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Abteilung Neurologie mit Schwerpunkt
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The association of cognitive flexibility with prioritization and gait: A cross-sectional cohort study in healthy older adults

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CV	coefficient of variation
e.g.	for example
i.e.	that is
ICF	International Classification of Functioning, Disability and Health
IMU	inertial measurement unit
InChianti study	*Invecchiare in Chianti* (aging in the Chianti area) study
LRRK2 mutation	mutation in the gene encoding for Leucine-rich repeat kinase 2; this is an autosomal-dominant mutation associated with a highly increased risk of Parkinson's disease
PCI	Phase Coordination Index: this is a gait parameter measuring (ir)regularity of gait
PD	Parkinson's disease
TILDA	The Irish Longitudinal Study on Aging
TMT	Trail Making Test
TREND study	Tübinger evaluation of Risk factors for Early detection of Neurodegenerative Disorders study

1. Introduction

1.1 Why do older adults fall? Risk factors for falling and their association with cognition

Approximately about 30% of community-living people over 65 years of age fall (Gale et al., 2016; Gillespie, 2013; Rubenstein and Josephson, 2002). Falls lead to severe injuries, such as hip fractures in 5-10 % of the cases (Rubenstein and Josephson, 2002) and have a severe influence on quality of life (Stenhagen et al., 2014).

Several causes and risk factors of falls have been identified. The causes of falls describe the actual reason for a fall. Important causes of falls are accidents or external circumstances, gait and balance disorders, (sudden) weakness, vertigo and dizziness, drop attacks, syncopes, postural hypotension, and visual disorders (Rubenstein et al., 1994; Rubenstein and Josephson, 2002).

Risk factors are indicators of an increased risk, but do not directly or necessarily lead to falls. Important risk factors are age (Gale et al., 2016), female gender (Gale et al., 2016), gait and balance problems (Bergland and Wyller, 2004; Boele van Hensbroek et al., 2009; Gale et al., 2016), muscle weakness (Gale et al., 2016; Moreland et al., 2004; Pluijm et al., 2006), previous falls (Bergland and Wyller, 2004; Pluijm et al., 2006), fear of falling (Boele van Hensbroek et al., 2009; Landers et al., 2016), cognitive deficits and dementia (Kearney et al., 2013), arthritis, chronic disorders in general (Gale et al., 2016), (multi)medication (Boele van Hensbroek et al., 2009; Gale et al., 2016; Ruxton et al., 2015), and visual impairment (Boele van Hensbroek et al., 2009; Gale et al., 2016).

Prioritization, i.e., putting the main focus on a special action / task / object / aspect / etc. and not on another, seems to be a particularly relevant risk factor for falling (Bloem, Valkenburg, Slabbekoorn and Van Dijk, 2001). This is because prioritization is relevant during almost all walking episodes. This relevance has nicely been demonstrated by, e.g., a study investigating stops of walking during talking (Lundin-Olsson et al., 1997). The authors found that persons who stopped walking when talking have an increased risk for a future fall compared to those who did not stop walking in the same situation.

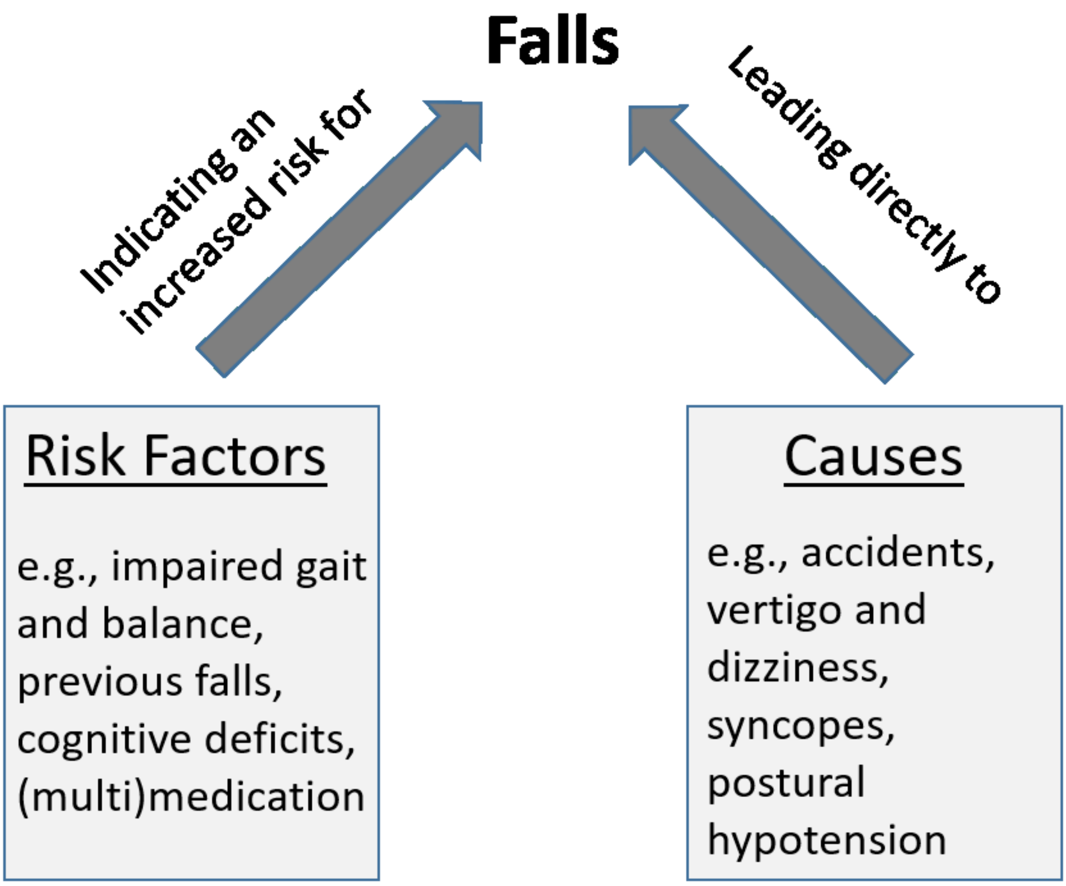

Figure 1: Schematic overview of a selection of risk factors and causes for falls, highlighting the difference between these terms.

This manuscript will focus on risk factors of falling. Based on recent reviews, impaired gait and balance, previous falls, and medication use are among the most relevant risk factors for falls (Ganz et al., 2007; Tinetti and Kumar, 2010). Of note, all three risk factors include cognitive aspects. It is thus probable that a better understanding of the interaction of cognition with gait and balance, knowledge about the influences of previous falls and (multi)medication has the potential to initiate interventions to reduce the risk of falling. In the following, the current knowledge about these interactions and associations will be discussed in more detail.

Impressive examples for the association of impaired gait and balance with cognitive deficits are cognitively demanding situations leading to falls (Robinovitch et al., 2013). Moreover, it has been shown that fallers have deficits in gait performance under dual tasking conditions but not under single tasking conditions (Yogev et al., 2007). We have recently shown that this deficit also occurs in patients with Parkinson's disease (PD). We investigated a cohort of 40 PD patients over a period of approximately three years, and found that higher dual task costs (i.e. the reduction in the performance of one task under dual tasking conditions when compared to the performance of the same task under single task conditions) significantly predicted the occurrence of the first fall (Heinzel et al., 2016). Pathomechanistic aspects of the interaction between cognition, gait and balance are discussed in the next chapter. Recent results from intervention studies support this association: motor training in combination with a cognitive task, e.g., when using a virtual reality setup is more effective in reducing the risk of falling in older adults (Mirelman et al., 2016) and in stroke patients (Pedreira da Fonseca et al., 2017), than motor training alone.

Psychological and behavioural changes often accompany falls, which may include cognitive deficits in a portion of the persons affected (Ansai et al., 2017; Mirelman et al., 2012). This situation may best explain the contribution of cognitive deficits to the falls risk factor “previous falls”. Another factor in this interplay is fear of falling, an emotion triggered by (previous) falls (Haertner et al., 2018; Hoang et al., 2017; Li et al., 2003).

Medication use, another risk factor for falls, is also associated with cognitive deficits (Dhalwani et al., 2017; Díaz-Gutiérrez et al., 2017; Ruxton et al., 2015). Psychoactive drugs can lead to increased risk of falling through confusion and sedation (Campbell et al., 1999; Díaz-Gutiérrez et al., 2017; Lord et al., 1995; Seppala et al., 2018). Antihypertensive drugs induce a higher risk of falling through, e.g., symptomatic hypotensive episodes (Shimbo et al., 2016). In contrast, some drugs improve cognition and can thus have a positive effect on walking and mobility, reducing the risk of falling. This effect has been shown with, e.g., galantamine, rivastigmine and methylphenidate (Chung et al., 2010; Gurevich et al., 2014; Henderson et al., 2016; Montero-Odasso et al., 2015). One of these studies (Montero-Odasso et al., 2015) investigated 43 patients with recently diagnosed Alzheimer’s disease (mean age of 77 years), found that improvement of mobility was associated with improvement of cognitive flexibility, an executive function. This study especially suggests that cognitive flexibility is an interesting candidate function for – and link between — the association of mobility (impairment) and cognition. This thesis investigates the association of cognitive flexibility in particular, with prioritization and gait parameters in a defined dual tasking paradigm in a large cohort of healthy older adults.

1.2 Supraspinal control of gait

For a long time, gait was considered to be an automatic process. This assumption was built on a famous experiment, showing that a decerebrated cat can walk on a treadmill (Brown, 1911). This finding led to the assumption that central pattern generators delivering sufficient information for the performance of walking are located in the spinal cord. The responsible structure has also been postulated in humans (Illis, 1995), as it has been shown that muscle activity and stepping movements could be evoked in patients with paraplegia by a treadmill (Dietz et al., 1994). However, the existence and role of these spinal pattern generators in healthy humans is still not entirely clear. Nevertheless, it is well accepted that the supraspinal control of gait is much more important in humans and other bipedal walkers than in animals walking on four legs (Jahn et al., 2010; Takakusaki, 2017). Insights into the mechanisms of supraspinal gait control have been gained by imaging studies using different techniques, such as positron emission tomography (after walking tasks (la Fougère et al., 2010; Malouin et al., 2003)) and functional magnetic resonance imaging (with imagination tasks of walking (Bakker et al., 2007; Jahn et al., 2004; Jahn, Deutschländer, Stephan, Kalla, Wiesmann, et al., 2008)). These studies showed that supraspinal brain areas project to the spinal cord, which can be interpreted as indirect evidence for the existence of spinal pattern generators. In any case, these projections enable us to adapt gait to external and internal obstacles and requirements. As several brain structures and networks contribute to supraspinal control of gait, only a simplified model is discussed here and shown in figure 2: The pontomedullary reticular formation is a central hub of this network (Takakusaki et al., 2016). It receives input from sensory tracts, the cerebellum and the midbrain locomotor region and projects to central pattern generators in the spinal cord (Takakusaki et al., 2016). In simple words, it "manages" the integration of gait modulation of the cerebellum and from the midbrain locomotor region. The midbrain locomotor region is another central hub of this network: it receives projections from "primary motor" (mainly motor cortex, basal ganglia and thalamus (Middleton and Strick, 2000)), "limbic" (mainly the limbic system and parts of the basal ganglia (Takakusaki et al., 2004)) and "frontal" circuits, all of which converge in the basal ganglia before they approach the above-mentioned hub (Joel and Weiner, 2000; Middleton and Strick, 2000; Pelzer et al., 2014). The midbrain locomotor region projects to the pontomedullary reticular formation. This hub therefore “manages” the integration of influences of different circuits that involve higher networks including cortical structures.

The “frontal” circuit plays a central role in this thesis. It consists mainly of frontal and prefrontal areas and the basal ganglia. This circuit manages, among other tasks, dual tasking, and a relevant number of publications suggest that it plays an important role in motor-cognitive interactions (Middleton and Strick, 2000; Suzuki et al., 2004).

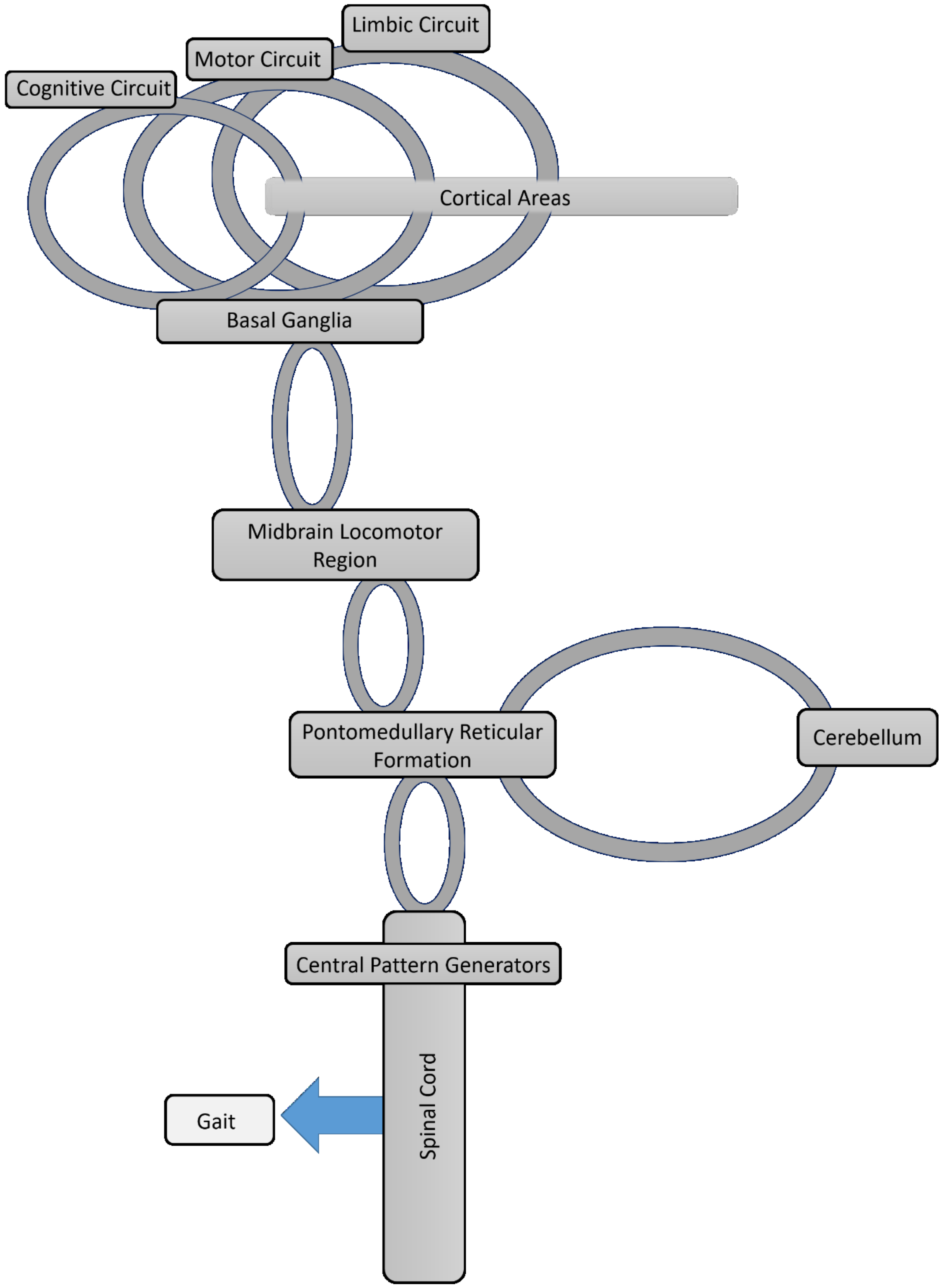

Figure 2: Simplified model of brain structures and networks involved in supraspinal control of gait. Figure adapted from (Hobert et al., 2014; Jahn, Deutschländer, Stephan, Kalla, Hüfner, et al., 2008).

1.3 Gait assessment strategies

In neurology gait is usually classified based on clinical observation and terms such as ataxic, parkinsonian, spastic, paretic, and anxious gait are used to describe pathological gait patterns (Jahn et al., 2010; Nonnekes et al., 2018; Snijders et al., 2007). This method relies strongly on the experience of the examiner, and is subjective and prone to bias. In recent years, the development has thus moved in the direction of quantitative and objective gait assessment strategies.

A simple method to quantify gait is measuring gait speed, i.e., the total time needed to walk a defined distance. Gait speed is, e.g., a sensitive parameter for, and predictor of, overall survival time (Studenski et al., 2011) and cognitive decline (Buracchio et al., 2010). This parameter can be easily measured with, e.g., a stopwatch.

More complex assessments of gait can be performed using lab-based techniques, such as optical and video-based systems (Kadaba et al., 1990), and pressure sensors on the floor or in special mats (Cutlip et al., 2000; McDonough et al., 2001). The main advantage of these methods is their high accuracy. Disadvantages are high costs and location dependency, e.g. in a gait lab.

The next important step in technological development has been the design of inertial measurement units (IMUs). They can readily assess quantitative gait parameters. For example, these sensors allow the measurement of small and defined movements with high accuracy outside the lab, e.g., in the patient's room and in the home environment of the patients and study participants. IMUs typically contain accelerometers (to measure acceleration), gyroscopes (to measure rotation), and often magnetometers (for the assessment of magnetic fields). IMUs can be worn on different locations of the body, mainly depending on the information that is to be collected (Hobert et al., 2014; Maetzler, Domingos, et al., 2013; Sánchez-Ferro et al., 2016). IMUs positioned on the lower back and the feet allow the extraction of important gait parameters (Salarian et al., 2013). Raw data of the sensors can be "transformed" by specific algorithms to clinically relevant and understandable parameters. Such parameters are, e.g. gait speed, number of steps/strides, step/stride time, double support time, gait variability, measures of gait regularity (e.g., phase coordination index (PCI) (Plotnik et al., 2007)), and gait asymmetry. Specific parameters may belong to different gait domains (Lord, Galna, Verghese, et al., 2013; Verghese et al., 2008). Verghese and colleagues (Verghese et al., 2008) proposed three gait domains: rhythm, pace, and variability. Step frequency, swing time and stance time belong to the rhythm domain, gait speed and stride length belong to the pace domain, and double support time, stride length variability and swing time variability belong to the variability domain.

Lab- and IMU-based assessments of gait are mainly performed under standardized conditions, e.g., to assess walking with and without dual tasking on a defined walking path. This aspect is relevant for this thesis. It should also be mentioned that more recent IMU-based studies are also assessing movements in unsupervised environments, e.g., in the homes of the participants (Ferreira et al., 2015; van Lummel et al., 2015; Pham et al., 2017).

1.4 Cognitive flexibility: An executive function associated with gait in older adults

Executive functions are a set of cognitive functions, including planning, problem solving, goal-directed behaviour, sustaining or switching attention, sequencing, and cognitive flexibility (Chan et al., 2008). A universally accepted model of executive functions is not yet available. Miyake and colleagues (Miyake et al., 2000; Miyake and Friedman, 2012) tested in 137 adults whether the three fundamental domains, updating, inhibition and shifting, are part of the executive functions. The authors performed a confirmatory factor analysis and a structural equation modelling analysis and found that the three domains reflect, at least partly, different aspects of executive functions (Miyake et al., 2000). The authors named this the “Unity and Diversity paradigm”. This model is currently widely accepted.

In more detail, the authors found that updating describes the actualisation of working memory. It can be measured with, e.g., the Operation Span Test and the Keep Track Task (Miyake et al., 2000). Inhibition describes the suppression of dominant responses. It can be measured with the Stroop Test and the Tower of Hanoi Test (Miyake et al., 2000). Finally, shifting describes switching of attention between different tasks. It can be assessed with, e.g., the Wisconsin Card Sorting Test and the Trail Making Test (TMT) (Bowie and Harvey, 2006; Miyake et al., 2000). Part of shifting is cognitive flexibility, which is necessary for e.g. dual tasking situations, where two tasks have to be performed simultaneously or alternating. It can be measured with the TMT (Miyake et al., 2000).

An association of cognitive flexibility with gait has repeatedly been shown (Ble et al., 2005; Coppin et al., 2006; Hirota et al., 2010; Killane et al., 2014). Most of these studies used dual tasking paradigms with walking. One of the first studies focusing on this association was the longitudinal *InChianti* study (Invecchiare in Chianti, aging in the Chianti area study). This study included, in the cross-sectional analysis, 1154 older adults with a mean age of 75 years (Ble et al., 2005). The authors categorized study participants according to results obtained from the TMT into three groups and examined whether these three groups showed different gait speeds during different walking conditions. They found no differences of gait speed in the walking at convenient speed condition between groups, but significant differences in the fast walking while avoiding obstacles condition: Participants with good TMT performance walked faster than did those with poor TMT performance. These results were confirmed in a more recent cross-sectional analysis in the same cohort, showing that poor TMT performers had slower gait speed under dual tasking conditions, but not under single tasking conditions (Coppin et al., 2006). These results suggested that cognitive flexibility influences walking during complex tasks (Ble et al., 2005; Coppin et al., 2006).

The *InChianti* study raised some questions. First, can we learn something more from a quantitative assessment of the secondary task? Second, can we improve our understanding of the interaction of cognition and gait by adding, e.g. IMU-based quantitative gait parameters to our analyses? Third, is performance under challenging conditions more effective for investigating and understanding the interaction between motor (gait) and cognitive function than performance under convenient conditions?

This thesis addresses all three questions by including quantitative strategies in the assessment protocol.

By addressing the first question (quantitative assessment of the secondary task), our study could investigate, to our best knowledge for the first time, whether cognitive flexibility is associated with prioritization. In the first publication of this thesis, the association of cognitive flexibility with prioritization during the dual tasking gait condition was analysed in almost 700 healthy older adults.

By addressing the second and third questions, the second publication of this thesis focused on the association of cognitive flexibility with distinct quantitative gait parameters and changes thereof during increasingly difficult walking conditions. The following studies highlight the relevance of this research question:

In a study with 493 Japanese adults, the influence of cognitive flexibility on gait speed was evaluated during different walking conditions (Hirota et al., 2010). The authors found an association between cognitive flexibility, measured with the

TMT, and parameters of mobility (i.e., gait speed and Timed- Up and Go test). Consistent with the results of the above-mentioned *InChianti* study (Ble et al., 2005; Coppin et al., 2006), the authors of this study found stronger associations between the respective parameters in more difficult walking conditions, such as walking at fast speed, dual tasking and obstacle avoidance during walking.

The Irish Longitudinal Study on Aging (*TILDA*) analysed the association of cognitive flexibility and gait during single and dual tasking during walking conditions in 4431 adults with a mean age of 62 years (Killane et al., 2014). The authors found that the Colour Trail Test (a variant of the TMT) was associated with gait speed in dual tasking but not in single tasking conditions. The authors argue for an important contribution of executive functions to gait performance, especially during complex walking situations.

As both above-mentioned studies reported only about gait speed and did not include further sensor-based gait parameters, the second publication of this thesis investigated the association of cognitive flexibility with gait performance by including IMU-based gait parameters, again on a cohort of almost 700 older adults.

1.5 Research questions

1. Is cognitive flexibility associated with prioritization?

2. Is cognitive flexibility associated with quantitative gait parameters and their changes across increasingly difficult walking situations?

This thesis attempts to answer these questions using the following approach:

- In the first publication, 686 healthy older adults performed walks under dual and single tasking conditions. Out of these tasks, dual task costs were calculated and compared between good and poor TMT performers.
- In the second publication, 661 healthy older adults wore a small IMU during walks under dual and single tasking conditions. Gait parameters and their changes over increasingly different walking conditions were analysed and compared with TMT values and between good and poor TMT performers.

2. Results

2.1 Publication 1: Poor Trail Making Test Performance Is Directly Associated with Altered Dual Task Prioritization in the Elderly – Baseline Results from the TREND Study

This section consists of the following publication:

Poor trail making test performance is directly associated with altered dual task prioritization in the elderly--baseline results from the TREND study.

Hobert MA, Niebler R, Meyer SI, Brockmann K, Becker C, Huber H, Gaenslen A, Godau J, Eschweiler GW, Berg D, Maetzler W.

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Poor Trail Making Test Performance Is Directly Associated with Altered Dual Task Prioritization in the Elderly – Baseline Results from the TREND Study

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Abstract

Background: Deterioration of executive functions in the elderly has been associated with impairments in walking performance. This may be caused by limited cognitive flexibility and working memory, but could also be caused by altered prioritization of simultaneously performed tasks. To disentangle these options we investigated the associations between Trail Making Test performance—which specifically measures cognitive flexibility and working memory—and dual task costs, a measure of prioritization.

Methodology and Principal Findings: Out of the TREND study (Tuebinger evaluation of Risk factors for Early detection of Neurodegenerative Disorders), 686 neurodegeneratively healthy, non-demented elderly aged 50 to 80 years were classified according to their Trail Making Test performance (delta TMT; TMT-B minus TMT-A). The subjects performed 20 m walks with habitual and maximum speed. Dual tasking performance was tested with walking at maximum speed, in combination with checking boxes on a clipboard, and subtracting serial 7 s at maximum speeds. As expected, the poor TMT group performed worse when subtracting serial 7 s under single and dual task conditions, and they walked more slowly when simultaneously subtracting serial 7 s, compared to the good TMT performers. In the walking when subtracting serial 7 s condition but not in the other 3 conditions, dual task costs were higher in the poor TMT performers (median 20%; range −6 to 58%) compared to the good performers (17%; −16 to 43%; $p<0.001$). To the contrary, the proportion of the poor TMT performance group that made calculation errors under the dual tasking situation was lower than under the single task situation, but higher in the good TMT performance group (poor performers, −1.6%; good performers, +3%; $p=0.035$).

Conclusion: Under most challenging conditions, the elderly with poor TMT performance prioritize the cognitive task at the expense of walking velocity. This indicates that poor cognitive flexibility and working memory are directly associated with altered prioritization.

Citation: Hobert MA, Niebler R, Meyer SI, Brockmann K, Becker C, et al. (2011) Poor Trail Making Test Performance Is Directly Associated with Altered Dual Task Prioritization in the Elderly – Baseline Results from the TREND Study. PLoS ONE 6(11): e27831. doi:10.1371/journal.pone.0027831

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Introduction

The application of dual task paradigms to evaluate the role of executive functioning during walking is generally well-accepted. Commonly used dual task paradigms include a walking task combined with a simultaneously performed non-walking task, and it has been suggested that some but not all combinations of walking with a non-walking task contribute to disturbed gait and, consecutively, to increased risk for falls with increasing age [1,2,3,4]. Walking is associated with higher-level cognitive resources, in particular with executive functions such as cognitive flexibility and working memory, which both deteriorate with increasing age [4]. Not surprisingly, an association between cognition and walking speed among elderly people has been demonstrated [5], and a decline in executive functions is one of the determinants of walking impairment that is often observed in older persons [6,7].

Another important part of executive functioning, and aspect in dual tasking is prioritization of one task over the other, following the motivation to minimize danger and maximize pleasure [4]. Healthy adults prioritize stability of gait when walking and simultaneously performing a cognitive task [2,8,9]. This seems to be different in Parkinson disease patients [10], in elderly fallers [11], and in Parkinsonian patients who fall regularly [12]. They have an increased probability to use a "posture second" strategy, and to prioritize the cognitive task at the expense of the stability of walking. However, most of these studies put their focus on the evaluation of the walking task but not on the non-walking task, thus knowledge about dual-task behaviour of older subjects, in particular with regard to non-walking tasks, is still limited. In addition, most of the studies used paradigms performed with habitual speed but not with maximum speed. This may lead to an oversight of subtle differences and false negative results [7,13,14].

To the best of our knowledge, the association of cognitive flexibility and working memory with dual tasking prioritization has never been investigated in a large cohort of healthy elderly. In this study, this was tested in 686 non-demented healthy older persons by evaluating the performance of walking and non-walking tasks under challenging conditions. The Trail Making Test (TMT) performance as a measure of cognitive flexibility and working memory was used to divide the cohort into a good, an intermediate, and a poor performance group.

Methods

Ethics

The study protocol was approved by the ethical committee of the Medical Faculty of the University of Tuebingen (Nr. 90/2009BO2), and all subjects provided written informed consent.

Objective

The primary objective of the study was to test whether poor performance on the Trail Making test as a measure of cognitive flexibility and working memory is associated with altered prioritization under dual tasking behaviour in a large cohort of older healthy persons. Secondary aim was to exploratively analyze direction and degree of prioritization in the defined subgroups.

Subjects

In the baseline assessment of the TREND study (**T**übinger evaluation of **R**isk factors for **E**arly detection of **N**eurodegenerative **D**isorders) 715 subjects aged 50–80 years with or without risk factors for Parkinson's and Alzheimer's disease (hyposmia, depression, REM sleep behavior disorder) were investigated prospectively in 2009 and 2010. A detailed description of the study outline, including inclusion and exclusion criteria, and baseline assessments, is given in (Berg et al., submitted). In brief, all subjects were pre-screened via telephone interview, and were excluded if they reported a history of psychiatric diseases (other than primary depression), dementia, epilepsy, stroke, multiple sclerosis, encephalitis and malignancies, intake of antipsychotics and other drugs that are able to promote Parkinsonian symptoms, and inability to walk without aids or assistance. In addition, disorders that could allow only incomplete study performance, such as paresis, sensory loss or significant impairment of vision or hearing all lead to primary exclusion of the subjects from the study.

From the investigated 715 subjects, a total of 29 subjects were excluded from this analysis due to the following reasons: Eleven met the criteria for Parkinson disease according to the UK Brain Bank Society criteria, eight had incomplete TMT data, five had negative delta TMT values, and five had a Mini-Mental Score Examination score <25. For demographic characteristics see table 1.

Single and dual task procedures

All subjects performed four single task trials: walking with habitual speed, walking with maximum speed, checking boxes with maximum speed, and subtracting serial 7 s with maximum speed. During the box-checking task, participants held a clipboard in their non-dominant, and a pen in the other hand. Then they had to mark each of 32 boxes with a cross on a sheet of paper with a pencil. The instruction was as follows: "Please mark each of the boxes on the sheet of paper with a cross as fast as you can." There was no instruction about where to start and to end with, and about the order of crossing. During the subtracting task, subjects had to subtract serial 7 s from a randomly chosen three-digit number until 10 subtractions were completed. The instruction was as follows: "Please subtract serial 7 s as fast as you can from the number I will shortly tell you, until I will interrupt you."

In the two dual task assessments, subjects performed both walking with maximum speed and checking boxes with maximum speed, and walking with maximum speed and subtracting serial 7 s with maximum speed. Instructions were as follows: "Please walk as

Table 1. Demographics and clinical assessments, and Trail Making Test performance.

Performers	good (N = 227)	intermediate (N = 226)	poor (N = 233)	P	Total cohort (N = 686)
Age [years]	61 (50–78)	64 (50–80)*	66(50–80)*#	<0.001	64 (50–80)
Male [%]	45.8	49.1	46.4	0.75	47.1
Education period [years]	15 (7–20)	14 (8–20)	13 (8–20)*#	<0.001	14 (7–20)
MMSE (0–30)	29 (26–30)	29 (25–30)*	29 (25–30)*#	<0.001	29 (25–30)
BDI (0–63)	6 (0–29)	6 (0–38)	7 (0–42)	0.22	6 (0–42)
Weight [kg]	71 (48–125)	74 (49–150)	75 (45–117)	0.31	73 (45–150)
Height [m]	1.70 (1.54–1.92)	1.71 (1.54–2.00)	1.70 (1.48–1.90)	0.38	1.70 (1.48–2.00)
TMT-A [s]	33 (16–90)	35 (20–88)	36 (15–100)*	0.006	35 (15–100)
TMT-B [s]	60 (34–97)	80 (58–140)*	120 (82–300)*#	<0.001	83 (34–300)
Delta TMT [s]	26 (0–35)	47 (36–58)*	80 (59–261)*#	<0.001	47 (0–261)

Good performers were defined as having a delta TMT score of less than 36 seconds, intermediate performers as having a delta TMT score of 36–58 s, and poor performers as having a delta TMT score higher than 58 s. Data are presented with median and range. P-values were assessed using the Kruskal Wallis test. P-values<0.05 were considered significant.
*p<0.05 compared to good performers;
#p<0.05 compared to intermediate performers. BDI, Beck's Depression Inventory; BMI, Body Mass Index; MMSE, Mini-Mental State Examination; TMT, Trail Making Test.
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fast as you can, do not run, do not risk falling, and mark each of the boxes on the sheet of paper with a cross as fast as you can," and "Please walk as fast as you can, do not run, do not risk falling, and subtract serial 7 s as fast as you can from the number I will shortly tell you." A randomly chosen three-digit number different from the number used for the single task assessment was told to the participant directly before the start sign was given. No hint for prioritization on any task was given, to omit an external influence on the prioritization process [15]. All assessments were performed in an at least 1.5 meters wide corridor allowing obstacle-free 20 meter walks.

Time was taken with a stopwatch and documented by the examiner, as were number of checked boxes, number of subtractions, and number of subtraction errors.

Cognitive assessment

The Trail Making Test (TMT) is a widely used paper-and-pencil task that evaluates the executive functions cognitive flexibility and working memory [7,16]. The TMT consists of two parts: On TMT Part A subjects have to connect numbers from 1 to 25, which are randomly spread over a sheet of paper, in ascending numerical order. On part B, participants are asked to connect randomly spread numbers (from 1 to 13) and letters (from A to L) in alternating numeric and alphabetical order (1-A-2-B-3-C-…-13-L). In case of an error the examiner draws the attention of the participant to the error, so that the participant completes the task without errors (at the expense of additional time) [17]. TMT performance was calculated taking the time needed to perform TMT-B minus time needed for TMT-A. This delta TMT value "removes" eventual bias due to differences in upper extremity motor speed, simple sequencing, visual scanning, and psychomotor functioning [7,16,17,18].

Data processing and statistical analysis

Data were analysed with JMP software (version 8.0.2, SAS), and are presented with median and range if not otherwise indicated. Subjects with delta TMT values>58 s were defined as poor performers (lowest tertile, N = 233), those with 36–58 s as intermediate performers (N = 226), and those with <36 s as good performers (highest tertile, N = 227). Demographic and basic clinical variables of the groups were compared by use of the Kruskal Wallis test (or, in case of categorical data the Chi square test), and post-hoc Wilcoxon test (Chi square test) (table 1). Outcome variables (table 2 and table 3) were corrected for age ($R^2 \leq 13\%$, with high values for the box checking task, and negligible values for subtracting serial 7 s), gender, education level ($R^2 \leq 5\%$), Mini-Mental State Examination score ($R^2 \leq 4\%$) and Becks Depression Inventory score ($R^2 \leq 4\%$) by use of a logistic regression model, and significance of each model effect was assessed by the likelihood ratio. Differences were considered significant at $p<0.05$ (two-sided). The parameters "box-checking speed" and "subtracting performance" were defined as numbers of checked boxes / subtractions over time needed for the task (seconds). Dual task costs were calculated using the following formula according to [12,19]:

$$DTC = \left(1 - \frac{dual\ task\ speed}{single\ task\ speed}\right) * 100$$

This formula gives information about the percentage of change compared to the single task value. A positive value indicates a decrease of speed. The parameter "subtraction errors" was defined by the proportion of people among a cohort which made at least one error.

Results

Six hundred eighty-six persons were included in the analysis. Details about demographic and clinical variables are supplied in table 1. Among the investigated single tasking conditions, habitual walking speed, maximum walking speed, and checking boxes speed were not significantly associated with TMT performance. Only subtracting serial 7 s speed (good versus poor performers, $p<0.001$) was associated with TMT performance. In addition, more poor than good performers made at least one error when subtracting serial 7 s ($p<0.001$, table 2).

Under dual tasking conditions, checking boxes speed when walking with maximum speed and maximum walking speed when checking boxes were not significantly associated with TMT performance. Subtracting serial 7 s speed when walking with maximum speed (good versus poor performers, $p<0.001$), and maximum walking speed when subtracting serial 7 s (good versus poor performers, $p<0.001$) were associated with TMT performance. More poor performers than good performers made at least one error when subtracting serial 7 s ($p = 0.002$). Details are supplied in table 2.

Dual task costs were not significantly different between the investigated groups for checking boxes speed and for subtracting serial 7 s speed, respectively. Also dual task costs at maximum walking speed when checking boxes was not significantly different between the groups. Dual task costs at maximum walking speed when subtracting serial 7 s was higher in the poor TMT performance group (good versus poor performers, $p<0.001$). In addition, among the good and intermediate performers, groups proportions that made an error when subtracting serial 7 s were higher under the dual task condition than under the single task condition. Among the poor performers, the proportion that made a calculation error when subtracting serial 7 s was *lower* under the dual task condition than under the single task condition (good vs. poor performers, $p = 0.035$). Detailed data are shown in table 3. A schematic overview of the abovementioned results is given in figure 1.

Discussion

The main new finding of this representative study of non-demented healthy elderly is that under most challenging dual tasking conditions, subjects with poor cognitive flexibility and working memory show higher dual task costs of the walking task but perform better in the subtracting serial 7 s task, compared to older persons with good cognitive flexibility and working memory. Thus, older persons with poor cognitive flexibility and working memory do not show a *comparably* increased slowing of motor and cognitive processes in dual tasking as one may expect, but prioritize the cognitive task at the expense of the gait task. As healthy adults prioritize stability of gait when walking and simultaneously performing a cognitive task [2,8,9], our findings argue for an altered prioritization process in older persons with poor cognitive flexibility and working memory. This is, to the best of our knowledge, the first study demonstrating a direct link between these executive functions in a considerably large cohort of healthy elderly.

This study used a similar approach as a former study [7]. In this former study the authors found that poor TMT performance was associated with poor performance when walking on an obstacle course. Despite some relevant differences regarding the study population between the former and our study (e.g., age at study

Table 2. Single and dual task results.

Performers	good	intermediate	poor	P
Single task conditions				
Walking with habitual speed [m/s]	1.39 (0.87–1.99)	1.38 (0.85–2.02)	1.36 (0.93–1.81)	0.85
Walking with maximum speed [m/s]	1.75 (1.04–2.51)	1.70 (1.06–2.53)	1.64 (1.06–2.59)	0.20
Checking boxes [1/s]	1.64 (1.00–2.30)	1.56 (0.99–2.37)	1.48 (0.81–2.81)	0.03
Subtracting [1/s]	0.41 (0.13–1.08)	0.36 (0.09–0.90)*	0.32 (0.07–0.93)*	<0.001
At least one subtraction error (proportion of cohort, %)	24.5	37.0*	43.8*	<0.003
Dual task conditions				
Walking when checking boxes [m/s]	1.53 (0.88–2.20)	1.47 (0.85–2.20)	1.42 (0.83–2.30)	0.08
Checking boxes when walking [1/s]	1.46 (0.60–2.59)	1.39 (0.55–2.44)	1.32 (0.46–3.66)	0.42
Walking when subtracting [m/s]	1.44 (0.92–2.15)	1.40 (0.68–2.53)	1.30 (0.74–2.06)*#	<0.001
Subtracting when walking [1/s]	0.48 (0.07–1.12)	0.45 (0.07–1.03)*	0.37 (0.05–1.05)*#	0.004
At least one subtraction error (proportion of cohort, %)	27.5	40.5*	42.2*	0.003

Data are presented with median and range. P-values were calculated using a logistical regression model and the likelihood ratio, with correction for age, gender, education level, Mini Mental Status Examination score and Becks Depression Inventory score.
*p<0.05 compared to good performers;
#p<0.05 compared to intermediate performers.
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inclusion was 64 years in our study, and 75 years in the former one; education period 14 versus 6 years; Mini-Mental State Examination score 29 versus <26 points; delta TMT of the poor performers in this study >58 s, of the *good* performers in the former study <78 s) and differing study outlines (no dual tasking paradigms in the former study) some aspects are comparable: All three TMT performance groups of the former study used similar speed when walking with habitual speed, and differences between the groups were only observable under the more complex walking situation. With regard to the abovementioned association between prioritization and dual task behaviour, it is tempting to speculate that those subjects who performed poor on the obstacle course in the former study would also differ from the good TMT performers regarding their prioritization pattern.

Dual task costs are defined as adaptation processes during the simultaneous performance of two tasks in comparison to perform each task solely. It is a measure of the effect of divided attention. As dividing attention is considered an executive function, we conclude that, under "dual" tasking conditions, every subject performed three processes simultaneously: (i) a motor task (use of lower limbs, walking), (ii) a motor task (use of upper limbs, checking boxes) or an executive task (subtraction of serial 7 s), and (iii) an executive task (division of attention). According to this mechanistic model, either *two* motor tasks and *one* executive function task, or *one* motor task and *two* executive function tasks were simultaneously performed. Dual task costs of poor TMT performers were not different from good TMT performers when performing two motor and one executive function tasks simultaneously. This may be due to simplicity of the tasks; however this does not explain why none of the tasks was prioritized. We hypothesize that, in this particular situation, persons with poor executive function have sufficient capacity to divide attention appropriately. Contrary, dual task costs were higher in poor performers when performing *one* motor and *two* executive function tasks which affected the lower limb motor task, and the dividing attention task (but not the serial 7 s subtraction task). Thus, subjects with poor executive function capabilities may suffer from a bottleneck when performing two executive functions simulta-

Table 3. Dual task costs.

Performers	good	intermediate	poor	P
Dual task costs				
Walking when checking boxes [%]	11.0 (−5.4–35.8)	10.9 (−76.0–65.0)	12.8 (−40.3–58.1)	0.11
Checking boxes when walking [%]	10.4 (−83.2–53.0)	10.2 (−66.8–54.1)	12.0 (−121.0–68.5)	0.51
Walking when subtracting [%]	16.7 (−16.1–43.4)	17.3 (−38.0–58.2)	19.8 (−6.3–58.6)*#	<0.001
Subtracting when walking [%]	−15.9 (−156.9–75.4)	−22.6 (−227.4–60.5)	−17.3 (−190.1–76.8)	0.20
At least one subtraction error (proportion of cohort, %)	3.0	3.5	−1.6*	0.07

Data are presented with median and range. P-values were calculated using a logistical regression model and the likelihood ratio, with correction for age, gender, education level, Mini Mental Status Examination score and Becks Depression Inventory score. Difference of subtraction errors were calculated with Chi square test.
*p<0.05 compared to good performers;
#p<0.05 compared to intermediate performers.
doi:10.1371/journal.pone.0027831.t003

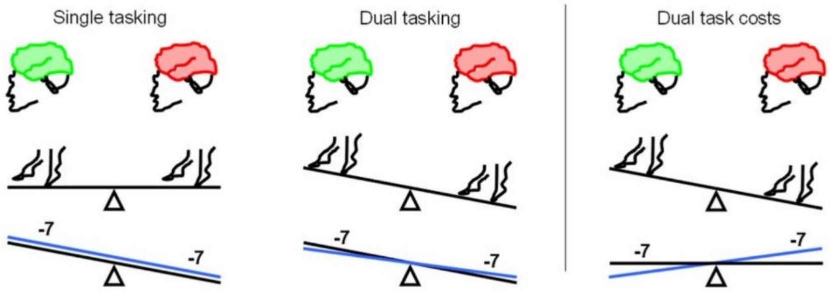

Figure 1. Good versus poor trail making test performers: overview of differences in single and dual tasking behaviour, and in dual task costs. Under challenging conditions, older persons with good Trail Making Test (TMT) performance (good cognitive flexibility and working memory; green brain, left) perform comparably well as poor TMT performers (red brain, right) regarding walking velocity, but better on a cognitive single task which is associated with executive functioning (subtracting serial 7 s). The black line represents subtraction velocity and the blue line subtraction errors. Under dual tasking conditions (maximum walking speed and subtracting serial 7 s with maximum speed), poor performers walk more slowly than good TMT performers. Velocity of the serial −7 s task is still lower in the poor TMT performers, but the difference in number of errors between good and poor TMT performers is smaller than under single task conditions. This is also reflected in the dual task costs: Regarding the walking task, dual task costs are higher in poor TMT performers than in good TMT performers. However, dual task costs of velocity of the serial −7 s task are not significantly different, and dual task costs of subtraction errors are even lower in poor TMT performers than in good TMT performers. This demonstrates that older persons with poor cognitive flexibility and working memory prioritize differently to those with good cognitive flexibility and working memory when performing a challenging dual task paradigm with a walking and a cognitive task.
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neously. In this situation, these subjects prioritize the subtracting serial 7 s task (but obviously not the dividing attention task) at the expense of the motor task. From a clinical point of view this may be of relevance: Older persons with poor cognitive flexibility and working memory may be at particular risk for walking problems and falls under dual tasking situations which include an executive task not only because they are more prone to bottleneck situations per se, but also because of deteriorated prioritization capabilities. Our hypothesis is corroborated by two recent studies: Parkinson disease patients [10] and elderly fallers [11] have been shown to perform a secondary task most accurately at the expense of walking velocity. In addition, slowing of walking speed during secondary tasks can increase balance demands due to an increase of time spent for balancing the body over the stance leg [20,21].

Interestingly, box checking with crosses did not add relevant information. As recently discussed by Al-Yahya and colleagues [22], this may not (only) be explained by the strong motor aspect of the task, but (also) by the observation that cognitive tasks that involve external interfering factors (e.g. reaction time) seem to disturb gait performance less than those involving internal interfering factors (e.g. mental tracking). In addition, the subtraction task may be considered more difficult than the box checking task and thus more informative regarding our working hypothesis. It has recently been shown that increased cognitive task complexity resulted in greater slowing of gait during dual tasking situations [23].

Limitations

First, falls frequency of the study participants was not evaluated. Although there is convincing evidence that executive dysfunction is associated with occurrence of falls [12,24] it would be interesting to compare this outcome parameter with prioritization aspects. Second, all groups performed better (faster) when subtracting serial 7 s under dual tasking, than under single tasking conditions. This may be best explained by learning effects (the dual task assessment was always performed after the single task assessment) or by a "rhythmicity" effect due to the simultaneously performed walking task. Nevertheless, this does not challenge the primary outcome of the study, i.e. the altered prioritization effect. Third, the cognitive test used for the assessment of cognitive flexibility gives rather crude information, and no test battery has been performed that more precisely differentiates between different forms of executive (dys)function. Future studies may thus use more detailed test batteries.

Conclusion

This study demonstrates that poor cognitive flexibility and working memory in older subjects does not automatically lead to comparable dual task costs in the walking and non-walking task. Under most challenging dual tasking conditions, these subjects prioritize the cognitive task at the expense of the motor task. This "posture second" strategy may have effects on gait stability.

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Author Contributions

Conceived and designed the experiments: MAH CB GWE DB WM. Performed the experiments: MAH RN SIM KB AG HH JG WM. Analyzed the data: MAH RN GWE DB WM. Contributed reagents/materials/analysis tools: MAH GWE DB WM. Wrote the paper: MAH WM. Revised the manuscript at least once: MAH RN SIM KB CB HH AG JG GWE DB WM.

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2.2 Publication 2: Gait is associated with cognitive flexibility: A dual-tasking study in healthy older people

This section consists of the following publication including the online published supplementary data:

Gait is associated with cognitive flexibility: A dual-tasking study in healthy older people.
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Gait Is Associated with Cognitive Flexibility: A Dual-Tasking Study in Healthy Older People

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Objectives: To analyze which gait parameters are primarily influenced by cognitive flexibility, and whether such an effect depends on the walking condition used.

Design: Cross-sectional analysis.

Setting: Tübingen evaluation of Risk factors for Early detection of Neurodegenerative Disorders.

Participants: A total of 661 non-demented individuals (49–80 years).

Measurements: A gait assessment with four conditions was performed: a 20 m walk at convenient speed (C), at fast speed (F), at fast speed while checking boxes (FB), and while subtracting serial 7s (FS). Seven gait parameters from a wearable sensor-unit (McRoberts, Netherlands) were compared with delta Trail-Making-Test (dTMT) values, which is a measure of cognitive flexibility. Walking strategies of good and poor dTMT performers were compared by evaluating the patterns of gait parameters across conditions.

Results: Five parameters correlated significantly with the dTMT in the FS condition, two parameters in the F and FB condition, and none in the C condition. Overall correlations were relatively weak. Gait speed was the gait parameter that most strongly correlated with the dTMT ($r^2 = 7.4\%$). In good, but not poor, dTMT performers differences between FB and FS were significantly different in variability-associated gait parameters.

Conclusion: Older individuals need cognitive flexibility to perform difficult walking conditions. This association is best seen in gait speed. New and particularly relevant for recognition and training of deficits is that older individuals with poor cognitive flexibility have obviously fewer resources to adapt to challenging walking conditions. Our findings partially explain gait deficits in older adults with poor cognitive flexibility.

Keywords: aging, dual tasking, executive function, gait, cognitive flexibility

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INTRODUCTION

Cognitive flexibility is part of the subdomain "shifting" of executive function (Miyake et al., 2000). It is controlled by the frontal lobe and associated areas (Miyake and Friedman, 2012), and influenced by aging (Wecker et al., 2005) and diseases, such as dementia (Stopford et al., 2012) and stroke (Rasquin et al., 2002). Cognitive flexibility is required for adapting behavior to external influences (Gilbert and Burgess, 2008; Klanker et al., 2013). This flexibility is necessary for the unrestricted performance of daily life during waking states, because it helps to make the right decisions in multitasking situations. Cognitive flexibility is often measured with the delta Trail-Making Test (dTMT) under experimental conditions (Ble et al., 2005; Bowie and Harvey, 2006; Coppin et al., 2006; Montero-Odasso et al., 2009; Hirota et al., 2010). Cognitive flexibility is likely associated with gait particularly during difficult walking situations, such as fast walking and walking when performing additional tasks, but this effect was not investigated in detail. This hypothesis arises from the following studies.

An investigation of 926 older community-dwelling persons with a mean age of 75 years using a single tasking (ST) 4 m walk at a convenient speed and a 7 m fast walk with obstacles (Ble et al., 2005) demonstrated an association between gait speed and cognitive flexibility, as measured with the dTMT in the fast walking with obstacles, but not in the convenient walking paradigm. This report was the first study to indicate an association of cognitive flexibility with gait speed in complex walking conditions in older adults (Ble et al., 2005; Coppin et al., 2006).

In another study of 493 Japanese individuals with a mean age of 74 years, the influence of cognitive flexibility on gait speed in particular under challenging walking conditions was also proposed (Hirota et al., 2010). The participants performed walking tasks of different levels of complexity, and the primary result revealed a stronger association of dTMT with the walking performance in more complex tasks compared to convenient walking.

Finally, the most convincing evidence for an interplay of cognitive flexibility and gait under dual tasking (DT) conditions comes from the Irish longitudinal Study on Aging (Killane et al., 2014). In this study, 4431 participants with a mean age of 62 years underwent walking tasks under ST and DT situations, and cognitive flexibility measures (i.e., the Color Trail Test) correlated significantly with gait speed only during DT, but not ST, situations.

Common in all of these studies is that they found associations of cognitive flexibility with gait. People with poor cognitive flexibility seem to have deficits in gait (control), especially in more difficult gait conditions. This might indicate that people with poor cognitive flexibility have a lower capacity to adapt to the demands of the more difficult walking condition. However, none of the above-mentioned studies reported other quantitative gait parameters beyond gait speed. As gait speed seems to be a sensitive but unspecific parameter to assess health in older age (Studenski et al., 2011), we were interested in whether cognitive flexibility is also associated with quantitative gait parameters "beyond" gait speed and with the "strategies" that are used in walking conditions with different levels of difficulty. This assessment can contribute to a mechanistic model of the interplay between cognitive flexibility and walking behavior.

MATERIALS AND METHODS

Study Participants and Clinical Assessment

Data of 715 healthy, non-demented individuals who participated in the baseline assessment of the TREND study[1] (Tübingen evaluation of **R**isk factors for **E**arly detection of **N**eurodegenerative **D**isorders) (Hobert et al., 2011) were considered for this analysis.

The study protocol has been reported elsewhere (Gaenslen et al., 2014). In brief, the TREND study aims at the early detection of neurodegenerative diseases and includes healthy community-dwelling people with or without risk factors for such diseases, i.e., REM sleep behavior disorder, depression, or hyposmia. Study participants were recruited via newspaper advertisements, information events and flyers. All underwent a telephone screening and were considered if they denied psychiatric disorders (other than depression), epilepsy, multiple sclerosis, stroke, dementia, encephalitis malignancies and the need of walking aids. The participants were investigated prospectively in 2009 and 2010.

Out of the 715 participants who performed the measurements, a total of 54 participants were excluded because of technical issues with the sensor system (32), negative or missing dTMT data (13), Mini-Mental State Examination (MMSE) <25 (4) (Folstein et al., 1975) or a diagnosis of Parkinson's disease (PD) (5) (Hughes et al., 1992). Therefore, 661 subjects were included in the analysis. Excluded participants did not significantly differ from the included cohort in age, sex, or education level. All participants included were between 49 and 80 years of age and able to walk independently without ambulatory aids or assistance. **Table 1** lists the demographic characteristics.

The ethics committee of the Medical Faculty of the University of Tübingen, Germany approved the study (Nr. 90/2009BO2). All subjects gave informed written consent.

Gait Assessment

Participants were instructed to walk along a 20 m long, obstacle-free path in an at least 1.5-m wide corridor under the following four conditions: (i) ST walking at a convenient speed; (ii) ST walking at a fast speed; (iii) DT walking at a fast speed and checking boxes at a fast speed; (iv) DT walking at fast speed and subtracting serial 7s at a fast speed. No prioritization of any task was given for the DT tasks. The order of the tasks was (i–iv) for all subjects. In the checking boxes task, study participants were asked to carry a clipboard with a sheet of paper on it. They had to mark the boxes of a table drawn on the paper with a cross as fast as possible. In the subtracting serial 7s task, participants had to subtract 7s from a random three-digit number

[1] www.trend-studie.de

TABLE 1 | Demographic data.

	Entire cohort $N = 661$	Good dTMT Performers $N = 219$	Poor dTMT performers $N = 224$	*P*-value
Female [%]*	53.0	54.8	53.6	0.80
Age [years]	63.2 (7.2)	60.9 (6.7)	65.3 (7.1)	**<0.0001**
MMSE (0–30)	28.8 (1.1)	29.2 (1.0)	28.5 (1.2)	**<0.0001**
TMT A [s]	36.5 (12.1)	34.8 (10.7)	38.8 (13.9)	**0.0009**
TMT B [s]	90.0 (35.8.)	60.3 (12.3)	126.5 (35.1)	**<0.0001**
dTMT [s]	53.5 (31.3.)	25.5 (7.2)	87.7 (28.6)	**<0.0001**
BDI (0–63)	7.9 (6.8.)	7.8 (6.4)	8.3 (6.9)	0.38
Weight [kg]	74.8 (13.5)	74.1 (14.0)	75.3 (13.2)	0.38
Height [cm]	170.8 (8.2)	171.2 (7.9)	170.4 (8.5)	0.27
Education period [years]	14.6 (2.7)	15.2 (2.6)	14.0 (2.7)	**<0.0001**

**Data are presented with mean and standard deviation or frequency, and p-values were assessed using Student's t-test and Chi-squared tests. Level of significance (two-sided) was set at 0.05. $p < 0.05$ are displayed bold. BDI, Beck's Depression Inventory; dTMT, delta Trail-Making Test (part B - part A); MMSE, Mini Mental State Examination; TMT, Trail-Making Test.*

continuously as fast as possible. The instruction were "Please walk with convenient gait speed and do not risk falling!" for task (i), "Please walk as fast as you can, do not run, do not risk falling!" for task (ii), "Please walk as fast as you can, do not run, do not risk falling, and mark each of the boxes on the sheet of paper with a cross as fast as you can!" for task (iii) and "Please walk as fast as you can, do not run, do not risk falling, and subtract serial 7s as fast as you can from the number I will shortly tell you!" for task (iv).

All subjects wore a small sensor unit (Dynaport Hybrid, McRoberts B.V., The Hague, The Netherlands) that was fixed at the lower back with a belt during the gait tasks. The sensor unit included a 3-axis accelerometer and 3-axis gyroscope with a sampling rate of 100 Hz. Only the middle 70% of steps of the recorded gait information were analyzed to avoid artifacts during gait acceleration and deceleration phases (Lindemann et al., 2008). Overall, number of steps that were included in the analyses ranged from 14 to 29. Quantitative gait parameters were calculated with established algorithms using acceleration in the anterior-posterior direction (Zijlstra and Hof, 2003; Brandes et al., 2006; Dijkstra et al., 2008; Houdijk et al., 2008) through the McRoberts web platform[2]. Raw data were filtered by a bandpass filter between 0.05 and 7 Hz and a tilt correction was used. The included parameters contribute basically to the following gait domains (Verghese et al., 2008): pace (gait speed, number of steps), rhythm (stride duration, double support time) and variability of gait (stride duration variability (calculated using the coefficient of variation (CV) of stride duration (Montero-Odasso et al., 2011)), phase coordination index (PCI, describing the regularity between right and left step phases) (Plotnik et al., 2008), and gait asymmetry (describing the relationship between the average swing times of right and left steps) (Yogev et al., 2007; Plotnik et al., 2009).

Cognitive Assessment: Trail-Making Test

The time needed to perform the Trail-Making Test (TMT) part B minus A was used to measure cognitive flexibility (dTMT = TMT part B – TMT part A). Details are described elsewhere (Crowe, 1998; Ble et al., 2005; Bowie and Harvey, 2006; Coppin et al., 2006). Briefly, numbers in part A must be connected on a sheet of paper in ascending order as fast as possible. This task primarily tests upper motor performance and visual scanning (Crowe, 1998). Numbers and letters in part B were connected in an alternating manner. This task tests motor performance, visual scanning, and additionally set shifting, i.e., cognitive flexibility (Crowe, 1998).

Statistical Analysis

Statistical analysis was performed using JMP software (version 11.1.1, SAS). Demographic and clinical parameters of the entire cohort and the subcohorts (see below) are presented as mean and standard deviation or frequency. Comparisons were performed using the Student's t-test and the Chi squared test. The level of significance (two-sided) was set at 0.05 because of the exploratory nature of the study.

Regression analyses with quantitative gait parameters and the dTMT score were performed to analyze the influence of cognitive flexibility on gait parameters. Age, sex, education period, MMSE, and Becks Depression Inventory (BDI) (Hautzinger, 1991) were considered relevant covariates for gait tasks as shown before in this cohort (Hobert et al., 2011) and therefore included in the model.

We also defined the highest and lowest tertile of dTMT performers based on the individual dTMT score, according to Ble et al. (Ble et al., 2005), whether cognitive flexibility influences patterns of significant parameter changes across different walking conditions (Ble et al., 2005; Hobert et al., 2011). We therefore performed intra-group comparisons of every gait parameter between the walking conditions performed at a fast speed (ST fast walk, DT fast walk with checking boxes and DT fast walk with subtracting serial 7s) within good and poor dTMT performers separately using the Wilcoxon test for paired samples. We then compared these patterns of significant parameter changes across different walking conditions between good and poor dTMT performers, i.e., whether we can find significant differences between walking conditions within a

[2]www.mcroberts.nl/analysis

dTMT performers group that does not occur in the other group.

RESULTS

Correlations between Gait Parameters and Delta TMT Values

No parameter in the convenient ST walking condition was significantly correlated with the dTMT. Two parameters (gait speed ($p = 0.03$) and number of steps ($p = 0.04$)) in the fast ST walking condition were significantly correlated with the dTMT. Two parameters [gait speed ($p = 0.009$) and stride duration ($p = 0.047$)] in the fast DT walking condition with checking boxes were significantly correlated with the dTMT. Five parameters [gait speed ($p < 0.0001$), number of steps ($p = 0.01$)], stride duration ($p = 0.0006$), gait asymmetry ($p = 0.02$), and PCI ($p = 0.01$) in the fast DT walking condition with subtracting serial 7s correlated significantly with the dTMT. Note that this result is not relevantly affected by applying a Bonferroni-corrected p-value ($0.05/28 = 0.0018$). **Table 2** provides the details.

There is the trend that the highest r^2 values, which indicated the strongest association with the dTMT, of all gait parameters included in the analyses, were found in gait speed across all four walking conditions. The highest r^2 (7.4%) was observed in the walking at fast speed with simultaneously subtracting serial 7s condition.

TABLE 2 | Correlation values between quantitative gait parameters and the delta Trail-Making Test.

	r^2	*P*-value
Gait speed ST convenient speed	0.024	0.07
Gait speed ST fast speed	0.046	**0.03**
Gait speed DT checking boxes	0.054	**0.009**
Gait speed DT subtracting serial 7s	0.074	**<0.0001**
Number of steps ST convenient speed	0.017	0.17
Number of steps ST fast speed	0.030	**0.04**
Number of steps DT checking boxes	0.024	0.21
Number of steps DT subtracting serial 7s	0.022	**0.01**
Stride duration ST convenient speed	0.000	0.84
Stride duration ST fast speed	0.010	0.54
Stride duration DT checking boxes	0.023	**0.047**
Stride duration DT subtracting serial 7s	0.029	**0.0006**
Double support time ST convenient speed	0.005	0.33
Double support time ST fast speed	0.000	0.80
Double support time DT checking boxes	0.009	0.39
Double support time DT subtracting serial 7s	0.008	0.19
Stride duration CV ST convenient speed	0.000	0.99
Stride duration CV ST fast speed	0.005	0.53
Stride duration CV DT checking boxes	0.000	0.24
Stride duration CV DT subtracting serial 7s	0.005	0.21
Asymmetry ST convenient speed	0.000	0.75
Asymmetry ST fast speed	0.001	0.55
Asymmetry DT checking boxes	0.000	0.57
Asymmetry DT subtracting serial 7s	0.005	**0.02**
PCI ST convenient speed	0.000	0.49
PCI ST fast speed	0.001	0.94
PCI DT checking boxes	0.000	0.63
PCI DT subtracting serial 7s	0.011	**0.01**

P-Values were corrected for age, Beck's Depression Inventory (BDI), education period, Mini Mental State Examination (MMSE), and sex. P-values below 0.05 were considered significant and displayed bold. CV, coefficient of variation, DT, dual task; PCI, phase coordination index; ST, single task.

Comparison of Gait Parameters between Good and Poor dTMT Performers

No parameter in the convenient ST walking condition was significantly different between the good and the poor dTMT performers. In the fast ST walking condition, two parameters [gait speed ($p = 0.003$) and number of steps ($p = 0.02$)] were different between groups. The following five parameters were significantly different between groups in the fast DT walking condition with checking boxes: gait speed ($p < 0.0001$), number of steps ($p = 0.02$), stride duration ($p = 0.002$), double support time ($p = 0.02$), and stride duration CV ($p = 0.01$). In the fast DT walking condition with subtracting serial 7s, the following six gait parameters were significantly different between the two dTMT groups: gait speed ($p < 0.0001$), number of steps ($p = 0.03$), stride duration ($p < 0.0001$), double support time ($p = 0.004$), gait asymmetry ($p = 0.01$), and PCI ($p = 0.04$). Details are provided in Supplementary Table 1.

Differences in Gait Adaptation Strategies between Good and Poor dTMT Performers

Both dTMT groups showed significant differences for gait speed, step time and double support time between the three walking conditions, and significant differences for number of steps between ST walking with fast speed and both DT walking conditions. In other words, the above-mentioned patterns of significant changes from one to another walking condition were identical between the good and poor dTMT performers. On the contrary, good, but not poor, TMT performers showed significant differences for stride time CV, gait asymmetry, and PCI between the DT walking condition with checking boxes and the DT walking condition with subtracting serial 7s. Poor, but not good, dTMT performers showed a significant difference for PCI between the ST walking condition with fast speed and the DT walking condition with checking boxes. In other words, the above-mentioned patterns of significant changes from one to another walking condition were different between the good and poor dTMT performers. **Figure 1** provides an overview of these significant changes, with square brackets that are different between cohorts marked in bold."

Note that use of a Bonferroni-corrected p-value of 0.0012 did not relevantly affect these results. Only double support time, a parameter relatively closely associated with the gait variability domain (Verghese et al., 2009; Callisaya et al., 2011), then also showed a different pattern of significant parameter changes across the walking conditions between good and poor dTMT

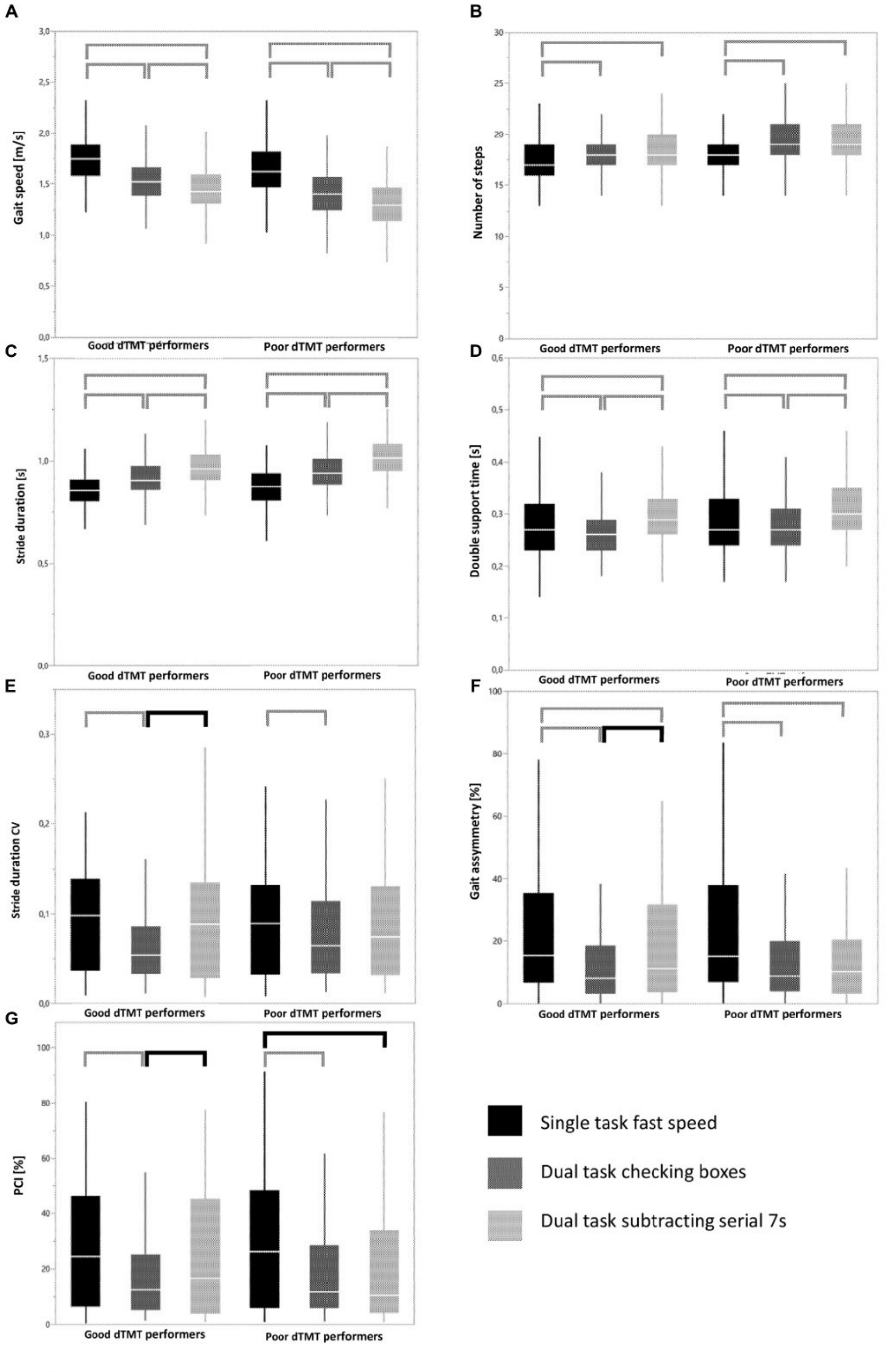

FIGURE 1 | Continued

FIGURE 1 | Overview of patterns of significant parameter changes across different walking conditions in good and poor delta Trail-Making Test (dTMT) performers in different gait parameters (A–G). Data are shown with box plots. Horizontal lines mark the mean, boxes the first and third quartiles, and whiskers the outermost data point within 1.5-fold the interquartile range above the third quartile or below the first quartile. Square brackets indicate significant differences between walking conditions within a group. Bold square brackets indicate significant differences between distinct walking conditions that occurred in one group but not in the other group. Lower standard deviations in particular in variability-associated parameters under DT than under ST conditions may indicate some rhythmicity, cueing and "magnet" effects induced by the secondary task. These effects have been described previously (Ebersbach et al., 1995; Beauchet et al., 2010). Note that differences of absolute parameter values between groups are not provided in this figure. They are available in Supplementary Table 1. Detailed *p*-values of the square brackets are presented in Supplementary Table 2.

performers. For sake of completeness, the correlations between gait parameters are provided in Supplementary Table 3.

DISCUSSION

This study evaluated quantitative gait parameters of four walking paradigms in a large cohort of healthy older adults wearing a small sensor unit at their lower back, and investigated the association of gait parameters and walking paradigms with cognitive flexibility. Recognizing and addressing such specific deficits in therapy and training settings may lead to improved gait performance in older adults with poor cognitive flexibility.

Our results partially confirm the results of previous studies (Ble et al., 2005; Coppin et al., 2006; Montero-Odasso et al., 2009; Hirota et al., 2010; Berryman et al., 2013; Killane et al., 2014): More challenging walking paradigms require more cognitive flexibility than simple paradigms. In our study, it is reflected by an increasing number of significantly different quantitative gait parameters with increasing difficulty of the walking condition. Accordingly, our observations suggest that the best walking task for the assessment of cognitive flexibility is the DT fast walk with subtracting serial 7s. This task exhibited the highest number of quantitative gait parameters that were significantly associated with the dTMT, and it also included the gait parameter that correlated strongest with the dTMT (gait speed). This observation may be simply explained by the increased influence of supraspinal control mechanisms on gait under more challenging walking conditions (Maetzler et al., 2013; Hobert et al., 2014). However, the obviously higher influence of cognitive flexibility on walking during subtracting serial 7s compared to walking when checking boxes requires further reflection. The control of a DT situation *per se* is a cognitive task, which means that a cognitive process is involved in sharing of resources or shifting of attention between the different tasks, and controls the prioritization of the tasks (Hobert et al., 2011). Based on this, we assumed that the following individual situations were present in our experimental setting. A study participant performed two tasks with mainly motor components (walking and checking boxes) during the checking boxes DT and one cognitive task (the above-mentioned cognitive control of the DT situation). A person during the serial subtraction task performed one task with a primarily motor component (walking) and two tasks with primarily cognitive components (serial subtraction and cognitive control of the DT situation). The bottleneck hypothesis proposes that the processing of two tasks using the same (or similar) network(s) create(s) a bottleneck (Ruthruff et al., 2001; Yogev-Seligmann et al., 2008). Therefore, a gait paradigm with *two* cognitive tasks performed in a (relatively) healthy cohort should exhibit "more" correlation with the dTMT than a gait paradigm with one cognitive task. This presumption was observed in our study.

Indirect support for the above hypothesis comes from studies investigating individuals with motor network deficits, e.g., patients with mild-to-moderate PD (i.e., at a disease stage, where the motor deficits are generally more prominent than the cognitive deficit). These patients might experience the performance of two motor tasks and one cognitive task as more challenging than the performance of one motor task and two cognitive tasks. Our prospective longitudinal study of PD patients with and without falls during an observation period of 3.5 years demonstrated that only DT deficits in the checking boxes task, but not in the subtracting serial 7s task, predicted the first fall in the former group (Heinzel et al., 2016). A recent study did not find any additional value of a cognitive DT paradigm on falls in 263 mild-to-moderate PD patients (Smulders et al., 2012). Unfortunately, the authors did not include a secondary task with a primarily motor component in their study protocol (Smulders et al., 2012).

After the association of cognitive flexibility with walking conditions, we analyzed the association of cognitive flexibility with different gait parameters: The parameter that was most closely associated with the dTMT was gait speed, followed by stride duration and number of steps. This result indicates that pace-associated parameters are more closely correlated with cognitive flexibility than variability-associated parameters, which is basically consistent with the results of a recent study (Martin et al., 2013). However, the authors in the previous study focused on the comparison of gait and executive function in general, and not specifically on cognitive flexibility (Martin et al., 2013). The result is still surprising, because one may associate cognitive flexibility with adaptation, rather than velocity aspects of gait. Regardless of the mechanisms for the "dominance" of gait speed over other quantitative gait parameters for, e.g., detection of gait deficits per se (Lord et al., 2013), motor-cognitive interference deficits (Al-Yahya et al., 2011), and aspects of general health and survival (Studenski et al., 2011), gait speed is a non-specific parameter. This fact is also true for the prediction of cognitive flexibility using this parameter. Gait speed (only) explained 7.4% of the variance of dTMT in the most challenging walking task of our setting.

As a general comment, single quantitative gait parameters may not reach sufficiently high prediction values for any kind of pathology or alterations of human movement that eventually enable an individual diagnosis. The more promising approach to differentiate between specific pathologies / alterations and control states and detect progression and changes due to therapy may be the use of "gait parameter panels" or multivariate regression models. Such models can account for the complex interplay between (dys)function and the compensation mechanisms that are involved in complex movements, such as gait and balance performance in particular under challenging conditions (Maetzler and Hausdorff, 2012; Lord et al., 2013; Maetzler et al., 2013).

This study demonstrated also that cognitive flexibility influences the "type" of walking pattern a person uses in distinct challenging walking situations. Good dTMT performers exhibited significantly increased variability, asymmetry, and irregularity of gait (Hausdorff et al., 2006; Plotnik et al., 2007; Montero-Odasso et al., 2011) in the subtracting serial 7s DT compared to the (easier) checking boxes DT. Notably, poor dTMT performers did not adapt their parameters accordingly, which indicates an impairment of this adaptation strategy. We interpret this finding as follows: Individuals with poor cognitive flexibility reach the maximum adaption capability of their walking pattern earlier than individuals with good cognitive flexibility in a sequence of walking tasks with increasing levels of complexity. A recent study (Lowry et al., 2012) indirectly supports our hypothesis. This study compared the gait parameters of walking along a figure 8 (where changes between walking patterns are necessary) with straight walking (no changes necessary) in 106 old adults and found a significant association between dTMT and the number of steps only when walking on the figure 8 (Lowry et al., 2012).

The present study has some limitations. First, quantitative gait parameters were assessed with a wearable sensor at the lower back. This technique may not be as accurate as more complex gait evaluation systems in measuring at least some of the gait parameters, e.g., double support time. Second, we analyzed approximately 14 m of steady state walking. Although other studies used even shorter distances (Ble et al., 2005; Montero-Odasso et al., 2011; Killane et al., 2014), longer walking distances may deliver more valid gait parameters. It has been shown that the reliability of gait parameters improves with increasing number of steps. This is the case for gait variability parameters (Galna et al., 2013), whereas gait speed reaches already the steady state after 2.5 m (Lindemann et al., 2008). Third, the different tasks were not randomized and may result in a learning effect, but this effect should be comparable in all groups.

CONCLUSION

This study demonstrates that cognitive flexibility is associated with walking, in particular under challenging walking conditions, in a cohort of older adults without relevant motor and cognitive deficits. We also demonstrated that older individuals with poor cognitive flexibility use a pattern in variability-related gait parameters across walking conditions that differs from individuals with good cognitive flexibility. This difference might indicate a lower capability of the former population to adapt to challenging walking situations with different demands. Our findings add relevant information to our understanding of gait and balance deficits in older adults with poor cognitive flexibility and may give a basis for interventional studies.

AUTHOR CONTRIBUTIONS

MH, DB, and WM made substantial contributions to the acquisition, analysis and interpretation of data for the work. MH, SM, SH, FM, US, and GE made substantial contributions to the acquisition of the data. MH and WM drafted the paper, all remaining authors revised the draft critically for important intellectual content. All authors gave their final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00154/full#supplementary-material

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Supplementary material

Supplementary Table 1: Comparison of gait parameters between good and poor dTMT performers

	Good performers Mean (SD)	**Poor performers** Mean (SD)	p-Value
Gait speed ST convenient speed	1.38 (0.17)	1.34 (0.17)	0.97
Gait speed ST fast speed	1.75 (0.24)	1.64 (0.27)	0.003
Gait speed DT checking boxes	1.53 (0.20)	1.42 (0.23)	<0.001
Gait speed DT subtracting serial 7s	1.45 (0.23)	1.30 (0.23)	<0.001
Number of steps ST convenient speed	18.7 (2.35)	19.3 (2.6)	0.74
Number of steps ST fast speed	17.32 (2.15)	18.15 (2.67)	0.02
Number of steps DT checking boxes	18.40 (2.30)	19.25 (2.96)	0.02
Number of steps DT subtracting serial 7s	18.41 (2.57)	19.15 (2.75)	0.03
Stride duration ST convenient speed	1.01 (0.07)	1.01 (0.08)	0.23
Stride duration ST fast speed	0.86 (0.09)	0.87 (0.10)	0.44
Stride duration DT checking boxes	0.91 (0.09)	0.94 (0.10)	0.0019
Stride duration DT subtracting serial 7s	0.97 (0.09)	1.03 (0.17)	<0.001
Double support time ST convenient speed	0.28 (0.05)	0.29 (0.05)	0.07
Double support time ST fast speed	0.28 (0.07)	0.29 (0.07)	0.49
Double support time DT checking boxes	0.26 (0.05)	0.28 (0.05)	0.016
Double support time DT subtracting serial 7s	0.30 (0.05)	0.31 (0.07)	0.004
Stride duration CV ST convenient speed	0.06 (0.05)	0.06 (0.06)	0.05
Stride duration CV ST fast speed	0.09 (0.06)	0.09 (0.05)	0.36
Stride duration CV DT checking boxes	0.07 (0.04)	0.08 (0.06)	0.01
Stride duration CV DT subtracting serial 7s	0.09 (0.06)	0.08 (0.06)	0.69
Asymmetry ST convenient speed	13.6 (18.6)	16.4 (20.6)	0.13
Asymmetry ST fast speed	26.66 (29.12)	27.41 (30.11)	0.29
Asymmetry DT checking boxes	14.76 (20.10)	16.37 (20.30)	0.53
Asymmetry DT subtracting serial 7s	20.67 (23.35)	16.17 (19.66)	0.01
PCI ST convenient speed	15.7 (19.8)	17.5 (19.8)	0.09
PCI ST fast speed	28.14 (21.14)	28.42 (22.47)	0.68
PCI DT checking boxes	17.67 (15.99)	18.92 (17.45)	0.30
PCI DT subtracting serial 7s	24.73 (22.44)	20.04 (19.84)	0.04

Data are presented with mean and standard deviation. P-values were assessed with a regression model with correction for age, Beck's Depression Inventory (BDI), education period, Mini Mental State Examination (MMSE), and sex. P-values below 0.05 were considered significant. CV, coefficient of variation, DT, dual task; PCI, phase coordination index; ST, single task.

Supplementary Table 2: P-values for the comparisons of gait parameters across walking conditions within the good and poor dTMT groups (corresponding to Figure 1 a-g).

	ST / DT checking boxes	ST / DT subtracting	DT checking boxes / DT subtracting
a, Gait speed			
Good dTMT performers	<0.0001	<0.0001	<0.0001
Poor dTMT performers	<0.0001	<0.0001	<0.0001
b, Number of steps			
Good dTMT performers	<0.0001	<0.0001	1.0
Poor dTMT performers	<0.0001	<0.0001	0.5
c, Stride duration			
Good dTMT performers	<0.0001	<0.0001	<0.0001
Poor dTMT performers	<0.0001	<0.0001	<0.0001
d, Double support time			
Good dTMT performers	0.0003	0.0091	<0.0001
Poor dTMT performers	0.0088	<0.0001	<0.0001
e, Stride duration CV			
Good dTMT performers	<0.0001	0.3	<0.0001
Poor dTMT performers	0.026	0.5	0.1
f, Gait asymmetry			
Good dTMT performers	<0.0001	0.0088	0.0020
Poor dTMT performers	<0.0001	<0.0001	0.1
g, PCI			
Good dTMT performers	<0.0001	0.06	<0.0001
Poor dTMT performers	<0.0001	<0.0001	0.4

P-values were assessed with paired t-test between walking conditions within dTMT performer groups. CV, coefficient of variation, DT, dual task; dTMT, delta trail making test; PCI, phase coordination index; ST, single task.

Supplementary Table 3: Correlations between gait parameters within walking conditions separated in good and poor delta Trail Making Test (dTMT) performers.

	Good dTMT performers							**Poor dTMT performers**						
ST fast speed	Gait speed	Number of steps	Stride duration	Double support time	Stride duration CV	Asymmetry	PCI	Gait speed	Number of steps	Stride duration	Double support time	Stride duration CV	Asymmetry	PCI
Gait speed	1	**-0.5**	**-0.7**	-0.1	**0.2**	0.1	**0.2**	1	**-0.6**	**-0.7**	-0.1	0.0	0.1	0.1
Number of steps		1	0.0	-0.1	**-0.2**	-0.1	**-0.3**		1	0.1	0.0	0.1	0.1	0.1
Stride duration			1	**0.2**	**-0.2**	-0.1	-0.1			1	**0.2**	-0.1	**-0.2**	-0.1
Double support time				1	**0.3**	**0.3**	**0.4**				1	**0.3**	**0.1**	**0.3**
Stride duration CV					1	**0.2**	**0.7**					1	**0.3**	**0.7**
Asymmetry						1	**0.6**						1	**0.6**
PCI							1							1
DT checking boxes	Gait speed	Number of steps	Stride duration	Double support time	Stride duration CV	Asymmetry	PCI	Gait speed	Number of steps	Stride duration	Double support time	Stride duration CV	Asymmetry	PCI
Gait speed	1	**-0.5**	**-0.6**	**-0.3**	**0.1**	0.0	0.1	1	**-0.6**	**-0.6**	**-0.4**	0.1	0.1	0.1
Number of steps		1	-0.1	**0.2**	0.0	0.1	0.0		1	**0.1**	**0.2**	0.0	0.0	0.0
Stride duration			1	**0.2**	**-0.2**	-0.1	**-0.1**			1	**0.4**	-0.1	**-0.2**	**-0.1**
Double support time				1	**0.4**	**0.4**	**0.5**				1	**0.3**	**0.4**	**0.5**
Stride duration CV					1	**0.5**	**0.8**					1	**0.5**	**0.7**
Asymmetry						1	**0.7**						1	**0.7**
PCI							1							1
DT subtracting serial 7s	Gait speed	Number of steps	Stride duration	Double support time	Stride duration CV	Asymmetry	PCI	Gait speed	Number of steps	Stride duration	Double support time	Stride duration CV	Asymmetry	PCI
Gait speed	1	**-0.6**	**-0.7**	-0.1	**0.4**	**0.3**	**0.4**	1	**-0.4**	**-0.6**	**-0.3**	**0.2**	0.1	**0.3**
Number of steps		1	0.1	0.0	**-0.2**	**-0.2**	**-0.2**		1	-0.1	**-0.1**	**-0.2**	-0.1	**-0.2**
Stride duration			1	**0.2**	**-0.4**	**-0.3**	**-0.4**			1	**0.6**	-0.1	0.0	**-0.2**
Double support time				1	**0.4**	**0.3**	**0.4**				1	**0.4**	**0.3**	**0.4**
Stride duration CV					1	**0.4**	**0.8**					1	**0.4**	**0.8**
Asymmetry						1	**0.6**						1	**0.6**
PCI							1							1

P<0.05 between different parameters are marked in bold. CV, coefficient of variation, DT, dual task; PCI, phase coordination index; ST, single task.

3. Discussion

The results of the two publications (Hobert et al., 2011, 2017) presented within this thesis show that cognitive flexibility influenced walking behaviour in community-dwelling older adults. In the following section, the results of both publications are discussed separately. Then, a new section introduces a common framework for a more general understanding of the association of cognitive flexibility with falls.

3.1 Discussion of Publication 1

The first paper analysed the association of cognitive flexibility and gait, with specific consideration of prioritization aspects in a cohort of healthy older adults. For this purpose, we used single and dual tasking paradigms. Cognitive flexibility was measured with the TMT. We found an association of cognitive flexibility and gait speed in the dual task walking when subtracting condition, but not in the single tasking walking at fast and at convenient speed and in the dual task walking while checking boxes condition. The most relevant findings of the study were as follows: Under the dual task walking while subtracting serial 7s condition, participants with poor cognitive flexibility had higher dual task costs for gait speed and lower dual task costs for subtraction errors compared to study participants with good cognitive flexibility. Moreover, on an absolute level, participants with poor cognitive flexibility had fewer subtracting errors under the dual task condition than under the single task condition. Dual task costs for the dual task walking while checking boxes condition showed no significant differences between good and poor TMT performers.

3.1.1 Confirmation of previous studies

These results are interesting for the following reasons: The paper confirms results from previous studies investigating the association of cognitive flexibility and gait in cohorts of older adults (Ble et al., 2005; Coppin et al., 2006; Hirota et al., 2010). For example, the results of the present study were comparable with those of the *InChianti study,* the first study investigating this association. The authors of the latter study found in their cohort of 926 participants that participants in the lowest tertile of the delta TMT performance walked more slowly under a challenging walking condition (here: walking at fast speed with obstacles) than those in the highest tertile (Ble et al., 2005). Of note, participants investigated in the *InChianti* study were older (mean age 75 years compared to 64 years in our study), had a lower value in the MMSE (mean value 25.5 compared to 29 points in our study) and performed, as a mean, clearly worse in the TMT (the tertile with the *best* cognitive flexibility in the *InChianti* study was defined by delta TMT values below 78 s, while in our study the tertile with the *worst* cognitive flexibility was defined by delta TMT values above 58 s). It can thus be concluded that the observations made in the *InChianti* study (Ble et al., 2005) and the other studies investigating cognitive flexibility in association with gait (Hirota et al., 2010; Killane et al., 2014) obviously holds true for younger and cognitively more flexible cohorts.

3.1.2 Cognitive flexibility is associated with altered prioritization

The publication presented – in our view for the first time – that participants with poor cognitive flexibility prioritize the subtracting task over the walking task, which is not the case in participants with good cognitive flexibility (i.e., the "gold standard").

Why is this meaningful? The main and surprising aspect of this observation is that participants with poor cognitive flexibility use obviously a dangerous strategy during complex walking situations: They focus on the relatively "useless" subtraction task during a challenging dual tasking paradigm and *not* on the "evolutionarily relevant" walking task, which may eventually lead to severe consequences such as falls and fractures.

How can the behaviour of participants with poor cognitive flexibility be explained from a mechanistic point of view? A relatively simple model is based on the bottleneck theory. This theory describes the situation where two simultaneously performed tasks require the identical network, leading to a decrease of performance of at least one of the tasks due to an overload of the network (Pashler, 1994). This theory could explain our results: Our participants performed walking (a motor task), subtracting (a cognitive task), and dealing with a dual task situation (a cognitive task); that is, they performed two cognitive tasks and one motor task. The bottleneck was thus in the “cognitive network”, which may have been overloaded in the poor TMT performers who a priori have limited cognitive resources. Two further observations may support this hypothesis: In the same study, we did not find significant differences in dual task costs between poor and good performers in walking when checking boxes condition. Based on the proposed model, in this paradigm, two motor tasks (walking and checking boxes) and one cognitive task (the dual tasking situation per se) were performed. Here, a bottleneck in the motor system could become visible but was not apparent in the cohort. However, we have independently investigated a cohort in which such a “motor bottleneck” is most likely apparent. We investigated 36 early PD patients with the same paradigms and with a mean time interval of approximately four months prior to the first fall. Only the dual task walking while checking boxes, but not dual task walking while subtracting serial 7s, predicted the first fall (Heinzel et al., 2016). These individuals, suffering primarily from a central motor disorder, performed two motor tasks and one cognitive task, and it is most likely the bottleneck in the “motor network” that explained the results that were, upon initial inspection in the first view, contrary to those found in the publication discussed here.

3.2 Discussion of publication 2

The second publication evaluated the association of cognitive flexibility and selected gait parameters in single and dual tasking conditions, measured with an IMU at the lower back. In the first step, a correlation analysis between quantitative gait parameters and the TMT values was performed. Within this analysis, the numbers of significantly correlated parameters in each walking condition (single task walking at convenient speed, single task walking at fast speed, dual task walking while checking boxes, and dual task walking while subtracting serial 7s) were determined.

The main results of this first analysis step were as follows: Of all gait parameters and conditions assessed, gait speed in the dual task walking while subtracting serial 7s condition was the parameter explaining the highest proportion of variance of cognitive flexibility. The dual task walking while subtracting serial 7s condition showed the highest number of gait parameters significantly correlated with TMT performance.

Then, in the second analysis step, participants were categorized into groups according to TMT performance, and gait parameters were compared within each of the groups across the walking conditions, single task walking at fast speed, dual task walking while checking boxes, and dual task walking while subtracting serial 7s (single task walking at convenient speed was excluded as it was performed with a different gait speed compared to the above-mentioned conditions and thus not directly comparable). To estimate different strategies to adapt a fast gait to the demands of each condition, patterns of the significant differences within each group were visually compared between groups.

As the main result of this analysis, patterns of the changes across the different walking conditions were altered in poor TMT performers compared to good TMT performers. The differences affected variability-associated but not pace- and rhythm-associated gait parameters. How can these findings be best explained?

3.2.1 Gait speed explains the highest proportion of variance of cognitive flexibility

Gait speed was the parameter that explained the highest proportion of the variance of the TMT, confirming the importance of this parameter. It has been shown that gait speed is a sensitive - but not specific - marker, associated with, e.g., PD (Plotnik et al., 2007), atypical Parkinson syndromes (Raccagni et al., 2018), gait deficits (Lord, Galna and Rochester, 2013), deficits in different cognitive domains (Al-Yahya et al., 2011), and a higher risk of future dementia (Buracchio et al., 2011), as well as more generally with impaired health status and reduced life expectancy (Studenski et al., 2011). In our study, only 7.4% of the variance of the TMT was explained by gait speed although this was the most relevant parameter. Our result supports previous findings suggesting that single gait parameters are too “weak” to explain much of the variance associated with distinct conditions and pathologies (Lord, Galna and Rochester, 2013). Nevertheless, combinations or panels of gait parameters could be more promising, as has been shown in a study investigating 10 PD patients, 11 patients with normal pressure hydrocephalus and 12 controls: The parameters gait speed, step length and step length variability showed differences between both patient groups and controls, but not between the PD patients and patients with normal pressure hydrocephalus. The latter two groups were different in foot angle, step width and step height (Stolze et al., 2001). One more recent study compared quantitative gait parameters under single and dual tasking conditions between 38 patients with progressive supranuclear palsy (i.e., an atypical Parkinson syndrome) with 27 patients with normal pressure hydrocephalus (and 38 healthy controls). The accuracy of the discrimination between the two patient groups combining the gait parameters of all conditions was 97% (Selge et al., 2018). Another promising approach is to include gait parameters in more complex statistical methods, such as support vector machines. One study using data from foot mounted sensors in 23 PD patients and 16 controls found a precision of 97.7% for differentiating between PD patients and controls (Tien et al., 2010). In a study with an unbiased approach with pattern recognition methods, a correct classification rate for the differentiation between PD and controls of 81% was reached (Klucken et al., 2013).

Such methods may soon be used for clinical purposes, e.g., as diagnostic tools and as measures of disease progression and treatment effects.

Interestingly, parameters of the pace domain were more closely related to cognitive flexibility than were parameters of the variability domain. A previous study focusing on executive functions and gait found similar results (Martin et al., 2013). Indirect support of our findings was also found in a phase II trial with donezepil in 43 newly diagnosed patients with Alzheimer's disease (mean age of 77 years). In this study, cognitive flexibility and gait speed improved significantly under treatment, but gait variability did not improve (Montero-Odasso et al., 2015). Another study investigating 177 patients with Alzheimer's disease (mean age of 82 years) found that gait speed at baseline was associated with a decline in executive functions but not in the other cognitive domains (Taylor et al., 2017).

3.2.2 Dual task walking while subtracting serial 7s condition shows most significantly correlated parameters with cognitive flexibility

The dual task walking while subtracting serial 7s condition showed the highest number of gait parameters significantly correlated with TMT performance. We interpret this in the way that a certain level of complexity is necessary to detect (more) differences between different groups.

This effect has been found in previous studies. For example, a study with 25 asymptomatic carriers of a LRRK2 mutation (mutation in the gene encoding for Leucine-rich repeat kinase 2; this is an autosomal-dominant mutation associated with a highly increased risk of PD) and 27 controls found significantly higher values for gait variability in the carriers of the mutation only in the dual tasking (i.e., walking while subtracting serial 7s) but not in the single tasking condition (Mirelman et al., 2011). In a study with 30 PD patients (mean age of 71 years) and 28 controls (mean age of 70 years), differences between the cohorts increased with increasing difficulties among the four gait tasks performed. The largest difference between both groups was found in the task walking while subtracting serial 7s (Yogev et al., 2005). Comparably, a study investigating the effect of eight different dual task walking paradigms in 18 healthy younger (with a mean age of 24 years) and 15 healthy older adults (with a mean age of 67 years) found that older adults had significantly higher dual task costs of gait speed than younger adults only in more difficult conditions. The condition with the largest difference in dual task costs was walking on a walkway with obstacles with simultaneously checking boxes (Bock, 2008).

This finding may have implications for the design of future studies and clinical examination. Based on the model described above, individuals with a bottleneck in cognitive networks might show deficits mainly in (difficult) motor-cognitive interference tasks, while individuals with a bottleneck in motor networks might show them mainly in (difficult) motor-motor interference tasks.

3.2.3 Patterns across walking conditions: Parameters of the variability domain are most informative

In the comparison of the patterns of significant intra-group differences across walking conditions between the good and poor TMT performers, we found that both groups had the same patterns in the parameters gait speed, number of steps, step time and double support time.

In contrast, stride time variability (measured with coefficient of variation, CV), gait asymmetry, and PCI showed different patterns between the good and poor TMT performers: Only the good TMT performers showed significant differences in all three parameters between the conditions dual tasking walking while checking boxes and the condition dual task walking while subtracting serial 7s. Only the poor TMT performers showed a significant difference in the PCI between the single task walking at fast speed condition and the dual task walking while checking boxes condition.

This can be interpreted as the fact that older adults with poor cognitive flexibility seem to adapt less effectively to increasingly difficult walking conditions. A study with 50 adults with a mean age of 74 years performing a gait adaptability assessment with tasks to avoid obstacles and step on a defined target found similar results. Better performance in executive functions, as measured with the Stroop Test and the TMT, were associated with a better performance in the gait adaptability assessment (Caetano et al., 2016). Another study investigating executive functions and a difficult walking condition, i.e., curved walking, also supports our findings: A cohort of 106 older adults with a mean age of 77 years was asked to walk on a figure 8 as well as on a straight walking path. The authors found a significant positive association of number of steps and TMT performance only in the more complex figure 8 walking path and not in the straight walking (Lowry et al., 2012). Walking on walking paths that contain curves, is particularly interesting for studying the adaptability of gait, as walking a curve requires an asymmetrical gait with adaptation of step length of one leg. Another analysis from the *TREND* study (Tübinger evaluation of Risk factors for Early detection of Neurodegenerative Disorders study), including 1054 people with a mean age of 65 years, found different prioritization behaviours in poor TMT performers compared to good TMT performers only when walking on a circular walking path but not on a straight walking path (Salkovic et al., 2017).

The finding that people with poor cognitive flexibility do not as effectively adapt to increasingly difficult walking situations as people with good cognitive flexibility do may be reflected by trips and slips. Trips and slips are (external) perturbations which require (successful) adaptation of gait to prevent a subsequent fall. Therefore, the person has per definition to switch from an easier to a more difficult walking situation, with trips and slips reflecting (at least indirectly) the response to this suddenly increasing walking difficulty. Trips and slips have been found among the most frequent reasons for falls in a study with 704 women with a mean age of 75 years (Lord et al., 1993). There is hope that the active observation of a deficit in adapting to increasingly difficult walking situations can lead to an effective treatment. A randomized controlled trial with 212 older adults performing one single session of slip training with repeated unannounced slips caused by a moveable platform in the walkway found a significantly reduced fall rate prospectively over 12 months in the therapy group compared with the control group (Pai et al., 2014).

3.3 Discussion of publication 1 and 2

3.3.1 Proposed framework for the association of cognitive flexibility and falls

The two publications presented here provide (additional) evidence that cognitive flexibility is associated with both, adaptation of gait (Hobert et al., 2017) and prioritization (Hobert et al., 2011). How could these aspects be brought together and lead to a clinical benefit for patients, e.g., help the clinician who is caring for older adults with a positive fall history?

It is relatively easy to imagine the association of impaired gait adaptation and impaired prioritization capabilities with falls. Multitasking during gait with distracting elements can lead to a shift of prioritization, with preference of the non-walking task, and, consequently, to increased risk of falls. Similarly, the inability to adapt gait to environmental circumstances, e.g., uneven ground, can lead to a fall. For cognitive flexibility, this association with an increased risk of falling is not as obvious. The presented publications might close this gap: The association of cognitive flexibility with falls might work via the association of cognitive flexibility and (deficits in) prioritization and adaptation of gait. Figure 3 presents a framework for the association of impaired cognitive flexibility with falls.

Nevertheless, many more factors most likely contribute to the association between cognitive flexibility and falls, and more studies investigating this association are needed. Ideally, this evaluation is performed in a single and exhaustive study including all potentially contributing factors. Such a study would allow using statistical models that reflect the complexity of the interactions. We (Bettecken et al., 2017) recently used the International Classification of Functioning, Disability and Health (ICF) model (Kostanjsek, 2011) as a comprehensive framework for the statistical comparison of kinematic gait parameters with a measure of quality of life. However, it is very probable that even more complex, semi- or unsupervised models will eventually do the trick.

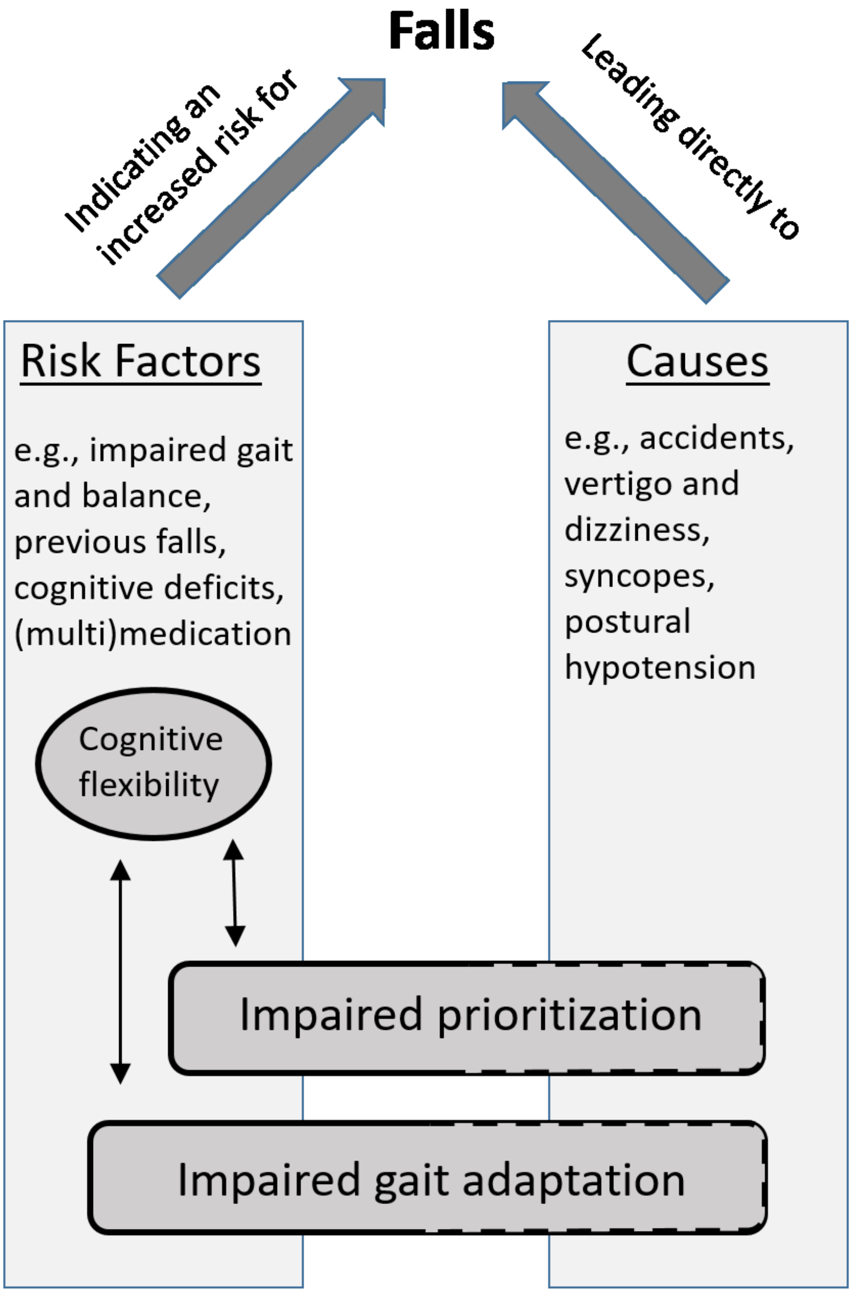

Figure 3: Proposed framework for the association between cognitive flexibility, prioritization and gait adaption with risk factors and causes of falls. Double arrows display the associations between cognitive flexibility and prioritization, and gait adaptation as found in the publications of this thesis. Continuous lines display contributions (to risk factors of falls) shown in previous studies. Scattered lines display suspected and very likely contributions (to causes of falls).

3.3.2 Outlook

The impact of the publications presented above and the more complex studies and analyses in this field that should take place in the future must allow an individual person with daily relevant deficits in motor-cognitive interaction to be identified, classified, specifically counselled and treated based on the factor(s) that primarily drive(s) the deficit. Therefore, individual assessments of patients with deficits of cognitive flexibility should also include an assessment of motor-motor and motor-cognitive interactions, to evaluate potential bottlenecks. Conversely, patients with a positive fall history should always be assessed with regard to potentially evident deficits in prioritization and adaptation of gait.

3.3.3 Limitations

The analyses shown here in both publications face some limitations. In addition to the limitations discussed in both publications themselves, the most important limitation is, in our view, that both publications contain only cross-sectional data and did not include a fall assessment. Such an assessment would allow direct conclusions about the predictive value of cognitive flexibility, prioritization and adaptation of gait for fall risk and falls. This aspect was considered for the follow-ups of the *TREND* study: a structured assessment of falls has been added to the more recent waves of this longitudinal study.

4. Summary

4.1 Summary in Englisch

In recent years, it has been shown that there is a supraspinal network for the control of gait. It consists of motor, cognitive and limbic structures and their projections. These supraspinal networks have an important influence on walking behaviour, e.g., in dual tasking situations. Dual tasking situations are very relevant in everyday life, because they occur very often, e.g. when talking while walking. Deficits in dual tasking can lead to impaired walking and falls. These deficits are most likely driven by deficits in executive functions, such as cognitive flexibility, as they play a particularly important role in the control of dual tasking behaviour.

This thesis presents and discusses two publications about the association of cognitive flexibility and prioritization, as well as the association of cognitive flexibility and quantitative gait parameters and their adaptation to dual tasking conditions.

In both publications, more than 660 healthy older people, aged between 50 and 80 years, were assessed using four single task conditions (subtracting, checking boxes, walking at convenient speed and walking at fast speed) and two dual task conditions (walking at fast speed with checking boxes and walking at fast speed with subtracting serial 7s). As a measure of cognitive flexibility, the Trail Making Test (TMT) was performed.

In publication 1, dual task costs (i.e., the percent decline of task performance under dual tasking compared to single tasking) were calculated. The dual task cost of each task was compared between the tertile of participants with the best (good TMT performers) and of the tertile with the worst (poor TMT performers) performance in the TMT. Under the dual tasking walking while subtracting serial 7s condition, good TMT performers prioritized walking over subtracting. Conversely, poor TMT performers prioritized the subtracting task over walking. These results suggested an association of cognitive flexibility and prioritization.

In publication 2, quantitative gait parameters, collected with a wearable sensor-unit, were correlated with performance of the TMT. We found that a higher

number of gait parameters were significantly correlated with the TMT when the gait task was more challenging. The strongest correlation was found for walking speed in the dual task walking while subtracting serial 7s condition. This indicates that gait speed is an important gait parameter for the investigation of the association of cognitive flexibility with gait, although the parameter is obviously unspecific. In addition, patterns of differences of gait parameters across the conditions of *single task walking at fast speed* and *dual task walking while checking boxes* and *dual task walking while subtracting serial 7s* were compared between good and poor TMT performers. Here, we found different patterns across conditions in the parameters gait variability, phase coordination index, and gait asymmetry. Subjects with good cognitive flexibility seem to switch or adapt strategies between tasks, while participants with poorer cognitive flexibility have limited resources for these adaptations. The findings of this analysis also suggest that cognitive flexibility is important for walking in older adults, and people with poor cognitive flexibility have deficits in adapting walking to challenging walking conditions.

The results of both studies suggest that cognitive flexibility is an important contributor to safe walking, especially under challenging walking conditions, e.g., dual tasking. We hypothesize that prioritization and adaptation mechanisms of gait are parts of a complex interaction network between cognitive flexibility (deficits) and falls. This should be investigated in more detail in further studies.

4.2 Summary in German / Deutsche Zusammenfassung

In den letzten Jahren konnte gezeigt werden, dass es eine supraspinale Kontrolle des Gehens gibt. Dieses Netzwerk umfasst neben motorischen Hirnarealen vor allem auch kognitive und limbische Strukturen und deren Projektionen. Dieses supraspinale Netzwerk hat einen wichtigen Einfluss v.a. auf das Verhalten während des Gehens z.B. in Dual Task Situationen. Dual Task Situationen sind sehr alltagsrelevant, da sie häufig vorkommen, z.B. in Form von Sprechen während des Gehens. Defizite in der Dual Task Fähigkeit beeinflussen die Qualität des Gehens und können z.B. zu Stürzen führen. Diese Defizite begründen sich wahrscheinlich auf Störungen der exekutiven Funktionen, wie z.B. kognitive Flexibilität, da diese eine wichtige Rolle in der Steuerung von Dual Task Verhalten spielen.

Diese Arbeit besteht aus und diskutiert zwei Publikationen, die sich mit der Assoziation von kognitiver Flexibilität und Priorisierung, sowie kognitiver Flexibilität und quantitativ erhobenen Gangparametern und deren Anpassung bei Dual Task Aufgaben beim Gehen befassen.

Für beide Publikationen wurden über 660 gesunde Probanden zwischen 50 und 80 Jahren mit einem Assessment untersucht, das aus vier Single Task Aufgaben (*Subtrahieren, Durchführen einer Ankreuzaufgabe, Gehen mit normaler Gehgeschwindigkeit und Gehen mit schneller Gehgeschwindigkeit*) und zwei Dual Task Aufgaben (*Gehen mit schneller Gehgeschwindigkeit mit gleichzeitigem Durchführen der Ankreuzaufgabe* und *Gehen mit schneller Gehgeschwindigkeit mit gleichzeitigem Subtrahieren*) bestand. Als Maß der kognitiven Flexibilität wurde der Trail Making Test (TMT) durchgeführt.

In Publikation 1 wurden die Dual Task Kosten berechnet, die die Leistungsverschlechterung in einer Aufgabe unter Dual Task im Vergleich zur Durchführung der gleichen Aufgabe unter Single Task Bedingungen beschreiben. Die Dual Task Kosten der einzelnen Aufgaben wurden zwischen dem Tertil der Probanden mit der besten und dem Tertil mit der schlechtesten Leistung im TMT verglichen. Es zeigte sich, dass die Probanden mit schlechterer Leistung im TMT die kognitive Aufgabe und nicht das Gehen in der Dual Task

Aufgabe *Gehen mit schneller Gehgeschwindigkeit mit gleichzeitigem Subtrahieren* priorisierten. Die Probanden mit besserer Leistung im TMT hingegen priorisierten die motorische Aufgabe gegenüber dem Subtrahieren. Dies weist auf eine Assoziation zwischen kognitiver Flexibilität und Priorisierung hin.

In Publikation 2 wurden quantitative Gangparameter, die mittels eines tragbaren Bewegungssensors erhoben wurden, mit dem Ergebnis des TMT korreliert. Es zeigte sich, dass je schwerer die Gangaufgabe war, desto mehr Gangparameter signifikant mit dem TMT korreliert waren. Die stärkste Korrelation mit dem TMT wurde für den Parameter Gehgeschwindigkeit unter der Aufgabe *Gehen mit schneller Gehgeschwindigkeit mit gleichzeitigem Subtrahieren* gefunden. Dies unterstützt frühere Arbeiten die der Gehgeschwindigkeit eine hohe Relevanz in der Beschreibung von kognitiven Defiziten zugeordnet haben. Allerdings handelt es ich dabei um einen recht unspezifischen Marker. Zusätzlich wurden die Muster der Veränderungen der einzelnen Gangparameter über die Single Task Aufgabe *Gehen mit schneller Gehgeschwindigkeit* und die Dual Task Aufgaben *Gehen mit schneller Gehgeschwindigkeit mit gleichzeitigem Durchführen der Ankreuzaufgabe* und *Gehen mit schneller Gehgeschwindigkeit mit gleichzeitigem Subtrahieren* zwischen den guten und schlechten Tertial im TMT verglichen. Hierbei zeigten sich unterschiedliche Muster in den Parametern für Gangvariabilität, Gangregularität, und Gangasymmetrie. Die Probanden mit besserer kognitiver Flexibilität scheinen die Strategien zwischen den Aufgaben gewechselt, bzw. an die Aufgaben angepasst zu haben, was die Probanden mit schlechterer kognitiver Flexibilität nur eingeschränkt machten. Zusammengefasst deuten die Ergebnisse darauf hin, dass kognitive Flexibilität wichtig für das Gehen bei älteren Leuten ist und Probanden mit einer schlechteren kognitiven Flexibilität durchaus Probleme haben könnten, das Gehen an herausfordernde Geh-Bedingungen anzupassen.

Die Ergebnisse beider Studien zusammen weisen darauf hin, dass kognitive Flexibilität sehr wichtig für das Gehen unter herausfordernden Geh-Situationen ist, wie z.B. Dual Tasking. Unsere Daten weisen auch darauf hin, dass Priorisierung und Adaptationsfähigkeit des Gehens Teil eines komplexen

Netzwerkes zwischen Defiziten in kognitiver Flexibilität und Stürzen sind. Es liegt daher nahe, dass Defizite in der Priorisierung und der Anpassung des Gehens an situative Erfordernisse, mögliche und wichtige Mechanismen hierfür sein könnten. Dies sollte jedoch in weiteren Studien gezielt untersucht werden.

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6. Declaration of contribution

6.1 Declaration of contribution in Englisch

Declaration of contribution to publication 1:

Manuscript 1 is based on data collected within the frame of the *TREND* study. Markus Hobert performed the quantitative movement assessment of 715 study participants with another doctoral student (Sinja Meyer). These data represent the main data set of the publication. After data collection, Markus Hobert and Sinja Meyer entered the data into the database. In addition, further data from the *TREND* study, e.g., clinical and neuropsychological data collected by other staff members and doctoral students associated with the *TREND* study, were also included in the analysis. Markus Hobert spent approximately one year for data collection. The concept and hypothesis of the analysis was developed by Markus Hobert under the supervision of Prof. Dr. Walter Maetzler and with input from Prof. Dr. Daniela Berg and Prof. Dr. Gerhard Eschweiler. Markus Hobert carried out the statistical analysis with input by Dr. Raphael Niebler and Prof. Dr. Walter Maetzler. The manuscript was written by Markus Hobert and Prof. Dr. Walter Maetzler. All co-authors critically reviewed the manuscript. The revision during the submission process was carried out by Prof. Dr. Walter Maetzler together with Markus Hobert. The contributions of the individual authors are also documented in the "Author Contributions" section of the publication.

Declaration of contribution to publication 2:

Manuscript 2 is based on data collected within the frame of the *TREND* study. Markus Hobert performed the quantitative movement assessment of 715 study participants with another doctoral student (Sinja Meyer). These data represent the main data set of the publication. After data collection, Markus Hobert and Sinja Meyer entered the data into the database. In addition, further data from the *TREND* study, e.g., clinical and neuropsychological data collected by other staff members and doctoral students of the *TREND* study, were also included in the analysis. Markus Hobert spent approximately one year for data collection. Raw data sets of the quantitative motion analysis were converted by Markus Hobert to another data format, and the markers set during the measurement were checked and corrected with the software provided by the manufacturer of the sensor-unit (McRoberts, The Hague, The Netherlands). Then, data sets were uploaded to the McRoberts analysis platform and analysed using an algorithm provided by McRoberts. Afterwards, Markus Hobert checked these data for plausibility and transferred them to the database. The concept and hypothesis of the analysis was developed by Markus Hobert under the supervision of Prof. Dr. Walter Maetzler. Markus Hobert carried out the statistical analysis independently. The manuscript was written by Markus Hobert and Prof. Dr. Walter Maetzler. All co-authors critically reviewed the manuscript. The revision during the submission process was carried out by Markus Hobert together with Prof. Dr. Walter Maetzler. The contributions of the individual authors are also documented in the "Author Contributions" section of the publication.

6.2 Declaration of contribution in German / Erklärung zum Eigenanteil

Erklärung zum Eigenanteil von Publikation 1:

Die der Arbeit zugrunde liegenden Daten wurden im Rahmen der *TREND*-Studie erhoben. Markus Hobert führte die quantitative Bewegungsanalyse bei 715 Studienteilnehmern mit einer weiteren Doktorandin (Sinja Meyer) durch. Diese Daten stellen den Hauptdatensatz der Publikation dar. Nach der Datenerhebung erfolgte die Dateneingabe durch Markus Hobert und Sinja Meyer. Darüberhinaus flossen auch weitere Daten aus der *TREND*-Studie, z.B. klinische und neuropsychologische Daten in die Analyse ein, die von anderen Mitarbeitern und Doktoranden der *TREND*-Studie erhoben wurden. Insgesamt war Markus Hobert ca. ein Jahr mit der Datenerhebung befasst. Das Konzept bzw. die Hypothese der hier durchgeführten Analyse entwickelte Markus Hobert selbständig unter Anleitung von Prof. Dr. Walter Maetzler und Input durch Prof. Dr. Daniela Berg und Prof. Dr. Gerhard Eschweiler. Die statistische Auswertung führte Markus Hobert nach Anleitung durch Dr. Raphael Niebler und Prof. Dr. Walter Maetzler selbstständig durch. Das Manuskript entwickelte Markus Hobert in Zusammenarbeit mit Prof. Dr. Walter Maetzler. Alle Ko-Autoren halfen durch die kritische Durchsicht des Manuskripts. Die Revision wurde von Prof. Dr. Walter Maetzler in Zusammenarbeit mit Markus Hobert durchgeführt. Die Beiträge der einzelnen Autoren sind außerdem in der Publikation im Abschnitt „Author Contributions“ dokumentiert.

Erklärung zum Eigenanteil von Publikation 2:

Die der Arbeit zugrunde liegenden Daten wurden im Rahmen der *TREND*-Studie erhoben. Markus Hobert führte die quantitative Bewegungsanalyse bei 715 Studienteilnehmern mit einer weiteren Doktorandin (Sinja Meyer) durch. Diese Daten stellen den Hauptdatensatz der Publikation dar. Nach der Datenerhebung erfolgte die Dateneingabe durch Markus Hobert und Sinja Meyer. Darüberhinaus flossen auch weitere Daten aus der *TREND*-Studie, z.B. klinische und neuropsychologische Daten in die Analyse ein, die von anderen Mitarbeitern und Doktoranden der *TREND*-Studie erhoben wurden. Insgesamt war Markus Hobert ca. ein Jahr mit der Datenerhebung befasst. Die Datensätze der quantitativen

Bewegungsanalyse wurden von Markus Hobert ein anderes Format konvertiert, die während der Messung gesetzten Marker kontrolliert und mit der, vom Hersteller der Bewegungssensoren (McRoberts) bereitgestellten, Software korrigiert. Anschließend wurden die Datensätze auf die Analyseplattform von McRoberts hochgeladen und die Ergebnisse mit einem von McRoberts bereitgestellten Algorithmus analysiert. Diese Daten wurden von Markus Hobert anschließend auf Plausibilität überprüft bevor sie in die Datenbank übernommen wurden. Das Konzept bzw. die Hypothese der hier durchgeführten Analyse entwickelte Markus Hobert selbständig unter Anleitung von Prof. Dr. Walter Maetzler. Die statistische Auswertung führte Markus Hobert selbstständig durch. Das Manuskript entwickelte Markus Hobert in Zusammenarbeit mit Prof. Dr. Walter Maetzler. Alle Ko-Autoren halfen durch die kritische Durchsicht des Manuskripts. Die Revision wurde von Markus Hobert in Zusammenarbeit mit Prof. Dr. Walter Maetzler durchgeführt. Die Beiträge der einzelnen Autoren sind außerdem in der Publikation im Abschnitt „Author Contributions“ dokumentiert.

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This thesis would not have been possible without the support and contributions of many people.

First I want to express my deepest gratitude to my supervisor Prof. Dr. med. Walter Maetzler who supported me, guided me during the work done for this thesis and other projects. He also kept on motivating me and introduced me into "the world of scientific and clinical research" in Neurology and Geriatrics. In addition I want to thank also Prof. Dr. med. Daniela Berg who supported me and who initiated the TREND Study together with Prof. Dr. med. Walter Maetzler and Prof. Dr. med. Gerhard Eschweiler.

I would like to give a special thanks to all members of the TREND Study team, especially Dr. med. Sinja Meyer and Dr. phil. Raphael Niebler, all co-authors, and to all other members of the Functional Neurogeriatrics Research Group and the Clinical Neurodegeneration Research Group at the University of Tuebingen, as well as the Neurogeriatrcs Research Group at the University of Kiel.

I thank also the reviewers, who had helpful comments which improved the quality of the manuscripts. I want to thank all study participants for their participation.

Last but not least I want to express my gratitude to my parents and my brother Sebastian for all the support and motivation.

8. Publications

Publications part of this thesis:

Poor trail making test performance is directly associated with altered dual task prioritization in the elderly--baseline results from the TREND study.
Hobert MA, Niebler R, Meyer SI, Brockmann K, Becker C, Huber H, Gaenslen A, Godau J, Eschweiler GW, Berg D, Maetzler W.
PLoS One. 2011;6(11):e27831.

Gait is associated with cognitive flexibility: A dual-tasking study in healthy older people.
Hobert MA, Meyer SI, Hasmann SE, Metzger FG, Suenkel U, Eschweiler GW, Berg D, Maetzler W.
Front Aging Neurosci. 2017 May 24;9:154.

Contributions to conferences related to this thesis:

Oral presentations at conferences:

Poor trail making test performance is directly associated with altered dual task prioritisation in 686 elderly.
Hobert MA, Niebler R, Meyer SI, Brockmann K, Becker C, Huber H, Gaenslen A, Godau J, Eschweiler GW, Berg D, Maetzler W.
1st Joint World Congress of International Society of Posture and Gait Research (ISPGR) and Gait & Mental Function 2012, Trondheim, Norway.

Einfluss von kognitiver Flexibilität auf das Gehen bei gesunden Älteren.
Hobert MA.
Jahrestagung der Gesellschaft für Neuropsychologie (GNP) 2015, Luebeck, Germany.

Poster presentations at conferences:

Quantitative gait parameter changes in good and poor Trail Making Test performers under challenging single and dual tasking conditions: Cross-sectional analysis in 673 elderly.
Hobert MA, Meyer SI, Niebler R, Gaenslen A, Brockmann K, Wurster I, Eschweiler GW, Berg D, Maetzler W.
2st Joint World Congress of International Society of Posture and Gait Research (ISPGR) and Gait & Mental Function 2013, Akita, Japan.

Hat kognitive Flexibilität etwas mit dem Gangmuster zu tun? Quantitative Gangparameter von 673 Älteren unter Single- und Dualtasking Bedingungen.
Maetzler W, Meyer SI, Niebler R, Metzger F, Eschweiler GW, Berg D, Hobert MA.
Kongress der Deutschen Gesellschaft für Geriatrie (DGG) 2013, Hof, Germany.

Quantitative gait parameter changes under challenging single and dual tasking conditions are associated with Trail Making Test performance: Cross-sectional analysis in 661 elderly.
Hobert MA, Hasmann SE, Eschweiler GW, Berg D, Maetzler W.
Jahrestagung der Deutschen Gesellschaft für klinische Neurophysiologie und funktionelle Bildgebung (DGKN) 2015, Tuebingen, Germany.

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Validierung des Geriatrie-Checks in einer Kohorte von stationären neurologischen Patienten.
Hobert MA, Bernhard FP, Bettecken K, Sartor J, Maetzler W, Jamour M.
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