score, but there was no significant difference between the walking conditions (H=3.84 (3), p=0.28). Table 5.1 provides descriptive characteristics across all four walking conditions

Concerning descriptive aspects of the walking parameters, the study participants used slightly fewer steps under ST conditions than under DT conditions. Under ST normal pace, the lowest values for mean DLS, mean ASYM, and mean STV were obtained. Under ST fast pace, participants had the lowest mean number of steps, walked the fastest on average, and showed the highest mean STV. Under DT walking-cognitive, they walked the slowest and had the highest mean DLS and mean ASYM (Figure 5.1, Table 5.1).

Under DT walking-cognitive condition higher DTC were found for number of steps, gait speed, DLS and STV. For ASYM, DTC were approximately zero. The highest DTC were observed in the STV (46.9%). Under DT walking- motor condition higher DTC were found in the parameters number of steps and gait speed, respectively. Again, DLS did not show relevant DTC. Both ASYM (by about 40%) and STV (by about 5%) showed negative DTC (Table 5.1).

In the exploratory group comparison, patients who required a walking aid had significantly higher scores in the MDS-UPDRS III than patients without walking aid in all three walking conditions (ST normal pace: W=391, p=0.02, ST fast pace: W=244, p=0. 005, DT walking-cognitive: W=77, p=0.004) as well as lower gait speed (ST normal pace: W=901, p=0.001, ST fast pace: W=534.5, p=0.006, DT walking-cognitive: W=278, p=0.02) and STV (St normal pace: W=353, p=0.004, ST fast pace: W=575, p<0.001, DT walking-cognitive: W=297, p=0.02). Under DT walking-cognitive condition, patients with walking aid showed higher $\text{DTC}_{\text{Walking}}$ at ASYM (median=78.1 vs. median= 7.44, W=69, p=0.003) and STV (median=108 vs. median=-3.88, W=69, p=0.003) than patients without walking aid. Under ST fast pace condition, patients with walking aid were older (median=79 vs. median= 74, W=215, p=0.01) and took more steps (median=42 vs. median= -36, W=193.5, p=0.005). There were no significant differences regarding ΔTMT, DLS and ASYM and in gender distribution between these groups. Suppl.-Table 5.1 provides detailed information.

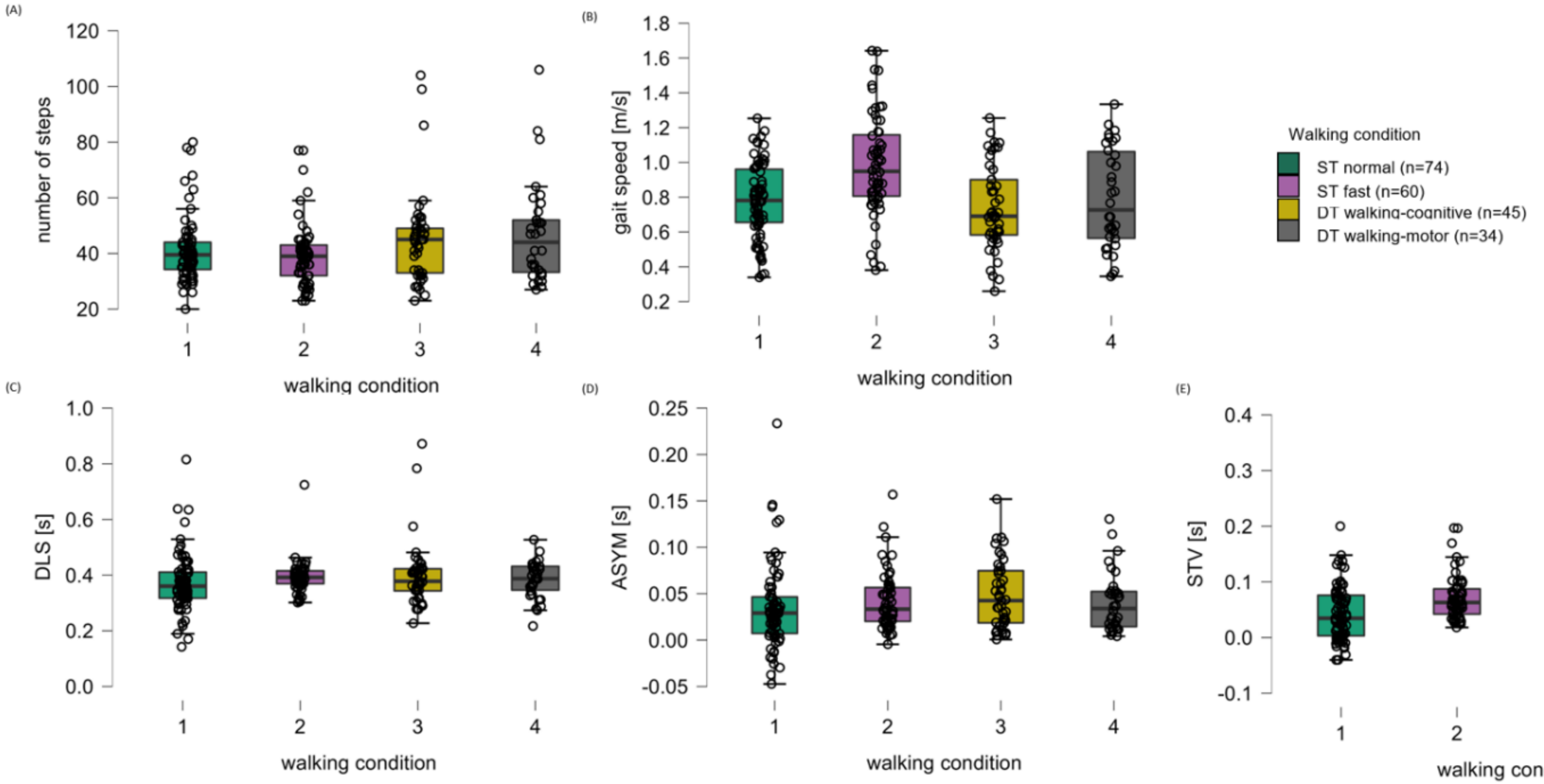

Figure 5.1: Box plots for all walking parameters over all walking conditions. For the five walking parameters, (A) number of steps, (B) gait speed (meters per second), (C) double limb support (DLS, seconds), (D) asymmetry (ASYM, seconds) and (E) step time variability (STV, seconds), the medians (thick black horizontal lines), the interquartile range (IQR, black-bordered boxes) as well as lower and upper whiskers (values within ±1.5xIQR), single subject data points (black circles) are given for walking conditions single task normal pace (green, 1), single task fast pace (violet, 2), the dual task walking-cognitive (yellow, 3) and the dual task walking-motor (grey, 4).

Table 5.1: Descriptive characteristics of demographic, clinical and walking parameters over all four walking conditions and of DTC$_{\text{Walking}}$ over both DT walking conditions.

demographic and clinical parameters	**ST normal pace**		**ST fast pace**		**DT walking-cognitive**		**DT walking-motor**	
	n	**M (SD) [min; max] {Median; IQR}**	**n**	**M (SD) [min; max] {Median; IQR}**	**n**	**M (SD) [min; max] {Median; IQR}**	**n**	**M (SD) [min; max] {Median; IQR}**
age [years]	74	72 (8.39) [48;87] {75; 12}	60	73 (8.78) [48;83] {77; 12}	45	72 (9.55) [48;83] {77; 12}	34	71 (10.0) [48;81] {76.5; 14}
female [n (%)]		25 (34)		17 (28)		12 (27)		7 (21)
education [years]		10 (1.88) [6;14]		10 (1.79) [6; 14]]		10 (1.89) [6;14]		10 (2.12) [6;14]
disease duration [years]		10 (6.85) [0;25]		10 (7.02) [0;25]		9 (6.48) [0;24]		8 (5.68) [0;20]
Hoehn & Yahr		{3; 1}		{3; 1}		{3; 1}		{3; 0}
LEDD [mg]		748 (370.7) [100;1811]		717 (368.5) [100;1811]		707 (389.8) [100;1811]		648 (373.9) [100;1811]
MoCA		23 (3.27) [15;29]		23 (3.36) [15;29]		24 (3.30) [17;29]		23 (3.57) [15;29]
DIA-S		3 (2.3) [0;9]		2 (2.35) [0;9]		2 (2.47) [0;9]		2 (2.55) [0;9]
ΔTMT [s]		129 (81.5) [16;399] {104; 116}		128 (81.5) [16;399] {104; 88}		111 (78.2) [16;399] {83; 55}		125 (79.3) [16;303] {83.5; 116}
MDS-UPDRS III		30 (14.8) [4;60] {28.5; 25}		30 (14.4) [4;60] {28; 23}		28 (14.9) [4;60] {26; 23}		24 (14.0) [4;60] {22; 18}
occurrence of dyskinesia [n (%)]		15 (21)		11 (18)		6 (13)		5 (15)
impact of dyskinesia [n (%)]		5 (7)		3 (5)		2 (4)		0 (0)
occurrence of FOG		29 (39)		25 (42)		15 (33)		9 (27)
walking aid [n (%)]		23 (31)		17 (28)		11 (24)		(0) 0
walking parameters								
number of steps	74	41.2 (11.7) [20;80]	60	39.2 (11.6) [23; 77]	45	45.1 (16.8) [23; 104]	34	46.5 (17.8) [27; 106]
gait speed		0.78 (0.21) [0.34;1.25]		0.98 (0.29) [0.38; 1.64]		0.74 (0.25) [0.26; 1.25]		0.76 (0.29) [0.29; 1.33]
DLS		0.37 (0.1) [0.14; 0.82]		0.39 (0.06) [0.3; 0.72]		0.4 (0.12) [0.23; 0.87]		0.38 (0.07) [0.22; 0.53]
ASYM		0.03 (0.05) [-0.05; 0.23]		0.04 (0.03) [-0.005; 0.16]		0.05 (0.04) [0.0006; 0.15]		0.04 (0.03) [0.004; 0.13]
STV		0.04 (0.05) [-0.04;0.2]		0.07 (0.04) [-0.02;0.2]		0.06 (0.05) [0.0001; 0.34]		0.06 (0.03) [0.02; 0.13]
DTC$_{\text{Walking}}$								
DTC$_{\text{Walking}}$ Number of Steps [%]					44	6.35 (20.6) [-84.0; 58.6]	33	13.4 (16.8) [-22.2; 43.2]
DTC$_{\text{Walking}}$ gait speed [%]						8.14 (25.5) [-97.2; 61.2]		9.55 (33.3) [-136; 63.1]
DTC$_{\text{Walking}}$ DLS [%]						4.22 (18.9) [-42.6; 54.7]		0.30 (13.8) [-30.9; 34.4]
DTC$_{\text{Walking}}$ ASYM [%]						-0.41 (161) [-620; 348]		-40.1 (165) [-515; 209]
DTC$_{\text{Walking}}$ STV [%]						46.9 (139) [-191; 589]		-5.11 (82.7) [-281; 129]

ASYM, asymmetry; DIA-S, *Depression im Alter* Scale, DLS, double limb support; DT, dual task; DTC$_{\text{Walking}}$, dual task costs for walking while doing a second task (in percentage, %); FOG, Freezing of gait; IQR, interquartile range; LEDD, levodopa equivalence daily dose (in milligram, mg); M, mean; max, maximum; MDS-UPDRS III, Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale; min, minimum; MoCA, Montreal Cognitive Assessment total score; n, sample size; s, seconds; SD, standard deviation; ST, single task; STV, step time variability; ΔTMT, delta of Trail Making Test (part B minus part A).

Regression analyses

Single task walking conditions

Under the ST normal pace condition, the overall multiple linear regression model with gait speed as outcome parameter was significant (p=0.002) with a coefficient of determination of R^2_{adj}=24%. Therefore, the overall model, including age, gender, MDS-UPDRS III, walking aid and ΔTMT significantly explains 24% of gait speed variance. The effect was mainly driven by the use of a walking aid (β=-0.35, p=0.004) with a moderately negative post hoc correlation (ρ=-0.43, p=0.0001, Figure 5.3(A)) and, to less extent, by the MDS-UPDRS III (β=-0.21, p=0.06) with a moderately negative post- hoc correlation (ρ=-0.32, p=0.005, Figure 5.3(A)). ΔTMT (β=0.02, p=0.89), age (β=-0.12, p=0.32) and gender (β=0.04, p=0.71) had no significant effect in the model. Also, the overall multiple regression model for STV was significant (p=0.04) with R²adj=16%. Here, the effect was again mainly driven by the use of a walking aid (β=-0.25, p=0.05) with a moderately negative post-hoc correlation (ρ=-0.34, p=0.003, Figure 5.3(B)) and, to less extent, by age (β=-0.12, p=0.09) with a low negative post-hoc correlation (ρ=-0.27, p=0.09, Figure 5.3(B)). Despite the parametric regression models being significant, the Bayesian regression suggested moderate evidence for H0 indicating no relevant association of ΔTMT with neither gait speed (BF_{10}=0.12) nor STV (BF_{10}=0.13). Similarly, the Bayesian regressions provided moderate evidence for H0 with regard to the number of steps (BF_{10}=0.13), DLS (BF_{10}=0.13), and anecdotal evidence for H0 for ASYM (BF_{10}=0.36). Therefore, individually significant effects were not further interpreted. Table 5.2 provides detailed information for the significant multiple regression models.

For ST fast pace, the multiple linear regression model for gait speed was significant (p=0.02, Tab. 5.2)), with a variance resolution of R^2_{adj}=22%, driven by the MDS-UPDRS III (β=-0.27, p=0.04) with a moderately negative post-hoc correlation (ρ=-0.31, p=0.02, Figure 5.3(A)) and a negative trend for use of a walking aid (β=-0.27, p=0.06) with a moderate negative post-hoc correlation (ρ=-0.36, p=0.004, Figure 5.3(A)). For STV, the overall model was also significant (p=0.008) with a variance resolution of R^2_{adj}=18%. Here, the model was driven by use of a walking aid (β=-0.30, p=0.03) with lower STV in patients without walking aid compared to patients with walking aid, with a moderately negative post-hoc correlation (ρ=-0.45, p=0.0003, Figure 5.3(B)), and a trend towards significance in the gender parameter with lower STV in women compared to men (β=-0.24, p=0.06), with a moderately negative post hoc correlation (ρ=-0.36, p=0.005, Figure 5.3(B)). For number of steps, the overall model was also significant (p=0.04, Table 5.2) with a variance resolution of R^2_{adj}=19%, with no significant effect of a single predictor but trends towards significance for the use of a walking aid (β=-0.24, p=0.09), with a moderately negative post-hoc correlation (ρ=-0.37, p=0.004, Figure 5.3(C)) and the MDS-UPDRS III (β=-0.25, p=0.06) with no significant post-hoc correlation (ρ=-0.23, p=0.08, Figure 5.3(C)). Similarly, in the Bayesian regressions, there was moderate evidence for H0 for gait speed (BF_{10}=0.14), STV (BF_{10}=0.13), number of steps (BF_{10}=0.14), and DLS. For DLS (BF_{10}=0.23) there was no significant effects for the overall model of the multiple linear regression analyses. There was no significant effect for ΔTMT in any of the models. However, there was a significant negative correlation with ASYM (ρ=-0.29, p=0.03, see Figure 5.2(A)), but Bayesian Regression again indicated anecdotal evidence for H0 for ASYM (BF_{10}=0.40, no relevant association with gait speed with the ΔTMT included in the model).

Dual task walking conditions

For both DT conditions, there were no significant effects in any of the multiple linear regression models. There was no significant effect for ΔTMT in any of the models (Figure 5.2(B)). In the Bayesian regressions, there was moderate evidence for H0 under DT walking-cognitive for all walking parameters (BF_{10} between 0.15 to 0.19). The same was true for the multiple linear regression and Bayesian regression models including ΔTMT, MDS-UPDRS III, age and gender but not use of a walking aid under DT walking-motor for number of steps (BF_{10}=0.19), gait speed (BF_{10}=0.19), and STV (BF_{10}=0.26). For ASYM (BF_{10}=0.37) and DBL (BF_{10}=0.36), however, there was again anecdotal evidence for H0.

Dual task costs

With the cognitive task added, the overall multiple linear regression model was significant for $DTC_{Walking}$ of STV (p=0.01, Table 5.2) with a resolved variance of R^2_{adj}=23%, driven by a trend for age (β=0.26, p=0.09) with a significant moderately positive post-hoc correlation (ρ=0.32, p=0.04, Figure 5.3(D)). There were no further significant results for $DTC_{Walking}$ of any other walking parameter.

With the motor task added, there were no significant results for $DTC_{Walking}$ in the multiple linear regression models. Under both DT walking conditions ΔTMT did not show a significant association with $DTC_{Walking}$ in any of the regression models nor significant correlations (Figure 5.2(D)). In the Bayesian regression, there was moderate evidence for H0 for all $DTC_{Walking}$ under DT walking-cognitive conditions (BF_{10} between 0.16 and 0.31) as well as for all $DTC_{Walking}$ of all walking parameters except ASYM (where there was again anecdotal evidence for H0, BF_{10}=0.83) under DT walking-motor condition (BF_{10} between 0.19 and 0.26).

Figure 5.2 illustrates the results using correlation plots for all walking parameters with the ΔTMT for both ST conditions (A) and DT conditions (B) as well as for all $DTC_{Walking}$ under both DT conditions ((C), (D)). As for the walking parameters, the flat slopes of the regression lines and the wide dispersion of the data points suggest a lack of linear associations between ΔTMT and any of the walking parameters in all four conditions or the $DTC_{Walking}$ in both DT conditions. Post hoc Spearman's ρ correlation coefficients are also reported. Other than the above mentioned low negative correlation with ASYM under ST fast pace, there were no significant correlations to be found between the ΔTMT and any of the other walking parameters nor their $DTC_{Walking}$.

Figure 5.3 illustrates the effects of the MDS-UPDRS III total score and use of a walking aid on gait speed (A) and on STV (B) in the multiple linear regression models using correlations plots for both ST conditions. The slope of the regression degrees and the condensed location of the data points indicate a linear relationship between gait speed and both predictors The trends of the MDS-UPDRS III total score and use of a walking aid on number of steps are simillarly shown (C) as well as the age trend on $DTC_{Walking}$ of STV under DT walking-cognitive condition (D).

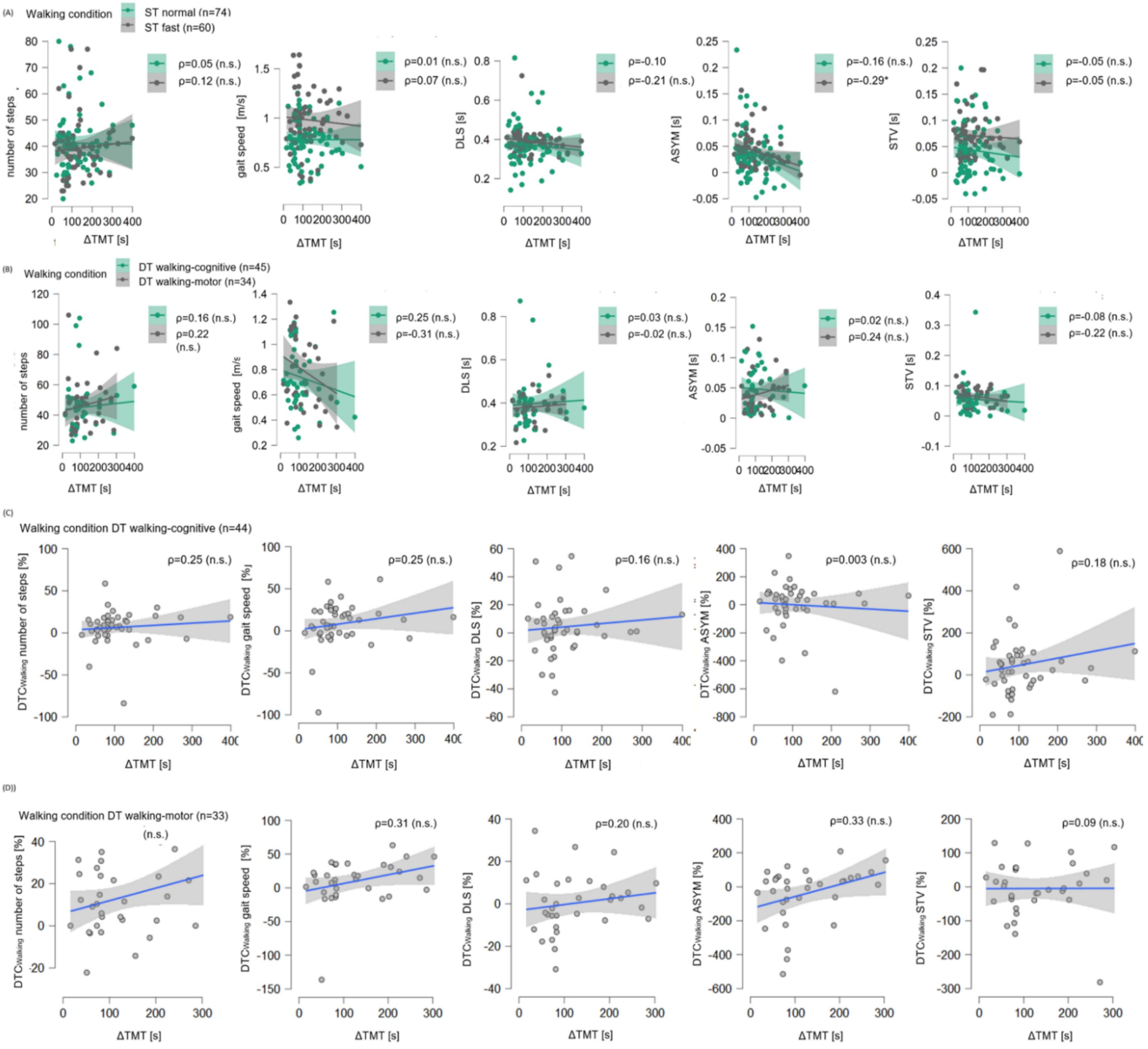

Figure 5.2: Correlation plots for ΔTMT with all walking parameters. In (A) for single task normal pace walking condition (ST Normal, green) and single task fast pace condition (ST Fast, gray) all five walking parameters number of steps, gait speed (in meter per seconds, m/s), double limb support (DLS), asymmetry (ASYM) and step time variability in seconds (STV, s) are shown on the ordinates, the delta of Trail Making Test (part B minus part A, ΔTMT) is on the abscissas. Sample size N is given as well as Spearman's rank correlation (ρ) between ΔTMT and each walking parameter, significant correlation coefficients are marked with * (level of significance p≤.05), non-significant ones are marked with (n.s). For each condition data points (dots) and regression lines with confidence intervals (lines with surrounding boxes) are shown. In (B) the same is shown for dual task motor-cognitive walking condition (DT motor-cognitive, green) and dual task motor-motor condition (DT motor-motor, gray). In (C) for DT motor-cognitive walking condition the dual task costs while walking in percentage ($DTC_{Walking}$, %) for all five walking parameters are shown on the ordinates, the delta of Trail Making Test (part B minus part A, ΔTMT) are on the abscissas as well as Spearman's rank correlation (ρ) between ΔTMT and each $DTC_{Walking}$). Data points (gray dots), regression lines with confidence intervals (blue lines with surrounding gray boxes) are shown for each parameter. The same is shown in (D) for the DT motor-motor walking condition.

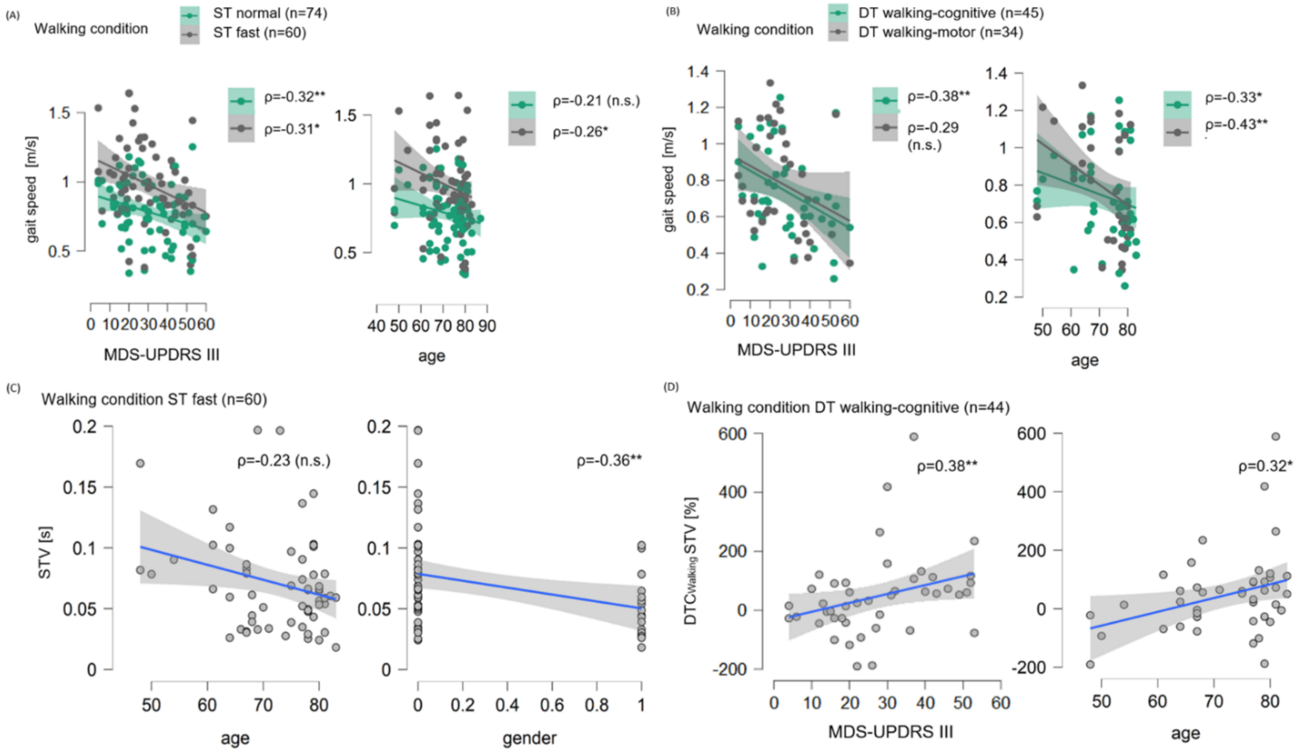

Figure 5.3: Correlation plots for significant multiple linear regression models for gait speed, STV, number of steps and $DTC_{Walking}$ for STV. In (A) for single task normal pace walking condition (ST Normal, green) and single task fast pace condition (ST Fast, gray) gait speed (in meter per seconds, m/s) is shown on the ordinates, the total score of the Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) and walking aid (0= "no walking aid", 1= "walking aid") are on the abscissas. Sample size n is given as well as Spearman's rank correlation (ρ) between gait speed and each parameter. For each condition data points (dots) and regression lines with confidence intervals (lines with surrounding boxes) are shown, significant correlation coefficients are marked with * (level of significance $p \leq .05$), ** (level of significance $p \leq .01$) and *** (level of significance $p \leq .001$), non-significant ones are marked with (n.s.). In (B) the same is shown for step time variability (STV in seconds, s) on the ordinates, and walking aid, gender (0= "male", 1= "female") and age on the abscissas. In (C) for ST fast pace number of steps is shown on the ordinates, MDS-UPDRS III and walking aid are on the abscissas. Here, data points (gray dots), regression lines with confidence intervals (blue lines with surrounding gray boxes) are given for each parameter. In (D) the same is shown for DT walking-cognitive walking condition for dual task costs while walking in percentage ($DTC_{Walking}$, %) of STV on the ordinate and age on the abscissa.

Table 5.2 Multiple linear regression models and Bayes factors for significant walking parameters and their $DTC_{Walking}$

	gait speed					STV					number of steps				
	ST normal pace (n=74)														
Walking parameters	$R^2_{adj.}$	F	BF_{10}	β	p	$R^2_{adj.}$	F	BF_{10}	β	p					
	0.24	4.31	0.12[a]		0.002**	0.16	2.55	0.13[a]		0.04*					
age				-0.12	0.32				-0.12	0.09					
gender				-0.04	0.71				-0.13	0.25					
MDS-UPDRS III				-0.21	0.06				0.04	0.73					
walking aid				-0.35	0.004**				-0.25	0.05*					
ΔTMT				0.02	0.89				-0.06	0.63					
	ST fast pace (n=60)														
	$R^2_{adj.}$	F	BF_{10}	β	p	$R^2_{adj.}$	F	BF_{10}	β	p	$R^2_{adj.}$	F	BF_{10}	β	p
	0.22	3.10	0.14[a]		0.02*	0.18	3.51	0.13[a]		0.008**	0.19	2.60	0.14[a]		0.04*
age				-0.17	0.21				-0.17	0. 21				0.17	0.22
gender				0.05	0.69				-0.24	0.06				-0.04	0.75
MDS-UPDRS III				-0.27	0.04*				0.09	0.45				0.25	0.06
walking aid				-0.27	0.06				-0.30	0.03*				0.24	0.09
ΔTMT				0.05	0.72				-0.02	0.87				-0.04	0.76
$DTC_{Walking-cognitive}$ [%] (n=44)	STV [%]														
	$R^2_{adj.}$	F	BF_{10}	β	p										
	0.23	3.50	0.18[a]		0.01**										
age				0.26	0.09										
gender				0.20	0.16										
MDS-UPDRS III				0.18	0.25										
walking aid				0.26	0.12										
ΔTMT				0.08	0.58										

[a], moderate evidence for H0; BF_{10}, Bayes factor as measure for strength of model evidence; β, standardized regression weights; DT, dual task; $DTC_{Walking}$, dual task costs for walking while doing a second task (in percentage, %); F, test statistic from ANOVA used for testing significance of the multiple regression models; MDS-UPDRS III, Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale; m/s, meter per seconds; n, sample size; $p \leq 0.05$*, significant on level of significance $\alpha \leq 0.05$; $p \leq 0.01$**, significant on level of significance $\alpha \leq 0.01$; $R^2_{adj.}$, multiple regression coefficient adjusted for sample size; s, seconds; ST, single task; STV, step time variability; ΔTMT, delta of Trail Making Test (part B minus part A).

Discussion

The aim of this study was to investigate to which extent EF and divided attention (measured by ΔTMT performance) are related to specific aspects of walking performance in acutely hospitalized participants with advanced PD under ST and DT walking conditions. To our best knowledge this is the first study to analyze several IMU-based spatio-temporal walking parameters and their DTC in this vulnerable cohort. Other studies either focused on single walking parameters (Rochester et al., 2008), excluded patients with advanced PD and cognitive impairment (Plotnik et al., 2011; Rochester et al., 2008; Salazar et al., 2017; Smulders et al., 2013; Stegemöller et al., 2014), used different statistical methods (e.g. only correlation analyses (Varalta et al., 2015)) or calculated group comparisons for ST and DT conditions (Johansson et al., 2021), which addresses different scientific questions. Our results suggest that especially severity of motor symptoms, use of a walking aid, age and gender have a relevant influence on walking performance in these patients. Concerning specific walking parameters, especially gait speed and STV were significantly influenced, mainly under ST conditions. Furthermore, with added cognitive task, increasing $DTC_{Walking}$ of STV were also significantly influenced. Surprisingly, EF and divided attentions do not seem to play a significant role.

Although some previous studies were able to reveal correlative and predictive relationships between EF and walking parameters, in this study, TMT performance was no significant predictor of specific spatio-temporal walking parameters, neither under ST nor under DT conditions. In one study that compared moderately affected patients with PD and healthy controls under ST and various DT walking conditions EF performance correlated significantly with gait variability (Yogev et al., 2005). The authors concluded that gait variability and rhythmicity represent automated processes in healthy older adults, but are more attention-demanding for patients with PD in the context of EF deficits in complex walking situations. In addition, studies have shown that different walking performance factors, such as spatio-temporal control, postural control, and variability, underlie different mechanisms that may also be differently affected by EF deficits in PD (Lord et al., 2011). For example, there is evidence that gait speed and stride length correlate positively with cognitive processing speed, whereas step width variability correlates positively with EF and attentional functions (as a calculated factor out of several cognitive tasks, (Stegemöller et al., 2014)). Also, patients with PD with poorer EF showed higher DTC, with EF accounting for 5% of the total DTC for gait speed and being identified as the best predictor of DTC (Rochester et al., 2008), along with motor symptoms. However, comparable with the results presented here, the authors could not uncover a significant relationship between EF, divided attention and gait speed in any of the walking conditions. EF were assessed with a different paradigm than the TMT and the walking distance was shorter, which would explain the different results in our study. In another study of advanced patients with PD (suffering from motor fluctuations) using comparable walking conditions and secondary tasks to this study, EF performance (measured by ΔTMT) was identified as a relevant predictor of DTC of gait speed (Plotnik et al., 2011). However, there were also differences in the methodology and characteristics of the subjects, which would explain the different results in our study. The walking distance was also four times longer than in our study and DTC were calculated differently. Furthermore, participants were on average eight years younger than the participants reported here, showed less severe motor symptoms (mean MDS-UPDRS III total score was 11 points lower), did not use a walking aid and did not suffer from clinically relevant cognitive impairment. Our results match with findings of another study on patients with advanced PD without cognitive impairment (Varalta et al., 2015). The duration of a three meter Timed-Up and Go Test (TUG) and EF (also measured by the TMT) correlated moderately under both ST and DT, but TMT performance was not a significant predictor. This and our findings suggest that performance in EF and divided attention tasks may not necessarily be linked linearly to common spatio-temporal walking parameters, such as gait speed on these patients. Rather, the severity of PD-specific motor symptoms seems indeed to inflict the walking performance in this and other PD cohorts. Especially under ST, the increase in motor symptoms explains a decrease in spatio-temporal walking parameters, e.g. gait speed, which is also consistent with previous studies (Rochester et al., 2008; Welzel et al., 2021). Moreover, our results suggest that patients with a walking aid are more affected by the underlying disease. Hence, being in need of a walking aid, which can be seen as an indicator of vulnerability, is another relevant factor with regard to a better understanding of deficits in walking performance in patients with advanced PD. Therefore, these factors should be prioritized regarding the diagnostics and treatment of walking performance deficits in an acute neurogeriatric setting.

Nevertheless, our results also provide evidence that cognitive aspects should not be disregarded in this vulnerable cohort. This may be particularly relevant for patients with dementia. Consistent with the literature, the results shown here indicate that patients with advanced PD show partly high costs in spatio-temporal walking parameters in situations where an additional demand is placed on them (Plotnik et al., 2011; Rochester et al., 2008)). Depending on the secondary task type (convergent vs. divergent, i.e. walking-cognitive respectively walking-motor) and motor difficulty, the costs vary (Plotnik et al., 2011). In the study presented here, DTC are most pronounced in STV. Patients in both divergent (walking-cognitive) and convergent (walking-motor) DT conditions exhibited increased $\mathrm{DTC}_{\mathrm{Walking}}$ for number of steps and gait speed, but not necessarily for DLS, STV and ASYM. These findings fit with a previous study showing that during walking under DT, patients with PD exhibited reduced gait speed and stride frequency compared to healthy controls (Salazar et al., 2017). Interestingly, for the number of steps and gait speed, $\mathrm{DTC}_{\mathrm{Walking}}$ tend to be higher in the convergent condition. This suggests that accomplishing another motor task while walking might require a higher level of brain capacity in similar areas and thus be more demanding on speed than an additional divergent task. In contrast to that, the highest $DTC_{Walking}$ were found for STV (47%) in the divergent condition. For $DTC_{Walking}$ of STV, the overall model explained about 23% of the variance. This suggests that in this cohort step time variability decreases when older patients with advanced PD are demanded to split attention between walking and a demanding cognitive task. This is also in line with a previous study (Yogev et al., 2005), in which it was detected that gait variability was impaired under DT only in the PD group. Together, this suggests that gait variability needs to be brought into clinical focus as a diagnostic parameter, especially when assessing the ability to cope with more complex walking situations. This is particularly relevant given that increased STV is associated with falls in patients with PD (Del Din et al., 2019; Fasano et al., 2017). Therefore, these patients should avoid those situations. This also can result in possible new implications for multimodal therapeutic interventions with regard to the trainability of STV under DT walking-cognitive condition. Interestingly, ASYM proved to be 40% better under DT than under ST in the presence of an additional convergent (i.e., predominantly motor) task. A possible explanation could lie in the specific execution of the motor task using a clipboard. The carrying of the clipboard and the demanded visual focus on the clipboard while checking boxes during walking could contribute to the compensation in the asymmetric walking performance. In addition, checking boxes itself, as an external rhythm generator, could support step time symmetry. However, this requires further investigation of the underlying pathophysiological mechanisms. Nonetheless, if this is true, it might be relevant with regard to clinical diagnostics as well as design of multimodal interventions, where this specific kind of additional task could be promising in training of symmetrical walking. In addition, for the DT walking-motor condition, only patients without walking aid could be considered by definition. This makes comparability with the other three walking conditions (which included also patients with walking aids) difficult. Future studies should further focus on this aspect, using other secondary motor tasks that can also be performed with a walking aid. However, we believe that our study provides new insight regarding important factors influencing walking performance in acutely hospitalized patients with advanced PD. As so far there has been a lack of knowledge regarding this cohort that deserves special attention due to its vulnerability, our results contribute to the optimization of diagnostics and treatment in the neurogeriatric setting.

Limitations

First, an influence of acute factors (e.g., infections, worsening of PD or other symptoms, and recent fall events) on the overall condition of the patients cannot be completely ignored. However, we argue that, as this group of patients requires special attention in treatment due to their health condition, a specific investigation of this cohort is justified. Second, the number of participants decreased successively with increasing the motoric task difficulty. Therefore, data of more severely affected patients are not included in the more complex gait tasks. Furthermore, randomization of the tasks was not possible for reasons of feasibility and to reduce errors in performance, as they were integrated into a comprehensive movement protocol (more detailed information provides (Geritz et al., 2020)). The decrease in the number of subjects in successful task performance with higher cognitive and motor complexity can be taken as an additional indication that these demands, as required in everyday life, can be increasingly poorly mastered by patients with advanced PD. Third, the tasks were adapted to the individual coping ability (with or without walking aid) of the patients. This was done with the rationale of realistically representing a neurogeriatric PD cohort and achieving the most meaningful sample size possible. Fourth, patients were tested during the "ON" phase to collect data in the patients' best possible condition. Therefore, we cannot draw any conclusions regarding the unmedicated ("OFF") status. Fifth, cognitive flexibility and divided attention were assessed with a previously established paradigm (TMT), which, however, only measures specific aspects of EF and attentional processes. It was selected because the purpose of the study was to detect associations using clinically established, well validated (see method section) and economically feasible methods. Sixth, due to the small sample size of this pilot, a more granular analysis of the severity of dyskinesia, the influence of freezing of gait or walking aids was not possible. Future studies with larger cohorts should focus on these aspects specifically for patients with advanced PD. Finally, our sample did not include healthy controls nor age-matched inpatients with other diseases as controls, which would allow more direct conclusions regarding pathology-specific aspects and to correct for effects of age and acute illness.

Conclusion

To our knowledge this is the first study to predict spatio-temporal walking parameters in acutely hospitalized patients with advanced PD. Therefore, these results provide new insights regarding walking performances in situations where an additional demand is placed on. A relevant predictive value of EF and divided attention for deficits in walking performance cannot be inferred from our study. However, our analyses provide evidence that more severe motor symptoms, being in need of a walking aid (and age) are associated with a reduced gait speed and higher STV especially under ST conditions as well as with increasing $DTC_{Walking}$ in STV when an additional cognitive task requires to split attention. Thus, for clinical diagnostics and treatment in an acute neurogeratric setting, it remains essential to consider clinical symptoms. Furthermore, potential cognitive influences under DT walking situations, which can pose limitations and hazards (such as increased falls due to distraction) also need to be taken into consideration when evaluating new assessment methods for walking performances such as IMU data. Future studies should investigate to what extent deficits in EF and attentional functions may influence the benefit of therapeutic interventions for patients with PD in acute need of hospital care.

6 Cognitive parameters can predict change of walking performance in advanced Parkinson’s disease – chances and limits of early rehabilitation

This chapter addresses the third research question stated in the introduction. The findings presented here are directed at the association between global cognitive performance, EF and divided attention and the change in walking performance under ST and DT straight walking conditions after individualized early rehabilitation in patients with advanced PD. The results were obtained from the analysis of data from the same subcohort of the ComOn study (presented in Chapters 4 and 5). The chapter was adapted to the formal style of this dissertation for consistency, and the content was published as an original research article in Frontiers in Aging Neuroscience:

Geritz, J., Welzel, J., Hansen, C., Maetzler, C., Hobert, M. A., Elshehabi, M., Knacke, H., Aleknonytė-Resch, M., Kudelka, J., Bunzeck, N., & Maetzler, W. (2022). Cognitive parameters can predict change of walking performance in advanced Parkinson’s disease – Chances and limits of early rehabilitation. Frontiers in Aging Neuroscience, 14(1070093), 1–17. https://doi.org/10.3389/fnagi.2022.1070093

Abstract

Introduction: Links between cognition and walking performance in patients with Parkinson's disease (PD), which both decline with disease progression, are well known. There is lack of knowledge regarding the predictive value of cognition for changes in walking performance after individualized therapy. The aim of this study is to identify relevant predictive cognitive and affective parameters, measurable in daily clinical routines, for change in quantitative walking performance after early geriatric rehabilitation.

Methods: Forty-seven acutely hospitalized patients with advanced PD were assessed at baseline (T1) and at the end (T2) of a two-week early rehabilitative geriatric complex treatment (ERGCT). Global cognitive performance (Montreal Cognitive Assessment, MoCA), EF and divided attention (Trail Making Test B minus A, delta TMT), depressive symptoms and fear of falling were assessed at T1. Change in walking performance was determined by the difference in quantitative walking parameters extracted from a sensor-based movement analysis over 20 meter straight walking in single (ST, fast and normal pace) and dual task (DT, with secondary cognitive respectively motor task) conditions between T1 and T2. Bayesian regression (using Bayes Factor BF_{10}) and multiple linear regression models were used to determine the association of non-motor characteristics for change in walking performance.

Results: Under ST, there was moderate evidence (BF_{10}=7.8 respectively BF_{10}=4.4) that lower performance in the ΔTMT at baseline is associated with lower reduction of step time asymmetry after treatment (R^2_{adj}=0.26, p≤0.008 respectively R^2_{adj}=0.18, p≤0.009). Under DT walking-cognitive, there was strong evidence (BF_{10}=29.9 respectively BF_{10}=27.9) that lower performance in the ΔTMT is associated with more reduced stride time and double limb support (R^2_{adj}=0.62, p≤0.002 respectively R^2_{adj}=0.51, p≤0.009). There was moderate evidence (BF_{10}=5.1), that a higher MoCA total score was associated with increased gait speed after treatment (R^2_{adj}=0.30, p≤0.02).

Discussion: Our results indicate that the effect of ERGT on change in walking performance is limited for patients with deficits in EF and divided attention. However, these patients also seem to walk more cautiously after treatment in walking situations with additional cognitive demand. Therefore, future development of individualized treatment algorithms is required, which address individual needs of these vulnerable patients.

Keywords: Parkinson's disease, geriatric care, cognition, straight walking, dual task, wearable sensors, fear of falling, depression

Introduction

People with advanced Parkinson's disease (PD), one of the most common age-associated neurodegenerative disorders, are particularly affected by a deterioration of their walking performance as well as cognitive deficits, depression and anxiety (so-called non-motor symptoms (Avanzino et al., 2018; Yogev-Seligmann et al., 2008)). These are associated with reduced mobility, increased need for assistive devices (e.g., walking aids), increases risk of falls, injuries and acute medical care as well as the probability of institutionalization as well as treatment intervention outcomes (Mirelman et al., 2019; Rochester et al., 2004; Vila et al., 2021; Zanardi et al., 2021), and can all significantly impact independent living and quality of life (Haertner et al., 2018; Hobson & Meara, 2015; Nonnekes et al., 2018; Rutten et al., 2021; Snijders et al., 2007). However, the role of cognitive and affective non-motor symptoms in the change of walking performance after early individualized rehabilitation in acutely hospitalized patients with advanced PD is still not sufficiently understood.

With the help of modern sensor technology, some progress has been made in the last twenty years regarding the identification and classification of quantifiable disease-specific walking profiles of PD as well as their progression, for instance on the basis of spatio-temporal parameters measured with inertial measurement units (IMUs, (Alberto et al., 2021; Bouça-Machado, Jalles, et al., 2020; C et al., 2021; Del Din et al., 2019; Maetzler, Klucken, et al., 2016; Schlachetzki et al., 2017)). Individuals with PD differ from healthy individuals in several domains of walking, meaning they tend to walk more slowly and asymmetrically (e.g. with higher step time asymmetry) with delayed rhythm (e.g. with higher step and stride time as well as higher walking variability (e.g. higher step time, higher double limb support variability (Bouça-Machado, Jalles, et al., 2020; Mirelman et al., 2019; Vila et al., 2021; Zanardi et al., 2021)). However, as recently reviewed, evidence was inconsistent or lacking for several parameters in terms of both validity and responsiveness, while others (e.g. gait speed, step time, stance time, double limb support or asymmetry measures) showed consistent evidence in different disease conditions (Polhemus et al., 2021). Although these studies have contributed to a better understanding of impaired walking performance in PD in recent years, heterogeneity in the selection of parameters is evident. Also, the clinical utility of individual parameters, especially for the treatment of patients with advanced PD, has not been sufficiently investigated (Bouça-Machado, Jalles, et al., 2020; Mirelman et al., 2019; Polhemus et al., 2021).

Associations of non-motor symptoms such as impaired cognitive performance, especially deficits in divided attention and executive functions (EF, so-called fronto-striatal associated functions of cognitive flexibility, set shifting and working memory (Owen, 2004)) and dementia with reduced walking performance, higher fall risk and reduced quality of life in individuals with PD have also been found in several studies (reviewed in (Avanzino et al., 2018; Dirnberger & Jahanshahi, 2013; J. M.

Domingos et al., 2015; Koerts et al., 2009, 2011; Lauretani et al., 2016; Moustafa, Chakravarthy, Phillips, Crouse, et al., 2016; Owen, 2004)). Recent studies in people with PD with and without mild cognitive impairment (MCI) have shown that deficits in EF are associated with reduced gait speed, lower stride length, and increased gait variability, especially under DT conditions (Amboni et al., 2012, 2022; Hillel et al., 2019; Hobert et al., 2017; Johansson et al., 2021; Liguori et al., 2021; Lord et al., 2010, 2011; Maidan et al., 2016; Mirelman et al., 2018; Nieuwhof et al., 2017; Plotnik et al., 2011; Rochester et al., 2008, 2014; Salazar et al., 2017; Salkovic et al., 2017; Smulders et al., 2013; Stegemöller et al., 2014; Varalta et al., 2015; Wild et al., 2013; Yogev-Seligmann et al., 2008; Yogev et al., 2005). Meanwhile, higher global cognitive performance (measured with the Mini Mental State Examination) was found to be determinant for maintenance of positive long-term effects of home based physical training in individuals with advanced PD (Nieuwboer et al., 2002). Also, depression and FOF are associated with increased walking variability as well as decreased walking speed and quality of life in individuals with PD (Albay & Tutuncu, 2021; Allen et al., 2013; Atrsaei et al., 2021; Brozova et al., 2009; Dragašević-Mišković et al., 2021; Jacob et al., 2010; Lindholm et al., 2014; Lord et al., 2013; Rahman et al., 2011; Rochester et al., 2008). FOF is also considered a determinant of increased risk of falling (Allen et al., 2013) alongside with avoidance of physical activity in situations with increased fall-related activity (Kader et al., 2016). However, most of these studies related to cognitive and affective non-motor symptoms and their association with walking performance in individuals with PD do not consider the non-motor symptoms as predictive characteristics for post interventional change in walking performance. In addition, in the advanced disease stage (i.e., severe motor symptoms or motor fluctuations), the use of a walking aid as well as having mild cognitive impairment (MCI) or dementia are often considered as exclusion criteria.

Over the past twenty years, a substantial amount of research has been conducted on both pharmacological and non-pharmacological treatment options for walking impairments in PD (Bouça-Machado, Rosário, et al., 2020; Debû et al., 2018; Ni et al., 2018; Radder et al., 2020; Smulders et al., 2016). Especially in the later stages of PD, as pharmacological treatment effects become increasingly insufficient, rehabilitation and physical training programs have been identified to have a crucial complementary role in improving motor symptoms, including impaired walking (reviewed in (Bloem et al., 2015; Dietrichs & Odin, 2017; J. Domingos et al., 2018)). Since DT walking situations can be daily-relevant for individuals with PD, DT interventions have been evaluated over the past years- with promising results mainly from a multi-centered randomized controlled trial with 120 patients with PD (Geroin et al., 2018; Strouwen et al., 2017, 2019). However, while gait speed was identified as consistently responsive (which is the most commonly used walking parameter in treatment efficacy studies focusing on walking impairment), there is still a gap of knowledge with regard to responsiveness to treatment of various spatio-temporal walking parameters (Polhemus et al., 2021;

Scherbaum et al., 2022). Hence, a “one-size-fits-all” treatment approach may not mirror the complexity of the disease adequately (Ginis et al., 2017; Nonnekes & Nieuwboer, 2018; Serrao et al., 2019; Witt et al., 2017). Therefore, individualized, skilled (i.e., goal-driven), multimodal therapy approaches as established as common practice in geriatric rehabilitation are receiving more and more attention as potential treatment models for older patients with advanced PD (Nonnekes & Nieuwboer, 2018; Swanson & Robinson, 2020). However, in order to plan and implement individualized walking rehabilitation in an evidence-based manner, practitioners need to know which characteristics of the patient and their condition predict the efficacy of such training approaches, intensities, and durations.

The study presented here aimed to identify relevant cognitive and affective characteristics (measured with a comprehensive geriatric assessment, CGA) in advanced PD at admission to an acute inpatient stay at a neurogeriatric ward that are associated with changes in spatio-temporal walking parameters after two weeks of early rehabilitative geriatric complex treatment (ERGCT). We hypothesize that preexisting cognitive impairment, especially deficits in EF and divided attention, together with presence of depressive symptoms and FOF have a constraining effect on change in walking performance in terms of improvement during early rehabilitation.

Methods

Data for this study were collected as part of the multicenter, exploratory, observational study “Cognitive and Motor interactions in the Older population” (ComOn). The ComOn study examines the association of cognitive, motor and clinical characteristics (measured with quantitative and digital parameters of an extended CGA) in acutely hospitalized geriatric patients (at least 50 years old and have at least one chronic disease) during a stay on a geriatric ward of a Neurological Department of a University Hospital in Germany. The main aims of the study are to gain a better understanding of complex interactions of multifaceted geriatric symptoms and evaluate the efficacy of individualized geriatric inpatient treatment. Detailed information on all examinations performed have been published in the study protocol (Geritz et al., 2020).

The analyses presented here focus on the prognostic value of non-motor parameters of a CGA in patients with advanced PD on acute inpatient admission for the change in walking performance under ST and DT after two weeks early rehabilitative geriatric complex treatment (ERGCT, German Version of Operation and Procedure Code for hospitals (OPS) number 8-550.1). Data were collected between October 2017 and August 2021 at the Department of Neurology, University Hospital Schleswig-Holstein Campus Kiel (Germany). A written informed consent was obtained from all patients and, if applicable, their legal representatives (e.g., due to cognitive impairment or dementia). The study was reviewed by the ethics committee of the Medical Faculty of the University of Kiel (Ethics application number D 427/17).

Participants

For these analyses, data of N=47 patients with PD, diagnosed according to the Movement Disorder Society (MDS) clinical diagnostic criteria for PD were included (Marsili et al., 2018; Postuma et al., 2015). Participants were included if (i) they fulfilled the inclusion criteria of the ComOn study, i.e. were 50 years or older, able to walk independently over at least three meters with or without walking aid, had sufficient hearing and visual acuity as well as sufficient speech comprehension as judged by the investigator and (ii) received two weeks of ERGCT on the neurogeriatric ward. Patients were mainly administered to the inpatient stay for reasons of deterioration in mobility or walking ability, general condition, actual falls or reduced drug effects. Patients with previously described mild cognitive impairment (MCI) or mild to moderate dementia in their medical record as well as patients with severe motor symptoms measured with the MDS-revised version of the motor part of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III, (Goetz et al., 2008)) were included. Patients were excluded if they were suffering from delirium or other severe disorders of consciousness (clinical diagnosis), were below the cut-off of ≤5 points for severe dementia in PD in the Montreal Cognitive Assessment (MoCA, (Lawton et al., 2016; Nasreddine et al., 2005)), or had more than two falls in the past week due to safety reasons in the motor assessment.

Early rehabilitative geriatric complex treatment

ERGCT was performed in the neurogeriatric ward by a multi-professional geriatric team according to the guidelines and recommendations of the German geriatric societies (DRG-Fachgruppe OPS 8-550 2021, 2021; Meier-Baumgartner et al., 1998). This included at least 14 days of skilled treatment with at least one daily session of clinical therapy by trained therapists (30 minutes per session) and with at least two disciplines involved (occupational, physical and/or speech therapy). Contents of the therapy sessions were set according to an individualized indicated treatment plan. General core aspects of the treatment included strength, endurance and balance training, combined cognitive-motor training as well as training in activities of daily living. Clinical therapists were not involved in assessment nor analyses and interpretation of the collected data, and the individualized treatment plans were not adapted for study purposes. For the analyses presented here focusing on walking performance, only the number of sessions for physical and occupational therapy was considered.

Procedure

Patients were assessed within two days after admission (T1) to and before discharge (T2) from the neurogeriatric ward. At T1, a detailed medical history as well as self-reporting questionnaires on various behavioral and clinical aspects were taken. An extended CGA was carried out (see 2.4.2) to assess non-motor symptoms, followed by a comprehensive movement analysis using inertial measurement units (IMUs, see also 2.4.4) on a designated area on the ward corridor (>3 meters broad, well-lit). Each of these two latter assessments took about 60 to 90 minutes with a break of at least 60 minutes in between. Cognitive parameters were assessed during a neuropsychological assessment. Questionnaires were handed out to the patients during the admission interview with the request to complete them independently by the next day. Patients were offered help when needed. At T2, the movement analysis was carried out, preferably, at a similar daytime as T1. All patients were examined in medication ON state. For this purpose, medication was administered in close consultation with the clinic staff and the medication schedule was taken into account in order to provide a suitable time interval before the measurement.

Measures

Demographical and clinical parameters

Demographical characteristics like age, gender, years of education and geriatric aspects (e.g. care level, frailty, actual pain, problems with vision, hearing and urinary incontinence) were collected during the medical history interview. The geriatric screenings used for this purpose are described in more detail in the ComOn study protocol (Bellmann et al., 2013; Geritz et al., 2020; Lachs et al., 1990). Clinical aspects such as PD duration, previously described cognitive deficits or dementia as well as the number of occupational and physical therapy sessions between T1 and T2 were extracted from medical record. The levodopa equivalent daily dose (LEDD, (Tomlinson et al., 2010)) was determined based on the medication schedule at admission.

The severity of motor-symptoms was measured using the MDS-UPDRS III (Goetz et al., 2008) by defining scores as ≤30 (mild), 30 to 60 (moderate), and >60 (severe) for PD motor state (adapted from (Martínez-Martín et al., 2015)). Furthermore, using the three related Items of the MDS-UPDRS III the occurrence of dyskinesia (i.e. involuntary, random movements) during the examination as well as their impact on the rating of the MDS-UPDRS III, the occurrence of freezing of gait (FOG) and the modified Hoehn & Yahr Scale were recorded (Goetz et al., 2007, 2008, 2014).

Comprehensive geriatric assessment of non-motor symptoms

Global cognitive performance and executive function

Global cognitive performance was measured using the MoCA (Nasreddine et al., 2005). The total score ranges from zero to thirty points, one extra point is given for twelve or less years of education. Cut-offs are at <26 points for MCI (sensitivity of 90% , specificity of 75%) and <21 points for dementia (sensitivity of 81%, specificity of 95%) in patients with PD (Dalrymple-Alford et al., 2010).

EF and divided attention were measured using the paper-pencil speed test Trail Making Test (TMT, (Reitan, R. M., & Wolfson, 1985)). The TMT consists two parts, TMT A and TMT B (Strauss, E., Sherman, E. & Spreen, 2006). Components of perceptual tracking as well as processing speed are captured by both tasks. More complex EF such as set shifting and alternating sequencing (subdomains of cognitive flexibility) and divided attention are captured additionally by part B (Lamberty & Axelrod, 2012; Lezak et al., 2012; Strauss, E., Sherman, E. & Spreen, 2006). The recommended difference index ΔTMT (processing time in seconds (s) of TMT B minus TMT A) was calculated (Axelrod et al., 2000; Hester et al., 2005; Hobert et al., 2011; Lamberty et al., 1994; Lamberty & Axelrod, 2012; Vazzana et al., 2010). As this derived score corrects for processing speed, it therefore provides a better index of EF and was used for the analyses presented here.

Depressive symptoms

Depressive symptoms within the last 14 days were assessed using the screening questionnaire for geriatric patients *Depression im Alter* Scale (DIA-S,(Heidenblut & Zank, 2010)). The DIA-S consists ten dichotomous items (scoring “0” and “1”). The total sum score ranges from zero to ten points, cut-offs range from ≤2 points (no depressive symptoms), 3 points (depression suspected) to ≥4 points (clinically relevant depression is likely). The DIA-S shows good reliability (Cronbach's alpha=0.84) and convergent validity as well as high sensitivity (0.81 to 0.92) in geriatric patients and is straightforward to use in the clinical setting (Heidenblut & Zank, 2014; Wunner et al., 2022).

Fear of Falling

FOF was assessed using the international version of the Falls Efficacy Scale (FES-I, (Delbaere et al., 2010; Yardley et al., 2005)). The FES-I captures concerns about falling in specific daily activities with 16 items in a four-point response format (0="not at all concerned" to 4="very concerned"). The total score is between 16 and 64 points with a cut off of ≥23 points for high concern to fall (Delbaere et al., 2010). The FES-I shows good reliability (Cronbach's alpha=0.79) as well as convergent and predictive validity with regard to physical and psychological aspects (Delbaere et al., 2010).

Straight walking performance

Walking conditions

From the comprehensive movement analysis, data for straight walking performance at T1 and T2 during four walks of a marked straight distance of 20 meters under ST and DT walking conditions was considered for this study. For each walk a different condition was set with increasing task complexity. Patients were allowed to use a walking aid, if needed. If patients had the capacity to perform all four walking conditions, the assessment was conducted in the following order: First condition *ST fast pace* (covering the distance walking as fast as possible without running), second condition *ST normal pace* (walking at a self-selected comfortable speed), third condition *DT walking-motor* (checking predetermined boxes with a cross as quickly as possible with a pen on a clipboard while walking at fast pace), fourth condition *DT walking-cognitive* (consecutively subtracting seven from a given three-digit number as fast as possible while walking at fast pace). The third condition was only possible for patients who did not require a walking aid as the checking boxes task while walking required the use of both arms. For the fourth condition, the given three-digit number was altered between T1 and T2 to avoid possible learning effects. If patients were unable to complete all walking conditions, the less complex tasks were prioritized.

IMU system

The CE-certificated IMU-system RehaGait® (Hasomed, Magdeburg, Germany (Byrnes et al., 2018)) was used. For these analyses, data was collected from the IMU attached with velcro-straps to the patient's lower back at the level of the fifth lumbar vertebra. The IMU includes a triaxial accelerometer (±16 g) and a triaxial gyroscope (±2000/s). Collected data (sampling frequency of 100 Hertz) was transmitted simultaneously via Bluetooth to a tablet with the RehaGait® application modified for the ComOn study in cooperation with the manufacturer.

Extraction of walking parameters and calculation of change in walking performance

IMU raw data were analyzed using a validated algorithm for step detection in PD to calculate the ten spatio-temporal walking parameters total number of steps, gait speed (distance divided by measurement duration, m/s), mean step time (s), mean stride time (s), mean swing time (s), mean stance time (s), mean double limb support time (DLS, s), mean double limb support time variability (DLSV, s; square rooted sum of variance of DLS for each foot divided by two), mean step time asymmetry (ASYM, s; absolute difference between mean step time difference between both feet) and step time variability (STV, s; square rooted sum of variance of step time for each foot divided by two) (Pham, Elshehabi, Haertner, Del Din, et al., 2017). For all walking parameters (except for gait speed) minimal detectable change (MDC) was examined in neurogeriatric subsample of the ComOn study for ST normal pace as described in detail in (Hansen et al., 2022). A linear correction of all parameters (except number of steps and gait speed) was applied to normalize for gait speed (to 1m/s), as recommended in previous biomechanical studies on sensor-based walking parameters (Warmerdam et al., 2021).

The change in walking performance after ERGCT was calculated for each of the extracted and corrected walking parameter as the difference (Δ, delta) between T1 and T2:

Δwalking parameter = paramter$_{T2}$ -parameter$_{T1}$.

The evaluation of the direction of this difference depends on the respective parameter and the overall profile. Here, a positive value for Δgait speed corresponds to an increased gait speed (i.e., patients walk faster at T2 than at T1, which means an improvement), while a negative value for ΔASYM corresponds to decreased ASYM (i.e., the gait pattern of the patients is more symmetric at T2 than at T1, which means an improvement), values around zero indicate no change between the two points of measurements.

Statistics

To address the scientific question which cognitive and affective non-motor symptoms in patients with advanced PD may have predictive value for the change in straight walking performance after two weeks individualized treatment, both Bayesian regression models and multiple linear regression models were calculated for all four walking conditions. Deltas of the walking parameters were set as dependent variables (Δnumber of steps, Δgait speed, Δstep time, Δstride time, Δswing time, Δstance time, ΔDLS, ΔDLSV, ΔASYM and ΔSTV). Each model included the MoCA total score or ΔTMT as well as DIA-S and FES-I total scores as predictors and MDS-UPDRS III total score, use of a walking aid (except for DT walking-motor), age and gender as covariates. Regression models were calculated separately for the two predictors MoCA and ΔTMT in order to avoid multicollinearity as well as for an exploratory differentiation between global cognitive performance and EF. For patients with one missing single item in the DIA-S (n=2, rate of completeness 90%) or a maximum of two missing single items in the FES-I (n=7, rate of completeness of 88%), the missing values were imputed using the individual median (for DIA-S) or mean imputation (for FES-I, (Shrive et al., 2006)). The total scores were subsequently recalculated for these patients. The Bayes factor BF_{10} was estimated (using the Bayesian Information Criterion, BIC, (Glen, 2018)) as a measure for strength of evidence between two different scientific theories (H0 vs. H1) provided by the data (H1 here: cognitive and affective non-motor symptoms can predict change in walking performance (Kass & Raftery, 1995; Wagenmakers et al., 2016)). The modified classification according to Lee and Wagenmakers (2013 (M. D. Lee & Wagenmakers, 2013)) was used categorizing $10<BF_{10}\geq30$ as “strong evidence for H1”, $3<BF_{10}\geq10$ as “moderate evidence for H1”, $1<BF_{10}\geq3$ respectively $0.10<BF_{10}\geq0.33$ as “anecdotal evidence for H0“, and $BF_{10}=1$ as “no evidence”. For models with at least moderate evidence, indicated by BF_{10}, multiple linear regression models (using stepwise backward entry method) were calculated (level of significance $\alpha<0.05$). Assumptions of multicollinearity (with Variance Inflation Factor and Tolerance), homoscedasticity, linearity and normality of residuals (with Q-Q-Plots) and independence of residuals (with Durbin-Watson) where checked for each regression model (Goss-Sampson, 2018). The coefficient of determination R^2_{adj} (adjusted for sample size n and multiple predictors using McNemar’s formula (Goss-Sampson, 2018)) was used as indicator for the goodness of model fit for the overall hierarchical multiple linear regression models, and standardized regression weights β as well as post hoc

Spearman's rho (ρ) correlation coefficients were determined and tested for significance (level of significance $\alpha<0.05$).

Differences between the four walking conditions were calculated for MoCA, ΔTMT, DIA-S, FES-I, MDS-UPDRS III, age and gender at T1 as well as for all Δwalking parameters. For continuous variables, the Kruskal-Wallis H-test and Dunn’s post hoc test (with Bonferoni-Holm-correction for paired comparisons, significant at $p_{holm}<0.05$) were used (Goss-Sampson, 2018). For categorical variables, the χ^2 test was used. (Goss-Sampson, 2018). As an additional exploratory analysis, changes of each walking parameter between T1 and T2 was examined for each of the four walking conditions using Wilcoxon signed-ranks test for dependent samples (Goss-Sampson, 2018). Outliers, defined as ±3SD, were excluded for the following parameters: ΔTMT score (n=2), for ST normal pace step time, stride time, stance time, swing time, DLS, ASYM, ΔASYM, ΔSTV (each n=1), Δstep time, Δstride time, Δswing time, Δstance time, ΔDLS and ΔDLSV (each n=2), for ST fast pace gait speed (n=2) and Δgait speed (n=2), for DT walking cognitive number of steps, DLSV, STV, ΔDLS and ΔSTV (each n=1), and Δnumber of steps, Δstride time, Δstance time, and ΔDLSV (each n=2) , and for DT walking-motor number of steps (n=1).

Data were preprocessed using MATLAB (version 2020b) and Python (version 3.9.1.), and statistical analysis were conducted using JASP (version 0.16.1).

Results

Descriptive characteristics

A total of n=47 patients with data from the CGA at T1 and the IMU-based movement analysis before and after therapy were included for this analysis (out of those n=8 did not perform the TMT due to lack of capacity or motivation). Patients were on average 73 years old (SD=8), 38% were female. Mean number of days between T1 and T2 was 11 days (SD=3), and patients had on average 10 sessions of physical therapy (SD=2) and 7 sessions of occupational therapy (SD=2) during this period. Mean disease duration was 10 years (SD=8), mean MDS-UPDRS III was 30 points (SD=14), median Hoehn & Yahr stage was 3 (IQR=1) with 60% at stage 3 and 30% at stage 4. Cognitive impairment was previously reported in the medical records in 17% of the cohort, of which 9% were prediagnosed with dementia. The mean MoCA total score was 23 points (SD= 3.7), thus below the cut-off for MCI in patients with PD (see section 2.4.2), mean ΔTMT score was 86.3s (SD=112). Mean total score of the DIA-S was 3 points (SD=2.2) with 28% of the cohort showing depressive symptoms (cut-off ≥4 points), mean FES-I total score was 30 points (SD=11) with 72% of the cohort showing high concern to fall. Patients were comparable over all four walking conditions regarding MoCA total score (H=0.61, p=0.89), ΔTMT performance (H=1.75, p=0.63), DIA-S total score (H=0.94, p=0.82), FES-I total score (H=1.57, p=0.67), age (H=0.03, p>0.99), gender (χ^2=0.66, p=0.88), and MDS-UPDRS III total score (H=6.49, p=0.09). Table

6.1 provides detailed information of descriptive and clinical characteristics of baseline T1 for all four walking conditions.

For both times, T1 and T2, n=47 patients successfully completed the 20m walking distance under ST normal pace, n=32 under ST fast pace, n=19 under DT walking-cognitive, and n=18 under DT walking-motor. As not all subjects were capable to participate in every condition, the sample size decreased with capacity-dependent task prioritization and increasing demands per condition (e.g., not necessarily all subjects who performed the ST normal pace condition could also perform ST fast pace due to reduced physical capacity). For the three walking conditions that were performable with a walking aid, 11% (DT walking-cognitive) to 23% (ST normal pace) of the patients used their walking aid. Differences between the four walking conditions for all Δwalking parameters as well as paired group comparisons between the conditions are illustrated in Figure 6.1. Results of the additional exploratory comparisons of all Δwalking parameters for each walking condition between T1 and T2 are shown in Supplementary-Table 6.1, significant differences after treatment are illustrated in Supplementary-Figure 6.1.

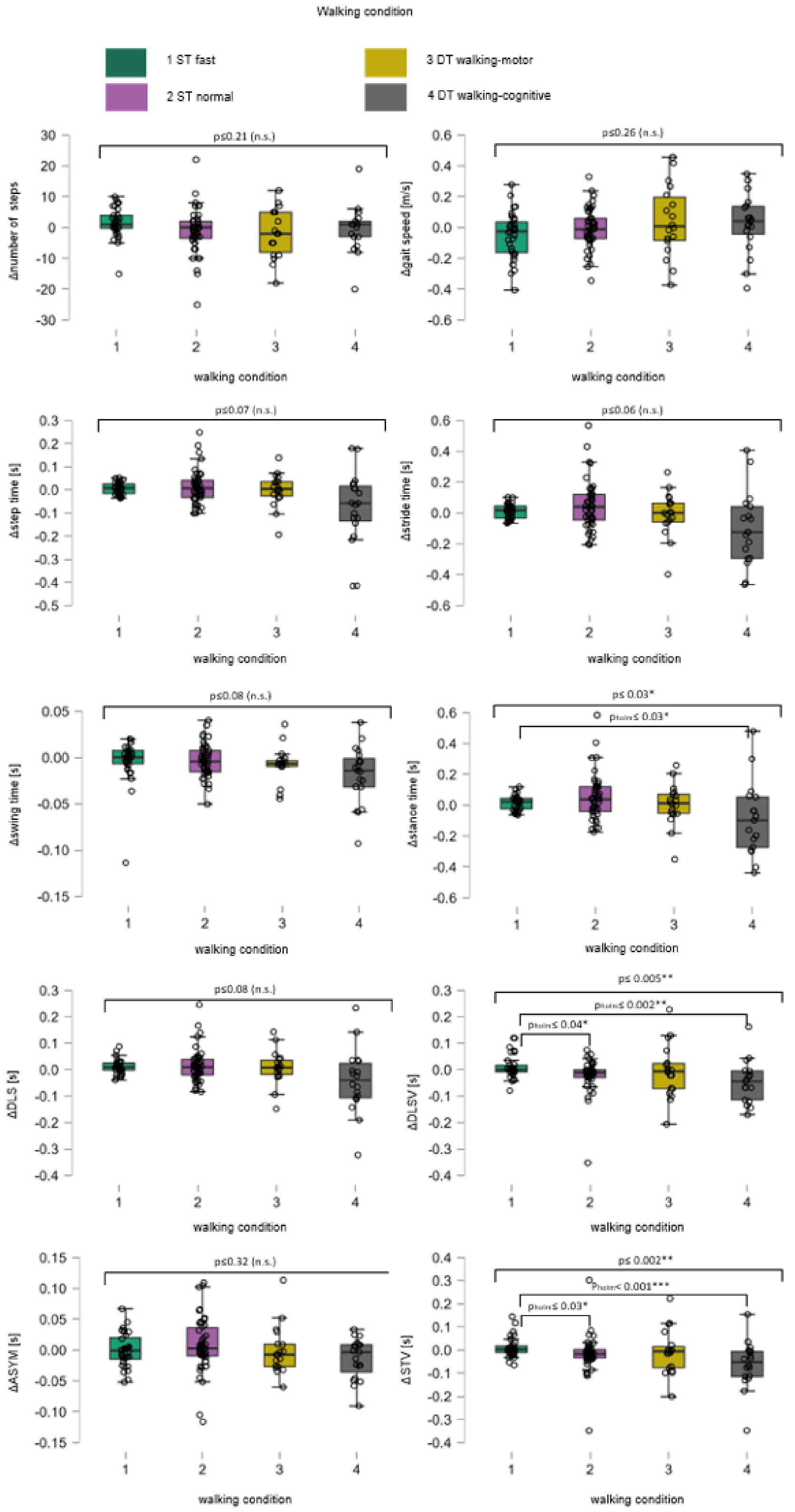

Figure 6.1. Box plots for change in all walking parameters over all walking conditions. For the change (delta of measurement point T1 minus measurement point T2, Δ) in number of steps, gait speed (meters per second, m/s), step time (seconds, s), stride time (s), swing time (s), stance time (s), double limb support (DLS, s), double limb support variability (DLSV, s), asymmetry (ASYM, s) and step time variability (STV, s), single subject data points (black circles) are given for walking conditions single task fast pace (green, 1), single task normal pace (violet, 2), the dual task walking-motor (yellow, 3) and the dual task walking-cognitive (grey, 4). Between the four walking conditions, differences in the change in walking performance are shown (long black square brackets, using Kruskal-Wallis H-Test, significant differences are marked with *, Bonferroni-corrected level of significance p≤.05; **, level of significance p p≤.01; non-significant ones are marked with (n.s.)) as well as post-hoc paired group comparisons between each walking condition (short black square brackets, using Dunn's post-hoc test, significant paired-group differences are marked with *, Holm-corrected level of significance p_{holm}≤.05; **, level of significance p_{holm}≤.01 and ***, level of significance p_{holm}≤.001).

Table 6.1 Descriptive characteristics of demographic, clinical and CGA parameters at baseline assessment, days between measurements, therapy sessions and deltas of walking parameters over all four walking conditions

parameters	ST normal pace		ST fast pace		DT walking-cognitive		DT walking-motor	
	n	M (SD) {Median; IQR}	n	M (SD) {Median; IQR}	n	M (SD) {Median; IQR}	n	M (SD) {Median; IQR}
age [years]	47	73 (7.80) {74; 11.5}	32	72 (7.31) {75; 10}	19	72 (9.11) {77; 12}	18	72 (8.96) {77; 12}
female [n (%)]		18 (38)		11 (34)		7 (37)		5 (28)
education [years]		10 (1.82)		10 (1.75)		11 (1.80)		10 (1.97)
days between measurements		11 (2.61)		11 (2.85)		11 (2.95)		11 (3.16)
physical therapy sessions		10 (2.38)		9 (2.58)		9 (2.96)		8 (3.03)
occupational therapy sessions		7 (2.11)		7 (2.49)		7 (2.47)		7 (2.69)
disease duration [years]		10 (7.54)		10 (7.88)		9 (7.97)		8 (6.84)
Hoehn & Yahr		{3; 1}		{3; 0}		{3; 0}		{3; 0}
LEDD [mg]		721 (349.4)		682 (325.4)		695 (377)		657 (334.5)
MoCA		23 (3.65) {23; 5}		23 (3.4) {23; 5}		24 (3.33) {24; 4.5}		23 (3.93) {23; 5.75)
ΔTMT [s] (8 missing, 2 excluded)		112 (72.9) {86; 79}		123 (75.2) {106; 68.75}		103 (62.4) {83; 44}		98 (64.4) {82.5; 52}
DIA-S[a]		3 (2.16) {2;3}		2 (2.17) {2; 2}		2 (2.40) {2; 2}		2 (2.64) {1.5; 3.5}
FES-I[b]		30 (10.8) {28; 14.5}		28 (8.63) {27.5; 8.5}		27 (7.95) {28; 9}		26 (7.27) {25; 8.5}
MDS-UPDRS III		30 (13.5) {32; 22.5}		28 (13.3) {26.5; 20.25}		23 (13.2) {20; 14}		22 (12.1) {20; 17.25}
occurrence of dyskinesia [n (%)]		[6; 14]		[4;14]		[1; 6]		[1; 7]
impact of dyskinesia [n; %]		[3; 6]		[2; 6]		[0; 0]		[0; 0]
occurrence of FOG[c]		[15; 32]		[9; 28]		[5; 26]		[4; 22]
walking aid [n (%)]		[11; 23]		[4; 13]		[2; 11]		[0; 0]
Δnumber of steps	47	-0.96 (7.33) {0; 5.50}	32	1.38 (4.92) {1; 4.25}	17	-0.59 (7.92) {1; 5}	18	-1.89 (7.99) {-2; 13}
Δgait speed [m/s]	46	-0.006 (0.13) {-0.01; 0.13}	31	-0.05 (0.15) {-0.02; 0.20}	19	0.03 (0.19) {0.04; 0.18}		0.04 (0.23) {0.007; 0.28}
Δstep time [s]	45	0.01 (0.07) {0.008; 0.07}	32	0.007 (0.02) {0.008; 0.04}	19	-0.08 (0.16) {-0.06; 0.15}		0.0005 (0.07) {0.0004; 0.06}
Δstride time [s]	45	0.05 (0.16) {0.04; 0.16}	32	0.01 (0.05) {0.02; 0.08}	17	-0.10 (0.24) {-0.12; 0.33}		-0.005 (0.14) {0.001; 0.12}
Δswing time [s]	45	-0.003 (0.02) {-0.004; 0.02}	32	-0.004 (0.02) {0.0004; 0.01}	19	-0.02 (0.03) {-0.01; 0.03}		-0.007 (0.02) {-0.007; 0.006}
Δstance time [s]	45	0.05 (0.15) {0.04; 0.16}	32	0.01 (0.05) {0.02; 0.07}	17	-0.09 (0.24) {-0.10; 0.33}		0.003.64 (0.14) {0.01; 0.12}
ΔDLS [s]	45	0.01 (0.06) {0.01; 0.06}	32	0.01 (0.03) {0.01; 0.03}	18	-0.04 (0.12) {-0.04; 0.13}		0.008 (0.079) {0.008; 0.05}
ΔDLSV [s]	45	-0.02 (0.06) {-0.01; 0.03}	32	0.01 (0.04) {0.0003; 0.03	17	-0.05 (0.08) {-0.04; 0.11}		-0.006 (0.10) {-0.007; 0.10}
ΔASYM [s]	46	0.008 (0.04) {0.003; 0.05}	32	-0.0003 (0.03) {-0.0009; 0.03}	19	-0.01 (0.03) {-0.003; 0.04}		-0.0006 (0.04) {-0.007; 0.04}
ΔSTV [s]	46	0.01 (0.04) {-0.02; 0.04}	32	-0.02 (0.08) {0.003; 0.03}	18	-0.06 (0.10) {-0.05; 0.11}		-0.007 (0.10) {-0.005; 0.09}

[a], imputed values using individual median imputation for cases with one missing single item; ASYM, asymmetry; [b], imputed values using individualized mean imputation for cases with one or two missing single items; [c], occurrence during measurement; DIA-S, *Depression im Alter* Scale, DLS, double limb support; DLSV, double limb support variability; DT, dual task; FES-I, Falls Efficacy Scale – International version; FOG, Freezing of gait; IQR, interquartile range; LEDD, levodopa equivalence daily dose (in milligram, mg); M, mean; m/s, meter per seconds; max, maximum; MDS-UPDRS III, Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale; min, minimum; MoCA, Montreal Cognitive Assessment total score; n, sample size; s, seconds; SD, standard deviation; ST, single task; STV, step time variability; Δ, delta of walking parameters as difference of measurements after and before therapy; ΔTMT, delta of Trail Making Test (part B minus part A); %, percentage.

Regression analyses

The main results of Bayesian and multiple linear regression analyses for the cognitive and affective parameters as independent variables and Δwalking parameters as dependent variables are summarized here and illustrated in Figure 6.2, while Table 6.2 provides more detailed information for all significant regression models. Under ST fast pace condition, Bayesian regression suggested moderate evidence in favor of the model with ΔASYM (BF_{10}=7.81), and ΔTMT and DIA-S. The overall backward multiple linear regression model was significant (p=0.008) with a coefficient of determination of R^2_{adj}=26%. The effect was driven by ΔTMT (β=0.56, p=0.004) with a moderately positive post hoc correlation (ρ=0.37, p=0.009, Figure 6.2(A)) and DIA-S (β=0.44, p=0.02) with no significant post hoc correlation (ρ=0.16, p=0.37, Figure 6.2(A)). This means, there is moderate evidence that, together, ΔTMT and DIA-S significantly explain about one quarter of the variance of ΔASYM, and that higher positive values of ΔASYM seem to be associated with higher ΔTMT and DIA-S scores. Furthermore, Bayesian regression suggested anecdotal evidence for H0 with regard to all other Δwalking parameters indicating no association with any of the independent variables in this cohort (all BF_{10}<3; all p's>0.05). Therefore, individual effects for these parameters were not further interpreted and are not shown here.

Under ST normal pace, Bayesian regression suggested moderate evidence for ΔASYM (BF_{10}=4.41) with ΔTMT and MDS-UPDRS III included (Tab. 6.2). The overall backward multiple linear regression model was significant (p=0.009, R^2_{adj}=18%), mainly driven by the ΔTMT (β=0.34, p=0.03) with a moderately positive post hoc correlation (ρ=0.44, p=0.008, Figure 6.2(B)). and to less extent by the MDS-UPDRS III (β=0.28, p=0.08) with no significant post hoc correlation (ρ=0.25, p=0.11, Figure 6.2(B)). This means, that, together, ΔTMT and MDS-UPDRS III explain nearly one fifth of the variance of ΔASYM, and that higher values of ΔASYM is associated with higher ΔTMT and MDS-UPDRS III scores. When the MoCA total score was included in the model, there was moderate evidence for ΔDLSV (BF_{10}=4.41) with DIA-S included (Tab. 6.2). The overall backward multiple linear regression model was significant with R^2_{adj}=11%, driven by a negative effect of the DIA-S (β=-0.36, p=0.01), but there was no significant post hoc correlation (ρ=-0.23, p=0.12, Figure 6.2(B)).

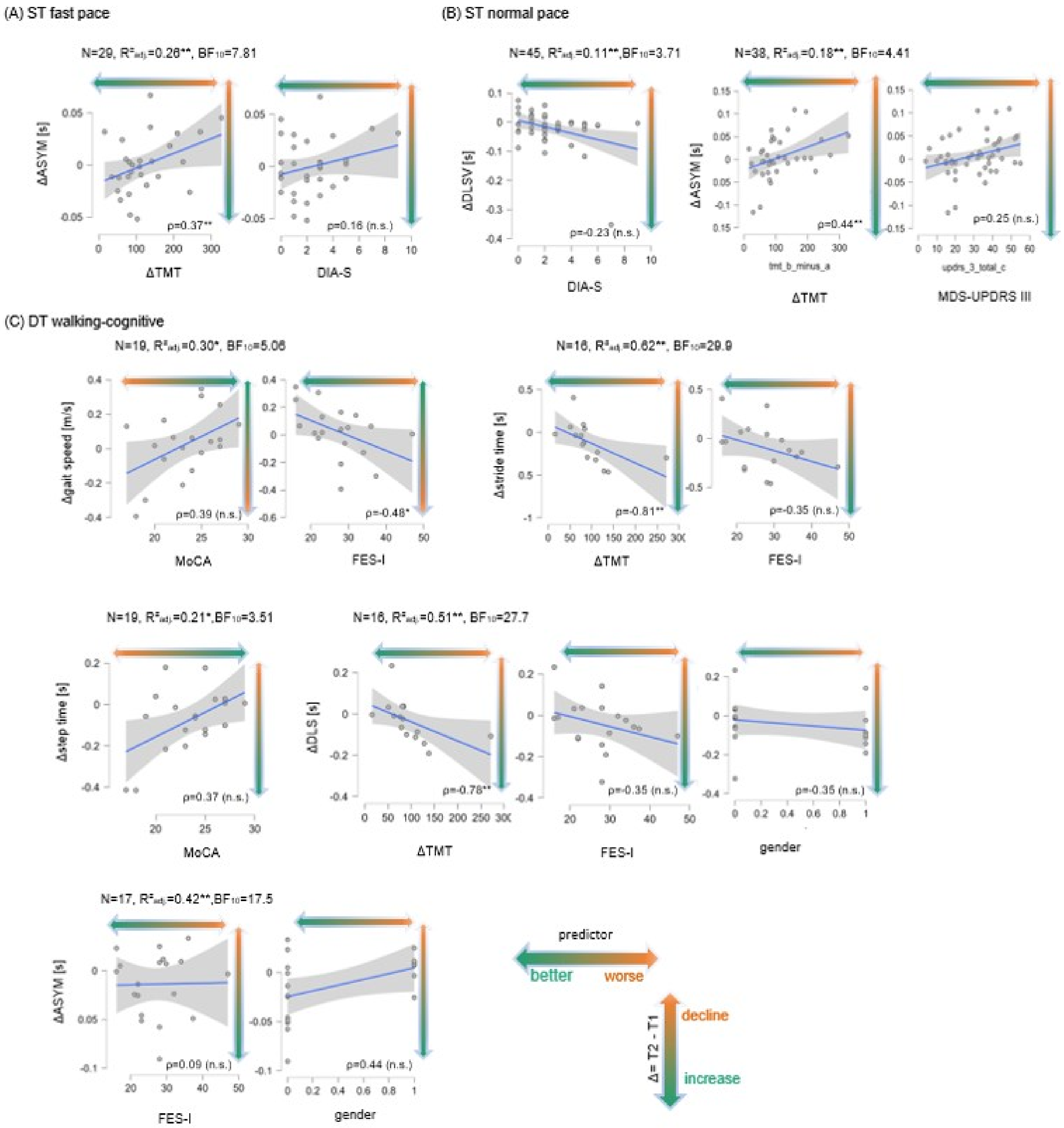

Figure 6.2: Correlation plots of the significant Regression models with the relevant model predictors for change in walking parameters. In (A) for single task fast pace walking condition (ST fast pace) the change (delta of measurement point T1 minus measurement point T2, Δ) in asymmetry (ASYM, in seconds, s) is shown on the ordinates, the delta of Trail Making Test (part B minus part A, ΔTMT, s) and the total score of the *Depression im Alter*-Scale (DIA-S) are on the abscissas. Sample size N is given as well as the adjusted coefficient of determination R^2_{adj}, Bayes factor BF_{10} and Spearman's rank correlation (ρ) between ΔASYM and ΔTMT and between ΔASYM and DIA-S, significant correlation coefficients are marked with * (level of significance p≤.05) and ** (level of significance p p≤.01), non-significant ones are marked with (n.s.). Data points (gray dots), regression lines with confidence intervals (blue lines with surrounding gray boxes) are shown for the Δwalking parameter. The colored direction of the arrow indicated the direction of the change in walking parameters from T2 to T1 from longer/slower (orange) to shorter/faster (green).In (B) the same is shown for single task normal pace walking condition for the change in double limb support variability (ΔDLSV,s) with DIA-S as well as for ΔASYM (s) and ΔTMT and the total score of the Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III). In (C) the same is shown for DT motor-cognitive walking condition (DT walking-cognitive) for Δgait speed (in meter per seconds, m/s) and the total score of the Montreal cognitive Assessment (MoCA), for Δstride time (s) and ΔTMT and the total score of the Falls-Efficacy-Scale-International version (FES-I), for Δstep time (s) and MoCA, for Δdouble limb support (DLS, s) and ΔTMT, FES-I and gender ("1", female) as well as for ΔASYM (s) and FES-I and gender.

Under DT walking-cognitive, Bayesian regression suggested moderate evidence for Δgait speed (BF_{10}=5.06) with MoCA and FES-I included (Tab. 6.2). The overall backward multiple linear regression model was significant (p=0.02) with R^2_{adj}=30%. The effect was mainly driven by a positive effect of MoCA (β=0.42, p=0.05) with a non-significant moderately positive post hoc correlation (ρ=0.39, p=0.10, Figure 6.2(C)) and to less extent by a negative effect of FES-I (β=-0.41, p=0.06) with a significant moderately negative post hoc correlation (ρ=-0.48, p=0.04, Figure 6.2(C)). This implies, that, together, total scores of MoCA and FES-I explain nearly one third of the variance of Δgait speed, and that lower values of Δgait speed is associated with lower MoCA scores and higher FES-I scores. Also, there was moderate evidence for Δstep time (BF_{10}=3.51) with the MoCA included (Tab. 6.2). The overall backward multiple linear regression model was significant (p=0.03) with R^2_{adj}=21%, driven by a positive effect of the MoCA (β=0.50, p=0.002) with a non-significant moderately positive post hoc correlation (ρ=0.37, p=0.11, Figure 6.2(C)); implying moderate evidence for the MoCA total score explains about one fifth of the variance of Δstep time, and lower values of Δstep time seem to be associated with lower MoCA total scores. In case the ΔTMT was included in the model, Bayesian regression suggested strong evidence for Δstride time (BF_{10}=29.90) and with ΔTMT, FES-I and gender included (Tab. 6.2). The overall backward multiple linear regression model was significant for Δstride time (p=0.002) with R^2_{adj}=62%, driven by negative effects of ΔTMT (β=-0.48, p=0.01), FES-I (β=-0.40, p=0.03) and gender (β=-0.38, p=0.05 (i.e., women have lower values in Δstride time than men). There were significant strongly negative post hoc correlations between Δstride time and ΔTMT (ρ=-0.81, p=0.0004, Figure 6.2(C)) and gender (ρ=-0.51, p=0.04, Figure 6.2(C)) and a non-significant moderately negative post hoc correlation with FES-I (ρ=-0.35, p=0.17, Figure 6.2(C)). Also, there was strong evidence for ΔDLS (BF_{10}=27.73) with ΔTMT, FES-I and gender included (Tab. 6.2). The overall backward multiple linear regression model was significant for ΔDLS (p=0.009) with R^2_{adj}=51%, driven by negative effects of ΔTMT (β=-0.46, p=0.03) with a significant strongly negative post hoc correlation (ρ=-0.78, p=0.0004, Figure 6.2(C)), and to less extent by negative effects of FES-I (β=-0.40, p=0.06), and gender (β=-0.32, p=0.12) with non-significant moderately negative post hoc correlations for FES-I (ρ=-0.35, p=0.17, Figure 6.2(C)) and gender (ρ=-0.38, p=0.12, Figure 6.2(C)). This implies with strong evidence, that the ΔTMT, together with FES-I total score and gender explains nearly two thirds of the variance of Δstride time as well as half of the variance of ΔDLS. Thus, lower values of Δstride time and ΔDLS are associated with higher values of ΔTMT and FES-I scores and female gender. Furthermore, Bayesian regression suggested strong evidence for ΔASYM (BF_{10}=17.51) with FES-I and gender included (Tab. 6.2). The overall backward multiple linear regression model was significant for ΔASYM (p=0.009) with R^2_{adj}=42%. The effect was mainly driven by a positive gender effect (β=0.69, p=0.004, i.e., woman have higher values in ΔASYM than men) with a nearly significant moderately positive post hoc correlation (ρ=0.44, p=0.06, Figure 6.2(C)), and by a negative effect of FES-I (β=-0.47, p=0.03) with no significant post hoc correlation

(ρ=0.09, p=0.71, Figure 6.2(C)). Under DT walking-motor Bayesian regression suggested only anecdotal evidence for H0 for all Δwalking parameters indicating no association with the parameters of the extended CGA in this cohort ($BF_{10}<3$; all p's>0.05). Therefore, individual effects were not further interpreted.

Table 6.2 Backward multiple linear regression models and Bayes factors for significant deltas of walking parameters

Dependent variables	**Independent variables found as predictors**	**n**	**$R^2_{adj.}$**	**F**	**BF_{10}**	**β**	**p**
			ST fast pace				
ΔASYM [s]^2		29	0.26	5.90	7.81^a		0.008**
	ΔTMT					0.56	0.004**
	DIA-S					0.44	0.02*
			ST normal pace				
Δstep time [s]^2		37	0.14	6.85	4.49^a		0.01**
	MDS-UPDRS III					0.40	0.01**
Δstride time [s]^2		37	0.16	7.70	6.50^a		0.009**
	MDS-UPDRS III					0.42	0.009**
Δstance time [s]^1		45	0.11	6.26	3.18^a		0.02*
	MDS-UPDRS III					0.36	0.02*
ΔDLS [s]^1		45	0.11	6.51	3.55^a		0.01**
	MDS-UPDRS III					0.36	0.01**
ΔDLSV [s]^1		45	0.11	6.60	3.71^a		0.01**
	DIA-S					-0.36	0.01**
ΔASYM [s]^2		38	0.18	5.41	4.41^a		0.009**
	ΔTMT					0.34	0.03*
	MDS-UPDRS III					0.28	0.08
			DT walking-cognitive				
Δgait speed [s]^1		19	0.30	4.94	5.06^a		0.02*
	MoCA					0.42	0.05*
	FES-I					-0.41	0.06
Δstep time [s]^1		19	0.21	5.66	3.51^a		0.03*
	MoCA					0.50	0.03*
Δstride time [s]^2		16	0.62	9.16	29.9^b		0.002**
	ΔTMT					-0.48	0.01**
	FES-I					-0.40	0.03*
	gender					-0.38	0.05*
ΔDLS [s]^2		16	0.51	6.19	27.7^b		0.009**
	ΔTMT					-0.46	0.03*
	FES-I					-0.40	0.06
	gender					-0.32	0.12
ΔASYM [s]^2		17	0.42	6.68	17.5^b		0.009**
	FES-I					-0.47	0.03*
	gender					0.69	0.004**

^{a}, moderate evidence for H1; ASYM, asymmetry; ^{b}, strong evidence for H1; BF_{10}, Bayes factor as measure for strength of model evidence; DIA-S, *Depression im Alter* Scale, DLS, double limb support; DLSV, double limb support variability; DT, dual task; F, test statistic from ANOVA used for testing significance of the multiple regression models; m/s, meter per seconds; MDS-UPDRS III, Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment total score; n, sample size; $p \leq 0.05$*, significant on level of significance $\alpha \leq 0.05$; $p \leq 0.01$**, significant on level of significance $\alpha \leq 0.01$; $R^2_{adj.}$, multiple regression coefficient adjusted for sample size and number of model parameters; s, seconds; ST, single task; β, standardized regression weights; Δ, delta of walking parameters as difference of measurements after and before therapy; ΔTMT, delta of Trail Making Test (part B minus part A); ^{1}, model included MoCA, DIA-S, FES-I, age, gender, walking aid and MDS-UPDRS III, ^{2}, model included ΔTMT, DIA-S, FES-I, age, gender, walking aid and MDS-UPDRS III.

Discussion

In our study we assessed cognitive and affective non-motor symptoms (namely global cognitive performance, EF and divided attention, depressive symptoms and FOF) as well as walking performance rehabilitation in acutely hospitalized in patients with advanced PD. The aim of this study was to investigate the relationship between these non-motor symptoms at admission and the change in walking performance under ST and DT conditions after two weeks of individualized early rehabilitation. The main result of our study is that cognitive performance at admission can predict the change of walking performance during the hospital stay. Particularly, reduced EF and divided attention should be considered as limiting factors for treatment success, especially in situations with additional cognitive demand while walking.

In summary, under both ST walking conditions the results of the regression analyses show a ceiling effect with regard to patients with higher performance in EF and divided attention that showed higher reduction of ASYM after treatment. This is also consistent with a comparative study showing that both individuals with PD and idiopathic fallers show a more asymmetric walking pattern under normal ST walking conditions than older healthy individuals and that under additional attention demand (in the sense of DT) ASYM is even more pronounced in these former two groups (Yogev et al., 2007). As ASYM is also known to be associated with higher PD disease severity (Polhemus et al., 2021; Vila et al., 2021), these findings suggest, that patients with higher capacity in EF and divided attention seem to be able to better compensate for their asymmetric gait pattern after treatment.

Under DT walking cognitive condition patients with lower performance in EF and divided attention showed more reduced stride time and DLS after treatment than patients with better performance in EF and divided attention. This reduction might reflect the acute medical indication with which the patients were admitted to the clinic and the advanced stage of the disease, which is associated with more rapid progression and more severe symptom fluctuations. However, while stride time and gait speed are readily interpretable for clinical aspects (e.g. lower gait speed and stride time is known to be associated with higher PD disease severity (Polhemus et al., 2021)), the stand-alone practical meaning and clinical utility as well as the expectable responsiveness to treatment of other parameters, such as DLSV, remains inconsistent throughout the literature (Bouça-Machado, Jalles, et al., 2020; Polhemus et al., 2021). Accordingly, considering the whole walking profile of our cohort (reduction of step time, stride time and DLS while walking slower in this DT walking-cognitive condition), patients with lower performance in EF and divided attention appear to walk more cautiously after treatment and compared to patients with better performance in EF and divided attention, especially under DT with additional cognitive demand. On the other hand, patients with higher global cognitive performance had an increased gait speed, but showed also less reduction in step time, while patients with lower global cognitive performance showed more decreased gait speed after treatment. This association between lower global cognitive performance and reduced gait speed in PD was also found under ST in another recent cross sectional study in a cohort of people with PD (comparable to our cohort with regard to age, global cognitive performance also measured with the MoCA and severity of motor symptoms measured with the MDS-UPDRS III but not acutely hospitalized, (Shearin et al., 2021). Furthermore, similar results were obtained in a study on targeted DT training for patients with PD, where patients with lower cognitive performance also showed a lower increase in gait speed (Strouwen et al., 2019). In addition, a higher level of depressive symptoms and more severe motor symptoms contributed to less extent, but in the same direction, to the change in DLSV and ASYM under ST walking conditions, and the same was true for higher FOF and gender with regard to the change in gait speed, stride time and DLS, under DT walking-cognitive condition. The more complex DT walking conditions could not be performed by more severely affected patients in our cohort. Therefore, further investigations are needed to validate the results of this study.

Overall, the results of the regression analyses show a ceiling effect in patients with higher performance in EF and divided attention as well as higher global cognitive performance, and with lower FOF, less depressive symptoms and less severe motor symptoms change less in their walking performance after ERGCT. This is comparable with results of another study in patients with advanced PD, that identified better mental state as determinant factor for long-term treatment effects of physical therapy training on physical activity (Nieuwboer et al., 2002).

The additional analysis performed in our study regarding significant differences in walking performance between the acute medical admission and at the end of the two-week treatment also indicated an overall tendency to decrease swing time in both DT conditions. In addition, although there were no significant changes in spatio-temporal walking parameters in both DT conditions as well as in walking with normal pace, there was also no deterioration in walking performance. Furthermore, when forced to walk in a fast pace, patients tend to show an increased number of steps and DLS after ERGCT, while their gait speed remains similar after treatment. Because fast walking corresponds to a higher level of motor difficulty, the results suggest that this group of patients cannot adequately compensate for the problems associated with faster walking. A comparison of treatment effects between the different walking conditions showed a significantly greater reduction in stance time, DLSV, and STV under DT than under ST. This finding might be explained by the described positive effect of external cueing in patients with PD, where the respective additional task corresponds to a rhythm generator (Ginis et al., 2017). Future studies with larger cohorts should consider this aspect in a detailed and sufficient individualized treatment protocol.

Therefore, our results indicate that two weeks of ERGT can modulate walking impairment of advanced PD in acutely hospitalized patients. However, pre-existing cognitive impairments, especially deficits in EF and divided attention seem to limit this effect. Therefore, for patients with pronounced cognitive and affective non-motor symptoms (i.e. high level of depressive symptoms and FOF), a different therapeutic framework than ERGT may be required to adequately address these symptoms and their influence on walking impairments. To our best knowledge this is the first study to analyze the change of several IMU-based spatio-temporal walking parameters after this sort of treatment in this vulnerable cohort with regard to the impact of pre-existing non-motor symptoms on treatment success. Other studies focused on standardized training protocols for such as DT training or external cueing (Geroin et al., 2018; Ginis et al., 2017; Strouwen et al., 2019), used longer intervention intervals and settings other than early rehabilitation (C et al., 2021; Geroin et al., 2018; Ginis et al., 2017; Nieuwboer et al., 2002; Serrao et al., 2019; Strouwen et al., 2017, 2019), excluded patients with advanced PD and/or cognitive impairment (C et al., 2021; Geroin et al., 2018; Ginis et al., 2017; Nieuwboer et al., 2002; Serrao et al., 2019; Strouwen et al., 2017, 2019), did not examine DT walking conditions (Serrao et al., 2019) and mainly calculated group comparisons between different training groups or individuals with PD and healthy controls, which addresses different scientific questions (C et al., 2021; Geroin et al., 2018; Ginis et al., 2017; Serrao et al., 2019; Vervoort et al., 2016). There is currently insufficient knowledge about this and, accordingly, there are no specific recommendations in rehabilitation guidelines nor sufficient information of treatment efficacy (Dietrichs & Odin, 2017; Nonnekes & Nieuwboer, 2018).

Limitations

First, acute factors of illness (e.g., infections, worsening of PD or other symptoms, and recent fall events.) may influence the overall condition of the patients, which was not controlled for in this study. However, due to the requirement of special attention in treatment along with their health condition, we argue that a specific investigation of this vulnerable cohort is justified. Second, due to capacity reasons and increased motor difficulty of the tasks, the number of participants decreased with increasing difficulty of the tasks. Therefore, more severely affected patients may not have performed more complex walking tasks and so the comparability of the tasks is limited. Furthermore, due to the integration into a comprehensive movement protocol (Geritz et al., 2020) randomization of the tasks was not possible for reasons of feasibility and error reduction during the examination. We argue that the decreased subject number for successful performance in tasks with higher cognitive and motor complexity can be taken as an additional indication that patients with advanced PD can less likely master those complex (but still required in everyday life) demands. Third, reporting detailed information about the content of single sessions of therapy was not possible here, as the study was implemented in a clinical routine of a neurogeriatric ward for acute and early rehabilitation according to personalized treatment plans based on the patients' needs. Therefore, the adaption of the content of the therapeutic sessions was not intended in the study protocol (Geritz et al., 2020) and no specific statements regarding treatment efficacy are possible from this analyses. Nonetheless, skilled individualized treatment is in our point of view a most sufficient way to address the needs of this vulnerable cohort in everyday medical care and should therefore be a point of focus in treatment studies. Fourth, patients with walking aids, FOG and dyskinesia were also included, but a more granular analysis of their influence on change in walking performance was not possible due to the small sample size. We still included these patients since they are a common part of our neurogeriatric PD cohort and to increase the sample size as much as possible. Future studies should focus on these aspects specifically with larger cohorts of patients with advanced PD. Fifth, in order to collect motor data while patients were at their best possible motor condition, patients were tested during the medication "ON" state. Therefore, no conclusions regarding the non-medicated ("OFF") status can be drawn from these analyses. Sixth, this study assesses general cognitive performance, as well as EF and divided attention; however, it should be noted that other specific cognitive domains were not assessed. Finally, neither healthy control subjects nor age-matched inpatients with other diseases as controls were included at this stage, which would provide more direct conclusions regarding pathology-specific aspects as well as differences in treatment efficacy.

Conclusion

This study provides new insights regarding the influential value of cognitive and affective non-motor symptoms for the change in spatio-temporal walking parameters in acutely hospitalized patients with advanced PD after two weeks early geriatric rehabilitation. Therefore, these results help close a gap in knowledge regarding relevant characteristics of this vulnerable group of patients, that need to be considered for planning and prognosis of individualized treatment of walking performance. There is evidence that, especially EF and divided attention (and global cognitive performance, together with FOF, depressive symptoms and severe motor symptoms) can be associated with change in walking performance (in particular ASYM and gait speed) under both ST and DT walking conditions. After treatment, patients with advanced PD and higher performance in EF and divided attention show reduced ASYM under ST. On the other hand, patients with lower performance in EF and divided attention in this cohort seem to have a more cautious walking pattern (characterized by reduced step time, stride time, and DLS while walking slower) when an additional cognitive task requires to split attention, while there is a ceiling effect for patients, that are less affected by deficits in global cognition, EF and divided attention, depressive symptoms and FOF. This might be a protective aspect with regard to the acute medical condition and the expected progression of walking problems without treatment at this stage of the disease. Thus, for the implementation of individualized multimodal care in an early rehabilitative neurogeriatric setting, it remains essential to consider cognitive and affective non-motor symptoms. Future studies need to take these factors into account and should focus on the development of algorithms to address the individual needs required due to differences in non-motor characteristics in an evidence-based manner. Furthermore, our results indicate, that even a short-term early geriatric rehabilitation can help to delay the progression of walking disabilities in acutely hospitalized patients with advanced PD. Therefore, it is an essential brick in the treatment concept for this vulnerable patient group and their complex disease.

7 General discussion

A better understanding of the complex link between EF and divided attention and mobility, and its possible influence on treatment effects is of fundamental importance for patients affected and their healthcare professionals. As previously stated, aging is associated with impairments in EF and mobility and is also a primary risk factor for the development of neurodegenerative diseases such as PD (see Chapters 1 and 2). Therefore, the aim of this dissertation was to improve the understanding of that link in healthy older adults and patients with advanced PD. On the one hand, this can be key to monitoring age- and disease-related progression of deficits and thus to initiate early therapeutic interventions with the aim to maintain individual ability and sustainability in daily life of affected individuals for as long as possible. On the other hand, this understanding is important for the management and optimization of multimodal individualized treatment approaches in the field of geriatrics. In this chapter, the main findings of the three studies (Chapters 3; 5 and 6) are summarized, the three overarching scientific questions of this dissertation are answered and placed in the context of the framing ComOn study (Chapter 4). This is followed by a discussion of implications for the management of advanced PD in the context of individualized multimodal geriatric treatment that are derivable from the presented results, the limitations of this work are pointed out, and an outlook for possible further research approaches in the field is given.

Main findings

Initially, it was investigated in a systematic literature search whether possible effects of CCT on the mobility of healthy older adults are supported according to the current state of research in Chapter 3. The hypothesized carryover effect of CCT on different domains of mobility (derived from the evidence for a link between cognition and mobility presented in Chapter 2) could not be confirmed by the results of the included studies. This might be due to the small number of studies as well as the heterogeneity in design and study quality, which also did not allow for further quantitative statistical analysis. However, in six of the seven studies examining walking performance under DT conditions, the respective CCT training groups were found to improve in at least one of the investigated walking parameters under DT, and this improvement was more pronounced than in the respective (active) control groups (de Bruin et al., 2013; Fraser et al., 2017; Pichierri et al., 2012; Schoene et al., 2013; Smith-Ray et al., 2014, 2015; van het Reve & de Bruin, 2014). Thus, healthy older adults might indeed achieve compensatory benefits for difficulties in walking performance from combined CCT and physical training in DT walking situations.

The subject of the second scientific question of this dissertation was to investigate to what extent a link can be shown between EF and divided attention (measured with the ΔTMT) and the straight walking performance (measured with sensor-based spatio-temporal walking parameters) as well as occurring DTC while walking (see Chapter 5). This was examined under both ST and DT walking conditions in advanced PD at acute inpatient admission to a neurogeriatric ward. The results did not support the hypotheses that reduced performance in EF and divided attention is associated with either reduced straight walking performance under ST and DT or with incident DTC while walking. Nonetheless, the results suggest that underlying attentional processes are involved in walking under DT, because the occurrence of DTC while walking indicate the additional attentional demand caused by a secondary cognitive task is particularly detrimental to step time variability. There were no significant linear associations between TMT performance and the selected walking parameters or their DTC in any of the four walking conditions. In addition, the results suggest, with overall moderate levels of evidence (BF_{10} between 0.12 and 0.18), that TMT performance does not contribute into the selected parameters for the profile of straight walking performance at admission in this vulnerable cohort, considering the severity of motor symptoms, age, and the utility of a walking aid.

Chapter 6 addressed the third main scientific question of this dissertation. Here, the link between performance in global cognition as well as in EF and divided attention (together with affective non-motor symptoms of depression and fear of falling) and the change in straight walking performance under ST and DT after two weeks of ERGCT in patients with advanced PD was investigated. The results support with moderate to high levels of evidence (BF_{10} between 3.51 and 29.9) the hypothesis that reduced performance in global cognition as well as in EF and divided attention (together with occurrence of depressive symptoms and fear of falling) are associated with less changes in some of the investigated walking parameters (namely ASYM, gait speed, step time, stride time and DLS) under both ST and DT. Thus, cognitive performance, and particularly EF and divided attention, can be considered as limiting factors on the treatment-related improvement of straight walking performance. After treatment, patients with higher TMT performance walk less asymmetrically at both self-selected and fast paces under ST. Moreover, the ceiling effect under DT with additional cognitive demand suggests that the progression of gait impairments of patients with higher global cognitive and TMT performance is slowed during treatment. Conversely, the walking profile (with reduction of gait speed, step time, stride time and DLS) in the same DT condition suggests a more cautious walking behavior of patients with lower TMT performance after treatment.

The Bigger Picture: Achievements from the ComOn study

The scientific questions addressed in this dissertation are part of the multi-center exploratory observational ComOn study, which was designed to comprehensively characterize a large cohort of geriatric patients and evaluate their individualized geriatric treatment. The subcohort of patients with advanced PD investigated here can be regarded as a suitable model in this respect. This can be derived from the neuropathological mechanisms of aging and PD (Burke & Barnes, 2006; Owen, 2004) as well as disease-specific motor and non-motor deficits (such as impaired mobility and cognitive function) in conjunction with age-related symptom-reinforcing processes. These occur as frequent neurogeriatric syndromes and account for a large proportion of the need for treatment (Jacobs et al., 2020; Maetzler et al., 2019; Maetzler, Grond, et al., 2016). The results from this dissertation serve as a contribution to achieve the three overarching major goals of the ComOn study presented in Chapter 2.

Of the total 167 patients with PD included by August 2021, 41% were able to complete the assessment extended by the TMT and the quantitative gait analysis at least in the ST walking condition at self-selected pace on admission, and 28% did so before discharge. Thus, the first mayor study aim of exploring quantitative markers of deficits in mobility (using modern technology) and cognition (using established neuropsychological tests) as well as their implementation into the inpatient daily routine of an extended CGA was feasible. The additional information gained on walking profiles and cognitive (and affective) non-motor symptoms allows a more comprehensive description and classification of the existing limitations of this geriatric PD cohort. Based on the comprehensive approach of using sensor-based spatio-temporal walking parameters (calculated using a validated algorithm for step detection in PD (Pham, Elshehabi, Haertner, Del Din, et al., 2017)), it could be shown that straight walking performance over 20m varied in certain aspects depending on the condition (Figure 5.1). Under DT, patients tended to walk more slowly, asymmetrically, and with prolonged DLS. This profile is consistent with other findings of studies on walking performance under DT in PD (Plotnik et al., 2011; Rochester et al., 2008; Varalta et al., 2015) and may be considered a potential risk factor for falls that needs to be addressed in terms of therapeutic management (Bouça-Machado, Jalles, et al., 2020; Polhemus et al., 2021).

As discussed in detail in Chapters 5 and 6, TMT performance could not be related to walking performance (neither under ST nor DT) or DTC while walking as measured by spatio-temporal parameters. These results are in line with PD studies with regard to ST and DT walking conditions (Sousa et al., 2021; Varalta et al., 2015) but differ from another study with a comparable cohort with regard to DTC while walking, which identified the TMT performance as one of the main predictors (Plotnik et al., 2011). Nonetheless, despite the lack of significant differences in global cognitive as well as TMT performance, age and the other described clinical characteristics across walking conditions (Table 5.1 and Table 6.1), the occurrence of DTC while walking also suggests that this task-dependent variability in walking performance is attributable to more fundamental neuropathological processes involving the fronto-striatal circuit (Maidan et al., 2016; Owen, 2004; Yildiz & Beste, 2015). In addition, TMT performance was shown to have a relevant limiting effect on the change in walking performance after treatment, in addition to global cognitive performance, disease severity and affective non-motor symptoms (depressive symptoms, fear of falling). These results are also in line with previous treatment studies showing that patients with moderate cognitive and motor impairments achieve the greatest treatment benefit (Nieuwboer et al., 2002; Nonnekes & Nieuwboer, 2018; Stegemöller et al., 2014; Strouwen et al., 2019).

Treatment evaluation in the inpatient geriatric setting was not the main focus of this dissertation. Instead, the purpose was to identify a baseline profile of clinical characteristic of patients with advanced PD and their prognostic value on the outcome of inpatient geriatric treatment in terms of a change in straight walking performance. Nevertheless, the secondary analysis on the change in straight walking performance over 20m described shortly in Chapter 6 (Suppl.-Table 6.1, Suppl.-Figure 6.1) offers first insights with regard to treatment outcome after ERGCT. In the mere comparison of mean values across the entire group between the two examination time points, there are only isolated trends and changes across the four conditions. Thus, after treatment, patients tended to take more steps and to show an increased DLS under ST fast pace, and they showed shorter swing time under DT. As already discussed in Chapters 2 and 6, the interpretation of individual sensor-based walking parameters is limited (Bouça-Machado, Jalles, et al., 2020; Mirelman et al., 2019; Polhemus et al., 2021). In a nutshell, a descriptive observation of the direction of change after treatment shows that the overall values under DT seem to correspond to a stabilization of the walking profile. At the same time, there is no direction of change under ST normal pace, and under ST fast pace even an opposite shift can be observed. More in-depth analyses of the data available here are necessary. Proposals for this are described in more detail in the Outlook section.

Implications for optimizing individualized treatment management of advanced PD in early geriatric rehabilitation

From the results presented, a number of aspects can be derived that can contribute to the optimization of acute inpatient early rehabilitation of geriatric patients with PD, both at the diagnostic and therapeutic level. These are presented below.

Individualized extension of the CGA based on indication

The CGA has been established for years as an integral part of the geriatric treatment routine to ensure optimal indication and treatment planning as well as preventive measures in the care of older patients (Ellis et al., 2017; Ellis & Langhorne, 2004; Parker et al., 2018). The requirements for the CGA are subject to constant monitoring and updating. In Germany, the publication of the new S3 guideline for CGA has been announced for autumn of 2023 (Denkinger, 2023). This guideline aims to review and assess the evidence, efficacy and application of CGA in different clinical settings and patient cohorts. As described in Chapter 1, CGA already measures relevant characteristics of geriatric patients in the domains of mobility, cognition and mood (Ellis et al., 2017; Krupp et al., 2022). The objective of the announced new guideline implies that beyond the CGA, disease- and syndrome-specific aspects have to be considered for further clarification. In this respect, the findings of this dissertation can contribute that an extension of the CGA before and after treatment including further neuropsychological tests like the TMT as well as quantitative sensor-based movement analysis is feasible and provides important additional information on disease-specific characteristics and their potential limiting impact on treatment outcome. For example, walking performance in the CGA is usually assessed using established mobility tests over short distances (e.g., 4m in the SPPB or 3m in the TUG, see Chapter 4) and under ST. Our results suggest that for a dedicated assessment of the walking profile of patients with advanced PD, walking performance has to be considered under both ST and DT, which is consistent with the literature (Bouça-Machado, Jalles, et al., 2020; Mirelman et al., 2019; Polhemus et al., 2021; Yogev-Seligmann et al., 2008). In addition, reliability of spatio-temporal walking parameters in older adults with primary neurological diseases over a distance of 20m seems to be higher than over shorter distances (e.g. 4m in the SPPB) as shown elsewhere using also ComOn data (Hansen et al., 2022).

As mentioned in the previous chapters, there is still a gap of knowledge about the impact of cognitive and affective non-motor symptoms on the treatability of gait disorders in patients with advanced PD (Mirelman et al., 2019). In a recent two-year follow-up study of patients with PD, the global burden of non-motor symptoms (such as attention-related cognitive deficits) was shown to increase both over time and compared with healthy controls (Santos-García et al., 2021), and was associated with reduced quality of life (Titova et al., 2017). Recommendations have been made for quite some time with respect to consider non-motor symptoms more strongly in the definition of the advanced stage of PD and, accordingly, to routinely map them in a more sophisticated manner in the diagnostic workup (Chaudhuri et al., 2006; Titova et al., 2017). The results of this dissertation suggest that patients with advanced PD suffering from reduced EF performance are limited in their benefit with respect to changes in walking performance after ERGCT. Thus, these results underline the necessity of integrating detailed diagnostics of specific cognitive deficits in the geriatric treatment setting beyond the measure of global screening scales usually used in the CGA (Krupp et al., 2022). However, the reduction of the sample size in the more complex walking conditions and the missing TMT values for individual patients (Tab.6.1) also indicates that the expansion of the CGA has limits. In fact, patients with more severe motor and cognitive deficits have difficulties coping with more complex tasks. Furthermore, motivational aspects must also be considered when planning the assessment. Thus, an extended CGA as well as the treatment should be adapted to the individual abilities of the patients (e.g., by prioritizing the task order and alternative auditive DT paradigms that are also feasible using a walking aid (D’Cruz et al., 2022)).

Optimizing treatment based on individualized prognostic characteristics

The approach of individualized multimodal therapy has long been a core component in geriatrics (Swanson & Robinson, 2020). The multiprofessional team can rely on established treatment methods and guidelines for the individual therapeutic areas, e.g. in physiotherapy for PD (J. Domingos et al., 2018). Nevertheless, to date, there is a lack of holistic evidence of the overall concept of individualized treatment and, consequently, a lack of sufficient knowledge about the predictive factors influencing treatment efficacy (Nonnekes & Nieuwboer, 2018). However, it was consistently shown by both our and other study results in patients with PD that this prognostic knowledge is essential in order to optimize treatment of complex disease constellations (Geroin et al., 2018; Hartelt et al., 2020; Nieuwboer et al., 2002; Scherbaum et al., 2022; Strouwen et al., 2019). The results of this dissertation serve as a first insight into which aspects should be particularly considered in the planning and modification of multimodal individualized treatment for patients with advanced PD. For example, patients with moderate motor symptoms and fewer cognitive deficits responded best to multimodal individualized treatment regime (including pharmacological symptom management and deficit-related exercises in therapy sessions), which was also shown in our cohort (see Chapter 6). Furthermore, the factors that may have an impact on treatment outcome are not necessarily directly related to the initial medical condition at inpatient admission. In our cohort, the severity of motor symptoms was a relevant factor for impaired walking performance at admission, whereas deficits in EF and divided attention did not seem to play a critical role (see Chapter 5). However, these cognitive deficits were important for predicting the change in walking performance after treatment (see Chapter 6). Specific treatment contents of ERGCT, however, were not the subject of this dissertation (see Chapter 6). Therefore, further studies are needed that focus on specific treatment parameters in order to develop sophisticated optimization proposals for individualized treatment.

As mentioned in Chapter 1 an increase in the need for inpatient treatment due to sociodemographic trends is expected (BARMER, 2017; Becker & Achterberg, 2022; Tönges et al., 2019). On the other hand, access to multimodal complex treatment with a specialized PD focus is regionally different and sometimes limited in Germany (D. Richter et al., 2019). Therefore, it seems reasonable that neurological expertise and knowledge of treatment concepts for PD-specific limitations (such as DT walking training, targeted EF and attention training, and combined cognitive and physical training) should be specifically integrated into the individualized approaches of ERGCT (Jacobs et al., 2020; Michels et al., 2022; Nonnekes & Nieuwboer, 2018). Today and in the years to come, health policy faces more than ever the challenge of finding appropriate and at the same time cost-effective treatment options for the aging population in general and for patient groups with complex disease constellations in particular (Becker & Achterberg, 2022). To this end, it is crucial to identify perfect matches between patient groups and treatment setting to ensure optimal individualized care (Achterberg et al., 2019). To achieve this objective effectively, the consideration of specific prognostic characteristics, not only for the deficits to be treated and their improvement, but also other functionality-associated parameters according to the domains of the ICF model is essential (Kudelka et al., 2022; Tosserams et al., 2020; World Health Organisation, 2001). Additionally, more sophisticated analysis methods (e.g., machine learning approaches or Bayesian Networks) can be used to explore the use of these specific prognostic markers in terms of describing profiles as comprehensively as possible, identifying risk and protective factors, and uncovering possible underlying interactions of mobility and cognition (L. Costa et al., 2016; Nilashi et al., 2018; Sood et al., 2023).

Integration of new technologies into clinical and home treatment contexts.

In this dissertation, new technological tools were explored with regard into the framework of routine clinical diagnostics (Chapters 4 to 6) and in treatment use (Chapter 3). The findings of further ComOn study data on IMUs (Braun et al., 2022; Hansen et al., 2021, 2022; Welzel et al., 2021) are in line with the advantages and disadvantages already described in other studies and lead to the conclusion that the implementation of wearable sensor technology in routine diagnostics is a useful addition ((Austen, 2015; Bouça-Machado, Jalles, et al., 2020; Dorsey et al., 2018; Gravitz, 2016; Herssens et al., 2018; Maetzler, Klucken, et al., 2016; Polhemus et al., 2021), see Chapters 2 and 6). Nevertheless, further validation studies are needed to increase the sensitivity, specificity and clinical interpretability of the obtained parameters.

With regard to cognitive trainings, computer-based programs, e.g. exergames, gain attraction in both clinical and home settings (Meulenberg et al., 2022; Pichierri et al., 2011). Those variants of CCT offer the possibility to link established cognitive training paradigms with mimics of real-life situations and at the same time to provide direct feedback to patients and practitioners. However, the benefit of CCT on mobility has not yet been sufficiently investigated and a possible carryover effect explored in this dissertation could not be identified on the basis of current literature. However, the results presented in Chapter 3 might be promising because positive CCT effects on spatio-temporal walking parameters were shown in four of the (good quality) studies with active control groups (de Bruin et al., 2013; Fraser et al., 2017; Pichierri et al., 2012; van het Reve & de Bruin, 2014). In all of these four studies, CCT was combined with the same physical training as was provided for the control group. In other studies was shown that particularly reduced EF performance (related to both aging and neurodegenerative diseases) is associated with problems in everyday life DT walking situations (Herman et al., 2010; Milman et al., 2014; Pichierri et al., 2011; Plummer et al., 2015). Therefore, CCT may offer a new additional treatment approach for both healthy older adults and geriatric patients with neurological disorders. However, as the results presented in this dissertation are neither generalizable nor transferable to specific patient groups, further studies need to be conducted in larger cohorts and in both home and clinical settings. Such studies also require an in-depth discussion of possible methodological and statistical artifacts that might be misinterpreted as putative intervention effects, as has recently been described for (non-evident) transfer effects between cognitive outcomes (Gobet & Sala, 2023). A promising approach to the implementation of CCT for patients with MCI has recently been published (Manser et al., 2023). The authors suggest that individual adaptation of CCT content to the requirements and needs of patients is particularly relevant for the motivation and the training efficacy. Particularly in the light of the pandemic-related restrictions of the last three years and the associated cuts in face-to-face care with rehabilitative services, CCT can be an important adjunct for new remote treatment concepts beyond the clinical setting. However, the necessary overarching structure for telemedicine rehabilitation, however, is still under development (Bloem et al., 2020; Meulenberg et al., 2022).

Limitations

The limitations of the ComOn study (the vulnerable multimorbid patient cohort, no standardized treatment, the risk for technical problems, the demanding scope of the assessment; see Chapter 4) as well as those of the sub analyses in the PD cohort (acute medical situation, no healthy control cohort, the task-dependent drop-out rate under DT, the heterogeneity with regard to motor complications and reliance on a walking aid, lack of information on the content of individual treatment sessions; see Chapters 5 and 6) have already been described in detail. In addition, three overarching limitation aspects of this dissertation shall be discussed at this point.

Mobility is a broad concept that contains a multitude of aspects. In this dissertation, the focus was almost exclusively on spatio-temporal parameters of straight walking performance. Other aspects of walking performance (e.g., turning and balance) or mobility (e.g., transfer behavior) were only considered in the literature review (Chapter 3), but were not part of further analyses. Accordingly, the conclusions drawn regarding walking performance in patients with advanced PD are limited to this aspect. However, it can be argued that straight walking performance under ST as well as DT conditions plays a significant role in the expression of gait disorders in PD (Mirelman et al., 2019) and therefore justifies this focus.

Furthermore, the straight walking performance was measured based on data from a single IMU at the lower back, which limits the interpretation of the results. In order to generate a more comprehensive movement profile and, if necessary, to be able to assign changes in the frequency signal more easily to, for example, occurring motor complications (FOG, dyskinesias) or also contextual factors during the measurements (suddenly occurring obstacles on the route, general exhaustion of the patient), the addition of further IMUs at other body parts could be useful. On the one hand, however, the focus was on the simplest possible handling in the clinical everyday context. On the other hand, the choice was made for these IMU data because the algorithm used for step detection in PD was tailored to the analysis of sensor-based data on the lower back (Pham, Elshehabi, Haertner, Del Din, et al., 2017).

EF performance was operationalized exclusively by the TMT. Accordingly, components of this cognitive functional domain (Miyake et al., 2000) that are not captured by the paradigm of the test were not considered and the focus was mainly on cognitive flexibility and divided attention. This leads to limitations in the methodological comparability with other studies that investigated similar scientific questions but used other cognitive paradigms (Rochester et al., 2008; Stegemöller et al., 2014) as well as the generalizability of the results presented in this dissertation. The TMT was selected as an established reliable and valid neuropsychological instrument in order to meet the requirement of the ComOn study to extend the CGA with tools that are feasible in a simple and time-efficient manner in clinical routine.

Where can we go from here: A view into the future of geriatric research

As discussed in the upper sections, an individualized extension of CGA and the use of new technological approaches seems reasonable. This is not limited to computer-based solutions for treatment or quantification of movement. Digital solutions for classical paradigms are also increasingly available in the field of neuropsychological assessments. The first steps in clinical diagnostics were already taken more than ten years ago, for example, with computer-based test batteries such as the TAP ((Zimmermann & Fimm, 2012), see Chapter 4). Newer solutions are becoming increasingly user-friendly and adaptable, and can be used as applications on mobile devices (Koo & Vizer, 2019). These digital variants of established test procedures such as electronic MoCA or digital TMT also allow standardized quantification of additional parameters of interest that were previously not detectable in paper-pencil versions or were only detectable via clinical impression (Berg et al., 2018; S. Y. Park & Schott, 2020; Wallace et al., 2019). Further validation studies and the quantification of normative data in healthy older adults and patient cohorts are needed for the use of these test procedures in clinical individual diagnostics. In the future, digital cognitive assessments could make a significant contribution to the detection of specific prognostic markers, the need for which has already been outlined for improved patient-oriented healthcare earlier in this chapter.

Evaluating the efficacy of individualized treatment faces a number of challenges (see Chapter 2). One main problem is that non-standardized treatment complicates the objective recording of single treatment session content. Accordingly, conclusions about actual treatment effects are limited with respect to changes in the symptom domains studied Therefore, and in order to gain a more precise understanding of the mechanisms of action, to identify potential confounding factors during training and to develop patient-oriented treatment adaptations, monitoring is required during the treatment sessions. (Stefanakis et al., 2022). A key requirement for such monitoring is to avoid interference with the treatment, since otherwise the monitoring becomes a confounding factor itself. Here, too, technological solutions such as IMUs and CCT programs offer a viable option. The data required to quantify the progress of treatment is collected simultaneously, can be integrated directly into the treatment process and sometimes allows direct feedback for both patients and therapist. The data collected in this way also provide an important complement to the prognostic markers collected in the clinical assessment and can serve as relevant decision support for further care beyond the inpatient geriatric setting.

In addition to higher resolution of prognostic clinical markers and profiles and deeper observation of individualized treatment, the context in which patients live and move should be increasingly focused on in geriatric research. Individuals often perform differently in clinical testing under supervised, standardized conditions than in their usual environment (Warmerdam et al., 2020). Accordingly, there is a bias with regard to the relevance to everyday life of parameters collected in a clinical examination. Difficulties that lead to restrictions in coping with everyday situations can sometimes not be adequately mapped in the clinical-diagnostic setting and with classic methods. Quantitative sensor-based measuring instruments offer the possibility to record the performance of patients beyond the scope of the inpatient stay and possibly reveal interferences of cognitive deficits with everyday movements. This has been already implemented in the ComOn study but was not subject of this dissertation. These data could provide insight into long-term outcomes following geriatric treatment as well as potential risk factors that necessitate hospitalization in the first place. In the light of demographic changes and associated demands of health care for older adults, a conceptual change of geriatric care landscape in Germany with even closer inclusion of the patients' everyday settings seems to point the way forward (Becker & Achterberg, 2022).

Conclusion

This dissertation contributes to a better understanding of the link between mobility and cognition, especially EF performance, and its influence on training in healthy older adults and individualized treatment in patients with advanced PD. Based on available studies in the literature on effects of CCT on mobility in healthy older adults, the hypothesized carryover effects could not be confirmed. Whether and to what extent isolated positive CCT effects are transferable to geriatric patient groups such as patients with advanced PD needs to be investigated on the basis of larger-scale studies and meta-analyses. The framework of this dissertation was the observational multi-center ComOn study. In this study, a large sample of geriatric patients was examined using a comprehensive assessment protocol, implementing new technological approaches in an acute geriatric inpatient clinical routine and extending the established CGA with quantitative parameters. In the subcohort of acutely hospitalized patients with advanced PD, it was shown that patients with more severe motor symptoms (who were older and in need of a walking aid) seem to suffer from more reduced walking performance, particularly under DT with an additional cognitive task demanding an attentional split. Furthermore, performance in EF and divided attention (measured with the ΔTMT) could not be identified as a relevant factor for straight walking performance under either ST or DT or for the occurrence of DTC while walking. Conversely, the results from chapter 6 show that both reduced TMT and global cognitive performance (together with increased FOF and more pronounced depressive and motor symptoms) are limiting for the change in walking performance under ST and DT in terms of improvement after two weeks of ERGCT in advanced PD. At the same time, disease-related progression of impaired walking performance appears to be delayed after treatment in patients less affected by these cognitive and affective non-motor symptoms. Together, the results of this dissertation show that an extension of the CGA with quantitative cognitive and walking parameters (using new technological instruments) is feasible and useful, that in advanced PD attentional processes play a role especially in DT situations, and that deficits in cognitive performance (especially in EF) seem to limit a beneficial treatment outcome in terms of changes in walking performance after multimodal individualized treatment. As such these findings represent an integral step in the understanding of relevant prognostic markers and pave the way for future research on individualized treatment of patients with advanced PD as well as in the field of patient-oriented geriatric care.

8 Summaries

Deutsche Zusammenfassung

Der demografische Wandel stellt das Gesundheitssystem vor die besondere Herausforderung, eine immer älter werdende und länger lebende Bevölkerung zu versorgen. Alter gilt als primärer Risikofaktor für die Entwicklung von neurodegenerativen Erkrankungen (Dong et al., 2016; Hou et al., 2019). Die Geriatrie verfolgt seit langem einen ganzheitlichen Ansatz bei der Diagnose und Behandlung von Einschränkungen und Krankheiten bei älteren Menschen. Ein umfassendes geriatrisches Assessment (CGA) und eine multimodale individualisierte Behandlung sind die Kernbestandteile dieser medizinischen Disziplin (Ellis & Langhorne, 2004). Dennoch ist die Studienlage zur Wirksamkeit einer individualisierten Behandlung in der Geriatrie noch unzureichend. Zu den häufigen geriatrischen Syndromen, die auch bei neurodegenerativen Erkrankungen auftreten, gehören Beeinträchtigungen der Mobilität und der Kognition (Jacobs et al., 2020). Die Prävalenz von Gangstörungen liegt bei etwa 35 % in der Altersgruppe von Menschen ab 70 Jahren und steigt mit zunehmendem Alter weiter an (Verghese et al., 2006). Die daraus resultierenden Stürze und ihre oft schwerwiegenden Folgen (z. B. schwere Verletzungen, Krankenhausaufenthalte und Tod) können die Lebensqualität und Autonomie erheblich beeinträchtigen. Patient:innen mit fortgeschrittenem Morbus Parkinson (PD) sind besonders betroffen von Mobilitätseinschränkungen, wie der Gehfähigkeit, und Defiziten in kognitiven Funktionen. Insbesondere betroffen ist die Leistung in den exekutiven Funktionen (EF, sog. höhere kognitive Kontrollprozesse um Aufmerksamkeit aufrechtzuerhalten und zielgerichtet zu lenken, logisch zu denken, zu planen und sich an die wechselnden Anforderungen des Alltagslebens anzupassen, (Diamond, 2013)). Insbesondere beim Gehen in sogenannten Dual-Task-Situationen (DT, Gehen unter zusätzlicher kognitiver Anforderung) zeigen Patient:innen mit PD im Vergleich zu gesunden älteren Personen eine verminderte Gehfähigkeit. Darüber hinaus sind die komplexen Anforderungen mit sogenannten *Dual Task Costs* (DTC) verbunden. DTC gelten als ein Indikator für einen Kapazitätsverlust in der jeweiligen Domäne (hier des Gehens, (Hobert et al., 2011; Mirelman et al., 2019; Plotnik et al., 2011)). Die Annahme, dass es einen Zusammenhang zwischen Gehfähigkeit und EF-Leistung gibt, scheint sinnvoll angesichts der Beteiligung fronto-striataler Hirnstrukturen an beiden Prozessen, die sowohl alters– als auch krankheitsbedingten Veränderungen unterliegen (Hupfeld et al., 2022; Stuart et al., 2019; Yogev-Seligmann et al., 2008). Die Ergebnisse der Studien, die sich mit diesem Zusammenhang beschäftigen, sind jedoch heterogen und es gibt kaum Studien zum fortgeschrittenen Stadium von PD (Mirelman et al., 2019). Der Einsatz von tragbarer Sensortechnik, sogenannten *Inertial Measurement Units* (IMUs), ermöglicht eine differenziertere Analyse des Bewegungsprofils in Bezug auf spatio-temporale Gangparameter und die Unterscheidung von physiologischen und pathologischen Bewegungsmustern wie bei PD (Bouça-Machado, Jalles, et al., 2020; Del Din et al., 2021; Polhemus et al., 2021). Allerdings unterscheiden sich die jeweiligen Parameter erheblich in ihrer methodischen Qualität und klinischen Interpretierbarkeit. Es mangelt auch an Wissen über die Relevanz des möglichen Zusammenhangs zwischen Mobilität und EF-Leistung als prognostischem Marker für den Behandlungserfolg von individualisierter Therapie. Dementsprechend fehlt es auch an Leitlinien, die darüber Aufschluss geben, wie welche individualisierte multimodale Behandlung am besten auf welche Klientel zugeschnitten werden kann (Becker & Achterberg, 2022; Nonnekes & Nieuwboer, 2018).

Ziel dieser Dissertation war es, zu einem besseren Verständnis des Zusammenhangs zwischen Mobilität und Kognition (insbesondere EF) sowohl bei gesunden älteren Personen als auch bei Patient:innen mit fortgeschrittenem PD beizutragen. Zudem sollte untersucht werden, ob dieser Zusammenhang einerseits anhand der Effekte von computergestütztem kognitivem Training (CCT) deutlich wird. Andererseits wurde ein möglicher Einfluss dieses Zusammenhangs auf den Erfolg von individualisierter multimodaler Behandlung von Patient:innen mit fortgeschrittenem Parkinson in einem akutgeriatrischen Setting untersucht. Daraus ergeben sich drei Hauptfragestellungen: 1. Kann die Annahme eines positiven *carryover* Effektes von CCT auf Mobilitätsparameter bei gesunden älteren Personen anhand der aktuellen Literatur gestützt werden? 2. Steht die Leistung in den EF und der geteilten Aufmerksamkeit in Zusammenhang mit der Gehfähigkeit beim Geradeausgehen unter ST- und DT-Bedingungen sowie mit den DTC des Gehens von Patient:innen mit fortgeschrittenem PD? 3. Steht die Leistung in der globale Kognition, den EF und der geteilten Aufmerksamkeit in Zusammenhang mit der Veränderung der Gehfähigkeit beim Geradeausgehen unter ST- und DT-Bedingungen von Patienten mit fortgeschrittenem PD nach einer individualisierten frührehabilitativen geriatrischen Behandlung? Den Rahmen dieser Dissertation bildete die prospektive, observationale, multizentrische Studie "*Cognitive and Motor interactions in the Older population*" (ComOn, Kapitel 4). Die Kernpunkte der ComOn-Studie waren die Definition von quantitativen Markern mit klinischer Relevanz für motorische und kognitive Defizite, die Untersuchung eines Zusammenhangs zwischen motorischen und kognitiven Defiziten und die Bewertung des Gesundheitszustands sowie des Behandlungserfolgs einer zweiwöchigen frührehabilitativen geriatrischen Komplex-Behandlung (ERGCT). Hierzu wurde das CGA in der klinischen Routine einer geriatrischen Station um eine sensorbasierte quantitative Bewegungsanalyse mit dem IMU-System RehaCom® (Hasomed, Magdeburg) und eine umfangreiche Batterie von neuropsychologischen Tests und Fragebögen erweitert. Eingeschlossen wurden Patient:innen ab einem Alter von 50 Jahren oder älter, wenn sie die Indikation zur geriatrischen Behandlung erfüllten (Sieber, 2017). Die Patient:innen wurden bei stationärer Aufnahme (T1) und vor der Entlassung (T2) nach zwei Wochen ERGCT untersucht.

Für diese Dissertation wurden die Daten einer ComOn-Subkohorte von akut hospitalisierten Patient:innen mit fortgeschrittenem PD analysiert. Als relevante Domänen wurden die EF und geteilte Aufmerksamkeit mit dem Delta *Trail Making Test* (ΔTMT, TMT-B minus TMT-A) sowie die globale kognitive Leistung mit dem *Montreal Cognitive Assessment* (MoCA) erfasst. Die Gehfähigkeit wurde mit der am unteren Rücken der Patient:innen befestigten IMU unter ST- (mit schnellem und normalem Tempo) und DT-Bedingungen (Gehen und dabei Kästchen ankreuzen als motorische Sekundäraufgabe, Gehen und dabei Subtrahieren von 7er-Serien als kognitive Sekundäraufgabe) über 20 Meter gemessen. Die spatio-temporalen Gangparameter wurden extrahiert und die DTC während des Gehens wurden für jeden der Parameter berechnet. Als zusätzliche klinische Parameter wurden die Verwendung einer Gehhilfe erfasst, der Schweregrad der PD-spezifischen motorischen Symptome mit Hilfe der von der *Movement Disorder Society* überarbeiteten Version des motorischen Teils der *Unified Parkinson's Disease Rating Scale* (MDS-UPDRS III) und die Depressivität der nicht-motorischen Symptome mit Hilfe der Depression im Alter Skala (DIA-S) und die Angst vor Stürzen (FOF) mit Hilfe der *Falls Efficacy Scale* (FES-I) bewertet.

Zur Beantwortung der ersten Hauptfragestellung dieser Dissertation bezüglich eines *carryover* Effektes von CCT auf Mobilität wurden in einem systematischen Review elf bis einschließlich Juni 2017 veröffentlichte CCT-Interventionsstudien ausgewertet, die als Endpunkte Parameter der Mobilität bei gesunden älteren Personen (Gang, Gleichgewicht, Transferverhalten) untersuchten (Kapitel 3). Die Studienqualität wurde anhand der Kriterien der *American Academy for Cerebral Palsy and Developmental Medicine* (AACPDM) kategorisiert und war im Allgemeinen hoch (Level I und II). Mobilitätsparameter, für die in den eingeschlossenen Studien ein positiver CCT Effekt beschrieben wurde, waren die Schrittlänge unter DT und die Ganginitiierung. Aufgrund der geringen Anzahl von Studien und der starken Heterogenität bei der Definition und Auswahl der Mobilitätsparameter konnte der angenommene *carryover* Effekt des CCT auf die Mobilität jedoch nicht statistisch überprüft werden. Auch wenn einzelne Studienergebnisse andeuten, dass gesunde Ältere von CCT insbesondere in DT Situationen profitieren, sind hierzu weitere randomisierte Kontrollstudien erforderlich.

Zur Beantwortung der zweiten Hauptfragestellung dieser Dissertation (bezüglich eines Zusammenhangs zwischen der EF-Leistung und der Gehfähigkeit sowie den DTC des Gehens beim Geradeausgehen, Kapitel 5) wurden die Daten von 74 Patient:innen mit fortgeschrittenem PD analysiert. Multiple lineare Regressionsmodelle und der Bayes-Faktor BF_{10} wurden für jeden Gangparameter und ihre DTC als abhängige Variablen berechnet. Als unabhängige Variablen wurde ΔTMT sowie als Kotrollvariablen MDS-UPDRS III, die Verwendung einer Gehhilfe, Alter und Geschlecht in die Modelle aufgenommen. In dieser Kohorte waren die reduzierte Gehfähigkeit unter ST und DT sowie die DTC während des Gehens signifikant mit der Verwendung einer Gehhilfe, dem Schweregrad der motorischen Symptome, dem Alter und dem Geschlecht, nicht aber mit der TMT-Leistung assoziiert. Insgesamt gab es ein moderates Maß an Evidenz dafür, dass die Gehfähigkeit nicht mit der TMT-Leistung assoziiert war, wenn der TMT in das Modell einbezogen wurde (BF10 zwischen 0,12 und 0,18). Unter DT mit kognitiver Sekundäraufgabe wurde 23% der Varianz im Gesamtmodell für die DTC der Schrittzeitvariabilität aufgeklärt, was im Model hauptsächlich durch das Alter getrieben wurde (β=0,26, p=0,09).

Zur Beantwortung der dritten Hauptfragestellung dieser Dissertation (bezügliches eines Zusammenhangs zwischen der EF-Leistung, und der Veränderung der Gehfähigkeit beim Geradeausgehen nach ERGCT, Kapitel 6) wurden die Daten von 47 Patient:innen dieser Kohorte analysiert, die die zweiwöchige ERGCT inklusive der sensorbasierte Bewegungsanalyse zu T2 abgeschlossen hatten. Multiple lineare Regressionsmodelle und der BF_{10} wurden für jede Differenz (Δ) der spatio-temporalen Gangparametern (ΔGangparameter = Gangparameter (T2) - Gangparameter (T1)) als abhängige Variablen berechnet. Als unabhängige Variablen wurden MoCA, ΔTMT, DIA-S und FES-I Gesamtscore sowie als Kotrollvariablen MDS-UPDRS III, die Verwendung einer Gehhilfe, Alter und Geschlecht in die Modelle aufgenommen. Bei Patient:innen mit einer geringeren TMT-Leistung bei der Aufnahme schien sich die Gehfähigkeit nach der Behandlung sowohl unter ST (d. h. geringere Verringerung der Schrittzeitasymmetrie) als auch unter DT (d. h. ein vorsichtigeres Gehmuster mit stärker reduzierter Schrittzeit und doppelter Doppelstandbeinphase bei langsamerem Gehen, wenn eine zusätzliche kognitive Anforderung zur Aufgabe hinzugefügt wird) nicht zu verbessern. Andererseits gab es bei Patient:innen mit höherer globaler kognitiver und TMT-Leistung einen Deckeneffekt in Bezug auf die Gehfähigkeitsveränderung, d. h. das krankheitsbedingte Fortschreiten schien bei diesen Patient:innen im Rahmen der Behandlung verlangsamt. Somit können eine reduzierte globale kognitive und TMT-Leistung (zusammen mit motorischen und affektiven nicht-motorischen Symptomen) als limitierende Faktoren für die behandlungsbedingte Verbesserung der Gehfähigkeit beim Geradeausgehen bei akut hospitalisierten Patienten mit fortgeschrittene PD angesehen werden.

Zusammengenommen zeigen die Ergebnisse dieser Dissertation, dass eine Ergänzung des CGA um quantitative Parameter für Kognition und Gehfähigkeit (unter Verwendung von neuen technologischen Instrumenten) umsetzbar und sinnvoll ist, dass bei fortgeschrittenem PD aufmerksamkeitsbezogene Prozesse vor allem in DT Situationen eine Rolle spielen und sich eine verringerte kognitive Leistung (insbesondere der EF) limitierend auf die Veränderung der Gehfähigkeit nach multimodaler individualisierter Behandlung auszuwirken scheint. Diese Erkenntnisse sind ein wichtiger Schritt zum besseren Verständnis relevanter quantitativer prognostischer Marker und ebnen so den Weg für künftige Forschungen zur individualisierten Behandlung von Patienten mit fortgeschrittener Parkinson-Krankheit sowie im Bereich der patientenorientierten geriatrischen Versorgung.

English Summary

Common geriatric syndromes that also occur in neurodegenerative diseases, such as Parkinson's disease (PD), include impairments in mobility and cognition, particularly executive functions (EF, (Jacobs et al., 2020; Mirelman et al., 2019)). Both are subject to age- and disease-related changes (Burke & Barnes, 2006; Collette et al., 2006; Hupfeld et al., 2022; Owen, 2004). Especially in complex dual-task (DT) walking situations, patients with PD show reduced in walking performance and higher dual-task-costs (DTC, an indicator of capacity loss in a certain domain) than healthy individuals (Hobert et al., 2011; Mirelman et al., 2019; Plotnik et al., 2011). Spatio-temporal walking parameters (measured using inertial measurement units, IMUs) can be used to detect impaired walking patterns in PD and their progression in the course of the disease (Bouça-Machado, Jalles, et al., 2020; Del Din et al., 2021; Polhemus et al., 2021). However, there is also a lack of knowledge about the relevance of a potential link between mobility and EF performance as a prognostic marker for individualized treatment outcome (Mirelman et al., 2019; Van de Weijer et al., 2018).The aim of this dissertation was to contribute to a better understanding of the link between mobility and cognition (especially EF) in healthy older adults as well as in patients with advanced PD. Furthermore, it was to be investigated whether this link is associated with a carryover effect of computer-based cognitive training (CCT) on mobility as well as with individualized early rehabilitative geriatric complex treatment (ERGCT) of patients with advanced PD.

The framework of this dissertation was the prospective, observational, multicenter study "*Cognitive and Motor interactions in the Older population*" (ComOn, Chapter 4). This study included a comprehensive geriatric assessment (CGA) extended by a quantitative movement analysis (using the IMU system RehaCom®, Hasomed, Magdeburg, Germany) and an extensive battery of neuropsychological tests and questionnaires. Geriatric patients aged 50 years or older were assessed at inpatient admission (T1) and prior to discharge (T2) after two weeks of ERGCT. For this dissertation, data from a ComOn subcohort of acutely hospitalized patients with advanced PD were analyzed. Walking performance was assessed under ST (fast and normal pace) and DT conditions (walking while checking boxes as a motor secondary task, walking while subtracting series of 7 as a cognitive secondary task) over 20 meters. Spatio-temporal walking parameters were extracted, their DTC while walking were calculated for each of the parameters. Change of walking performance (Δ) was calculated as difference between T2 and T1 for each walking parameter. EF and divided attention were assessed with the Delta Trail Making Test (ΔTMT, TMT-B minus TMT-A) and global cognitive performance with the Montreal Cognitive Assessment (MoCA). Additional clinical parameters recorded were use of a

walking aid, severity of PD-specific motor symptoms using the Movement Disorder Society revised version of the motor part of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III), and depressive symptoms using the *Depression-im-Alter- Skala* (DIA-S) and fear of falling (FOF) using the Falls Efficacy Scale (FES-I).

Initially, a systematic review evaluated eleven CCT intervention studies published up to and including June 2017 that examined mobility parameters of healthy older adults (gait, balance, transfer behavior) as primary outcome (Chapter 3). Mobility parameters for which a positive CCT effect was described in the included studies were step length under DT and gait initiation. However, because of the small number of studies and their high heterogeneity, the hypothesized carryover effect of CCT on mobility could not be statistically tested. To answer the question about a possible link between performance in EF and divided attention and straight walking performance under ST and DT conditions as well as the DTC while walking, the data of 74 patients were analyzed. Multiple linear regression and Bayes factor (BF_{10}) were calculated for each walking parameter and their DTC as dependent variables, and also included ΔTMT, MDS-UPDRS III, use of a walking aid, age and gender. Reduced walking performance under both ST and DT as well as DTC while walking were significantly associated with the use of a walking aid, the severity of motor symptoms, age and gender, but not with TMT performance (BF_{10} between 0.12 and 0.18). Under DT with cognitive secondary task, a resolved variance of 23% was observed in the overall model for step time variability DTC, driven mainly by age (β=0.26, p=0.09). To answer the question whether EF and global cognitive performance (together with depressive symptoms and FOF) were related to the change in straight walking performance under ST and DT after ERGCT, again multiple linear regression models and BF_{10} were calculated. The models included Δ of each spatio-temporal walking parameter were as dependent variables, and MoCA, ΔTMT, DIA-S and FES-I total score as independent variables as well as MDS-UPDRS III, use of a walking aid age and gender as covariates. Patients with lower TMT performance at admission did not seem to improve in walking performance after treatment under both ST (i.e. lower reduction of step time asymmetry) and DT. On the other hand, there was a ceiling effect for patients with higher global cognitive and TMT performance regarding the walking performance, i.e. the disease-related progression seemed to be delayable in these patients within the scope of the treatment.

Together, the results of this dissertation show that extending the CGA with quantitative cognitive and walking parameters (using new technological instruments) is feasible and useful, that attentional processes need to be considered in advanced PD especially under DT, and that deficits in cognitive performance (especially in EF) seem to limit the benefit of ERGCT in terms of changes in walking performance in this cohort. As such these findings represent an integral step in the understanding of relevant prognostic markers and pave the way for future research on individualized treatment of patients with advanced PD as well as in the field of patient-oriented geriatric care.

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10 Appendix

Supplemental Material

Suppl.-Tab. 5.1: Explorative group comparison between patients with and without walking aid regarding parameters relevant for the regression models for the walking conditions ST normal pace, ST fast pace and DT walking-cognitive

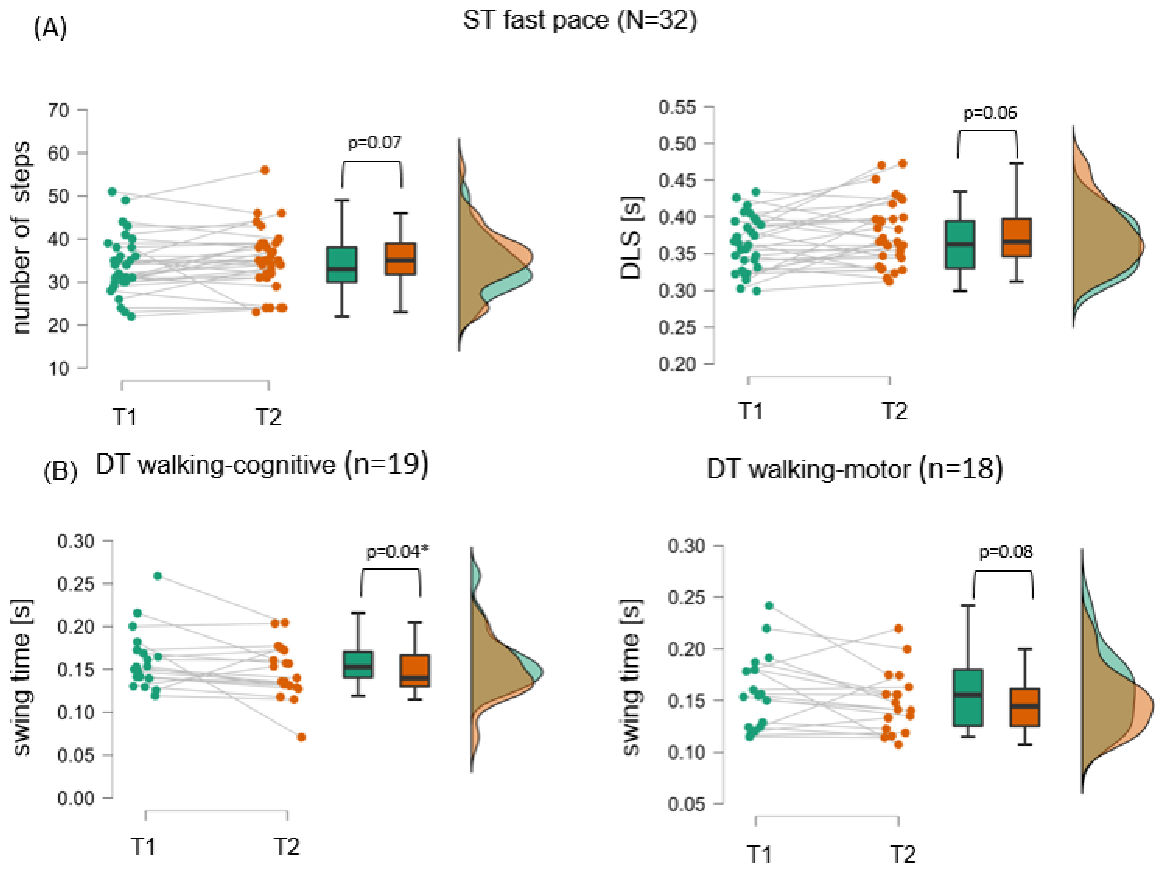
	ST normal pace			**ST fast pace**			**DT walking-cognitive**		
	Median (IQR)		**W[a]; p[a, b]**	**Median (IQR)**		**W[a]; p[a, b]**	**Median (IQR)**		**W[a]; p[a, b]**
walking aid group	**with**	**without**		**with**	**without**		**with**	**without**	
n	23	51		17	43	[b]	11	34	[b]
age [years]	77 (10)	74 (12)	435; 0.08	79 (5)	74 (12.5)	215; 0.01*	77 (11.5)	77 (14.25)	154; 0.39
female [n (%)]	10 (44)	15 (29)	0.29[b]	8 (47)	9 (21)	0.66[b]	5 (46)	7 (21)	0.13[b]
ΔTMT [s]	103 (81)	109 (129)	604; 0.84	105 (54)	103 (109)	338; 0.66	94 (29.5)	82.5 (65.5)	169; 0.67
MDS-UPDRS III	37 (23)	26 (22)	391; 0.02*	37 (18(	25 (20)	244; 0.05*	42 (17.5)	21 (16.5)	77; 0.004**
number of steps	40 (11.5)	39 (11)	480; 0.22	42 (7)	36 (12)	193.5; 0.005**	47 (5)	41.5 (17)	116; 0.06a
gait speed	0.68 (0.24)	0.83 (0.29)	901; <0.001***	0.83 (0.24)	102 (0.4)	534.5; 0.006**	0.60 (0.13)	0.74 (0.42)	278; 0.02*
DLS	0.35 (0.08)	0.37 (0.1)	653; 0.44	0.38 (0.06)	0.39 (0.05)	446; 0.19	0.36 (0.05)	0.40 (0.08)	232; 0.24
ASYM	0.02 (0.06)	0.03 (0.03)	666; 0.36	0.02 (0.05)	0.03 (0.03)	740; 0.50	0.05 (0.06)	0.04 (0.03)	155; 0.41
STV	0.004 (0.05)	0.05 (0.06)	835; 0.004**	0.04 (0.02)	0.07 (0.05)	575; <0.001***	0.02 (0.03)	0.06 (0.04)	297; 0.02*
$\text{DTC}_{\text{Walking}}$ number of steps [%] (n=44)							7.69 (14.3)	6.45 (17.7)	135; 0.21
$\text{DTC}_{\text{Walking}}$ gait speed [%] (n=44)							17 (23.5)	5.42 (25.2)	140 (42) 0.27
$\text{DTC}_{\text{Walking}}$ DLS [%] (n=44)							9.26 (10.2)	0.95 (19.4)	118 (42) 0.09
$\text{DTC}_{\text{Walking}}$ ASYM [%] (n=44)							78.1 (83.3)	7.44 (120)	69 (42) 0.003**
$\text{DTC}_{\text{Walking}}$ STV [%] (n=44)							106 (114)	-3.88 (106)	45 (42) <0.001***

[a], asymptotic p-value for Mann-Whitney-U-test (level of significance α≤0.05); ASYM, asymmetry; [b], p-value for Fisher's exact test (level of significance α≤0.05); DLS, double limb support; DT, dual task; $\text{DTC}_{\text{Walking}}$, dual task costs for walking while doing a second task (in percentage, %); IQR, interquartile range; LEDD, levodopa equivalence daily dose (in milligram, mg); MDS-UPDRS III, Movement Disorder Society-revised version of the motor part of the Unified Parkinson's Disease Rating Scale; n, sample size; s, seconds; ST, single task; STV, step time variability; W, test statistic for Mann-Whitney-U-test; ΔTMT, delta of Trail Making Test (part B minus part A); p≤0.05*, significant on level of significance α≤0.05; p≤0.01**, significant on level of significance p≤0.001***, significant on level of significance α≤0.001.

Suppl.-Tab. 6.2: Explorative descriptive comparisons for change in walking parameters between T1 and T2 for all four walking conditions

		ST Normal pace							**ST fast Pace**							**DT walking-cognitive**							**DT walking-motor**						
		n	**M**	**SD**	**Median**	**IQR**	**W**	**p**	**n**	**M**	**SD**	**Median**	**IQR**	**W**	**p**	**n**	**M**	**SD**	**Median**	**IQR**	**W**	**p**	**n**	**M**	**SD**	**Median**	**IQR**	**W**	**p**
number of steps	T1	47	39.1	10.4	37	8.50	502	0.36	32	34	6.84	33	8	105	0.07	18	38.9	8.47	39	12	76	0.70	17	42.18	10.29	42	16	95	0.40
	T2	47	38.2	7.63	38	7.50			32	35.3	7.32	35	7.25			18	38.6	8.37	38	12.75			17	40.29	8.95	40	10		
gait speed [m/s]	T1	47	0.78	0.20	0.78	0.30	549	0.93	30	0.98	0.18	0.96	0.27	280	0.34	19	0.76	0.25	0.72	0.35	70	0.33	18	0.73	0.28	0.65	0.36	70	0.52
	T2	47	0.79	0.22	0.77	0.24			31	0.97	0.24	0.94	0.29			19	0.79	0.27	0.79	0.31			18	0.77	0.28	0.73	0.28		
step time [s]	T1	46	0.59	0.11	0.56	0.09	517	1.00	32	0.49	0.05	0.49	0.07	176	0.16	19	0.62	0.15	0.60	0.13	127	0.21	18	0.61	0.14	0.59	0.17	102	0.50
	T2	46	0.59	0.10	0.57	0.10			32	0.50	0.06	0.49	0.08			19	0.59	0.09	0.59	0.12			18	0.58	0.08	0.57	0.10		
stride time [s]	T1	46	1.18	0.21	1.11	0.18	510	0.94	32	0.98	0.10	0.98	0.14	178	0.17	19	1.24	0.30	1.19	0.25	127	0.21	18	1.21	0.28	1.17	0.34	102	0.50
	T2	46	1.18	0.19	1.12	0.19			32	1.00	0.11	0.97	0.17			19	1.18	0.18	1.17	0.25			18	1.16	0.16	1.13	0.20		
swing time [s]	T1	46	0.15	0.03	0.14	0.03	542	0.79	32	0.13	0.02	0.13	0.02	261	0.96	19	0.16	0.03	0.15	0.03	147	0.04*	18	0.16	0.04	0.16	0.05	126	0.08
	T2	46	0.15	0.02	0.14	0.03			32	0.13	0.02	0.12	0.02			19	0.15	0.03	0.14	0.04			18	0.15	0.03	0.14	0.04		
stance time [s]	T1	46	1.03	0.18	0.97	0.14	519	0.99	32	0.86	0.09	0.85	0.15	179	0.11	19	1.08	0.26	1.03	0.21	125	0.24	18	1.05	0.25	1.00	0.28	9	0.58
	T2	46	1.03	0.17	0.98	0.18			32	0.88	0.10	0.85	0.14			19	1.03	0.15	1.04	0.20			18	1.01	0.14	0.99	0.21		
DLS [s]	T1	46	0.44	0.08	0.42	0.06	538	0.82	32	0.36	0.04	0.36	0.06	163	0.06	19	0.46	0.12	0.44	0.09	105	0.71	18	0.45	0.11	0.42	0.12	86	1.00
	T2	46	0.44	0.07	0.42	0.08			32	0.38	0.04	0.37	0.05			19	0.44	0.06	0.45	0.08			18	0.43	0.06	0.42	0.09		
DLSV [s]	T1	47	0.05	0.05	0.04	0.03	621	0.25	32	0.03	0.02	0.03	0.02	221	0.43	18	0.08	0.07	0.06	0.03	110	0.30	18	0.07	0.07	0.05	0.05	83	0.78
	T2	45	0.04	0.02	0.03	0.02			32	0.05	0.04	0.03	0.04			19	0.05	0.03	0.04	0.02			17	0.07	0.08	0.05	0.05		
ASYM [s]	T1	45	0.04	0.02	0.03	0.03	485	0.72	32	0.03	0.02	0.02	0.04	273	0.88	19	0.04	0.02	0.03	0.04	104	0.74	18	0.04	0.03	0.03	0.05	56	0.21
	T2	47	0.04	0.04	0.03	0.04			32	0.03	0.03	0.03	0.02			19	0.04	0.03	0.03	0.02			18	0.05	0.04	0.04	0.06		
STV [s]	T1	47	0.06	0.05	0.05	0.03	613	0.29	32	0.04	0.02	0.04	0.03	208	0.30	18	0.09	0.07	0.07	0.06	123	0.11	18	0.08	0.08	0.07	0.04	84	0.75
	T2	45	0.05	0.02	0.04	0.02			32	0.05	0.04	0.04	0.04			19	0.06	0.03	0.05	0.02			17	0.08	0.08	0.06	0.05		

ASYM, asymmetry; DLS, double limb support; DLSV, double limb support variability; DT, dual task; IQR, interquartile range; M, mean; m/s, meter per seconds; n, sample size; s, seconds; SD, standard deviation; ST, single task; STV, step time variability; T1, time of measurement at admission; T2 time of measurement before discharge; W, test statistic of Wilcoxon signed-ranks test for dependent samples to calculated differences between T1 and T2 for each walking parameter, $p \leq 0.05$*, significant on level of significance $\alpha \leq 0.05$.



Suppl.-Figure 6.1: Rainbow plots for Differences in walking parameters after treatment. In (A) for single task fast pace walking condition number of steps and double limb support (DLS in seconds, s) are shown on the ordinates, the two measurement points T1 (at admission) and T2 (after two weeks early rehabilitative geriatric complex treatment) are on the abscissas. Data points for each participant are given for T1 (green dots) and T2 (orange dots) with the single subject difference (gray lines). The medians (thick black horizontal lines), the interquartile range (IQR, black-bordered boxes) as well as lower and upper whiskers (values within ±1.5xIQR) also are given for T1 (green) and T2 (orange) as well as the distributions of the parameters for T1 (green curve) and T2 (orange curve). Sample size n is given as well as p-values for differences between T1 and T2 calculated by using Wilcoxon signed-rank test for paired samples (significant differences are marked with * (level of significance p≤.05), In (B) the same is shown for DT motor-cognitive walking condition (DT walking-cognitive) and DT walking-motor condition for swing time (s).

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