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Plasticity in the sensorimotor system and innovative sensorimotor training in frailty

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LIST OF ABBREVIATIONS

ANOVA	analysis of variance
APB	abductor pollicis brevis
AST	Attention Switching Task (CANTAB)
BDNF	brain-derived neurotrophic factor
CANTAB	Cambridge Neuropsychological Test Automated Battery
CES-D	Center for Epidemiologic Studies Depression Scale
CG	control group (in Study 2)
CI	confidence interval
CTSIB	Clinical Test of Sensory Integration of Balance
dB	decibel
EG	experimental group (in Study 2)
EMG	electromyography
EPI	echo-planar imaging
EQ-5D-5L	EuroQol-5D-5L
ES	effect size
FEFA	Frail Elderly Functional Assessment
FES-I	Falls Efficacy Scale – International Version
(f)MRI	(functional) magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
FI	frailty index
FP	frailty phenotype
IED	Intra-Extra Dimensional Set Shift (CANTAB)
kg	kilogram
LMM(s)	linear mixed model(s)
M1	primary motor cortex
MEP(s)	motor-evoked potential(s)

MKS	Marburg Competency Scale (Marburger Kompetenz Skala)
MMSE	Mini Mental State Examination
MNA	Mini Nutritional Assessment
mN	millinewton
OR	Odds Ratio
PC	parietal cortex
PFC	prefrontal cortex
PMC	premotor cortex
PPT	Purdue Pegboard Test
RMT(s)	resting motor threshold(s)
ROI(s)	region(s) of interest
RT	reaction time
RTI	Reaction Time Test (CANTAB)
S1	primary somatosensory cortex
SD	standard deviation
SE	standard error
SF-36	Short Form-36
SMA	supplementary motor area
SPPB	Short Physical Performance Battery
SSP	Spatial Span Test (CANTAB)
T0	baseline assessment (in Study 2)
T1	assessment 1 (in Study 2)
T2	assessment 2 (in Study 2)
TC	temporal cortex
TE	echo time
TMS	transcranial magnetic stimulation
TR	repetition time

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1 INTRODUCTION

Increase of average human life expectancy through the improvement of medical care can be considered as one of the most important achievements of modern civilization in the last hundred years. In the next decades, the proportion of the world's population aged over 60 will increase drastically, leading to tremendous demographic change and major challenges for the healthcare systems. As the incidence of many diseases positively correlates with age, a major focus of medical care for the elderly is the maintenance of health and quality of life. A special focus is the prevention of pathological conditions associated with a loss of function and independence. Two clinically relevant conditions are dementia, a syndrome characterized by cognitive deterioration and loss of everyday skills, and frailty, a state of increased vulnerability to stressors and adverse health outcomes resulting from a decline in function and capacity across multiple physiologic systems. Effective prevention and treatment require the identification of determinants, which underlie pathological aging and the development and evaluation of innovative pharmacological and behavioral interventions.

Neuroscientific models of aging emphasize that brain plasticity may play a key role in determining healthy and pathological aging. Neuroplasticity has been defined as the brain's ability to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function and connections (Cramer et al., 2011). Plastic changes can occur during development, in response to environmental experience, in support of learning, as a consequence of disease, or in the course of therapeutic interventions. One can differentiate positive or adaptive plasticity, which is associated with a gain in function, and negative or maladaptive plasticity, which is associated with detrimental consequences such as loss of function or increased injury (Cramer et al., 2011). Specifically, the loss of sensory and motor stimulation and reduced modulatory capacities are seen as core processes in the development of maladaptive plastic changes of the brain and subsequent cognitive and bodily decline, promoting frailty and multimorbidity in old age (Burke & Barnes, 2006; Mahncke, Bronstone, & Merzenich, 2006). In turn, novel interventions, which target neurocognitive deficits and enhance brain plasticity, such as sensorimotor training, might represent a useful behavioral treatment to increase relevant input to the brain and improve neuromodulatory function.

The goal of this dissertation was firstly to further characterize determinants of sensory and motor function associated with frailty and to demonstrate their relevance for the clinical diagnosis of frailty. In a second part, the efficacy of a neuroplasticity-based intervention on neuropsychological, brain-related and functional aspects of frailty was investigated. In the following chapters, mechanisms of pathological aging in sensory and motor systems and their role in frailty will be introduced. Principles of neuroplasticity-oriented interventions and previous work on behavioral and neuronal aspects will be described. Then, two empirical studies will be presented, which were conducted to investigate the above-mentioned questions. In chapter 1.4, the relevant research background underlying each of the two studies will be summarized to formulate the hypotheses. Then, materials and methods used in the two studies will be described in chapter 2. In chapter 3, the results of the two studies will be separately presented and discussed in relation to previous research. Finally, in chapter 4, a general discussion will integrate the findings across both studies und provide an outlook for future research.

1.1 Pathological and non-pathological aging

Healthy, or “successful aging” (Havighurst, 1961), has originally been considered to reflect aging without disease and disability, with high cognitive and physical functioning, and active engagement with life (Rowe & Kahn, 1997). However, this concept has been criticized for being too narrow in scope and describing an ideal that is rarely achieved (Rolfson, 2018; Rowe & Kahn, 2015). Instead, recent concepts of successful aging emphasize a behavioral perspective of aging, which takes into account the maximization of gains by compensating for aging-related losses and declines (Baltes & Baltes, 1990) as well as the ability of an older individual to proactively adapt to stressors of aging by drawing on internal coping strategies and external social resources (Kahana & Kahana, 1996). In fact, over the last decades, no less than several dozens of definitions of successful aging have emerged, underscoring the call for a comprehensive biopsychosocial concept that takes into account the diverse viewpoints from clinicians, researchers and older adults (Depp & Jeste, 2006).

From a functional perspective, normal aging has been associated with virtually unavoidable declines in various functional systems (Schirinzi, Canevelli, Suppa, Bologna, & Marsili, 2020). This includes the reduction of sensory acuity and sensitivity across multiple sensory domains (Pardhan, 2004; Rigters et al., 2017; Shaffer & Harrison, 2007), mild motor signs including a decrease of muscle strength, movement slowing and gait abnormalities (Beenakker et al., 2010; Bennett et al., 1996) as well as cognitive decline affecting executive functions and memory (Harada, Natelson Love, & Triebel, 2013; Small, Tsai, Delapaz, Mayeux, & Stern, 2002). Similarly, age-related physiological changes in the central nervous system have been reported in both healthy and impaired older individuals (Schirinzi et al., 2020), including brain atrophy (Seidler et al., 2010), small vessel disease (Pantoni, 2010) and accumulation of misfolded proteins (Markesbery, Jicha, Liu, & Schmitt, 2009). However, many older people do not exhibit cognitive or motor impairment or other symptoms of disease, although they show physiological characteristics of neurodegenerative pathologies, such as Alzheimer’s or Parkinson’s disease (Jellinger & Attems, 2013). Discovery of the determinants responsible for successful versus problematic aging may provide an essential basis for the development and evaluation of effective treatments to maintain and enhance independence and quality of life in old age.

In this vein, current views of aging assume that anatomical and cerebral impairment per se is not equal to disability because it does not reveal to what extent these

impairments affect a person's functional competences and independence (Lowry, Vallejo, & Studenski, 2012). In fact, there are substantial individual differences in the ability of older adults to maintain physical and cognitive functions during aging, even in the face of physiological decline (Daffner, 2010; Schirinzi et al., 2020). With the growing importance of the neuroscience of aging and an increasing emphasis on discovering structural and functional neural mechanisms of normal and pathological aging, the view of aging as a pervasive, irreversible decline has been challenged. In fact, neuroscientific research has emphasized the constructs of plasticity, functional reorganization and compensation as critical factors in understanding the aging mind (Reuter-Lorenz & Park, 2010). The increasing understanding of complex molecular pathways and mechanisms by which the brain reorganizes its structure and function in order to manage or counteract age-related changes or pathologies, has led to a move away from pure "lesion models" of aging (Jellinger & Attems, 2013; Reuter-Lorenz & Park, 2010).

Thus, the current view is that aging constitutes a multidimensional construct, rather than a unidirectional process determined by the simple number of diseases and conditions (Lowry et al., 2012). Therefore, instead of classifying an older individual as successful or unsuccessful, an aging person is now rather viewed on a "continuum" of achievements, with successful aging versus pathological aging and disability at opposite ends of the continuum. This suggests that successful and pathological aging belong to a common paradigm (Rolfson, 2018) that represents a dynamic process, i.e. subjects can move either way on the continuum (Lowry et al., 2012). In this context, the clinical syndrome of frailty has been viewed as a transition state between successful aging and disability (Cesari et al., 2016).

1.2 Clinical characteristics of frailty

The term “frailty” describes a clinical condition, which is characterized by an age-related decline in multiple physiological systems resulting in an impaired homeostatic reserve and a reduced physiological capacity, thereby increasing the organism’s vulnerability to stressors (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Morley et al., 2013). While the symptoms are diverse, frailty is most often characterized by reduced strength, endurance, physical function, mobility and nutritional status. The clinical relevance of frailty is reflected in the fact that individuals with frailty compared to non-frail individuals were shown to be at an increased risk for adverse health outcomes, including falls (Kojima, 2015), hospitalizations (Boyd, Xue, Simpson, Guralnik, & Fried, 2005), disability (Bandeen-Roche et al., 2006) and mortality (S. F. Chang & Lin, 2015). Recent epidemiological analyses across different countries revealed that the prevalence of frailty ranges from 16% in the age group over 60 up to 31% in the age group over 80 (O’Caoimh et al., 2021), suggesting that the majority of elderly individuals is not frail. Given that frailty is associated with reduced quality of life for those affected (Gobbens, Van Assen, Luijkx, & Schols, 2012) and increased health care utilization and costs (Bock et al., 2016), emphasis must be placed on identifying its underlying pathophysiology and perspectives for intervention.

1.2.1 Definition and assessment of frailty

Despite the great relevance in the field of gerontology, at the present time there is no standard for defining and diagnosing frailty (Bergman et al., 2007; Gobbens, Luijkx, Wijnen-Sponselee, & Schols, 2010). Numerous models have been developed to address the complex nature of frailty (Bouillon et al., 2013; de Vries et al., 2011), leading to a considerable heterogeneity in the conceptual and operational understanding of frailty. The two most commonly used approaches to frailty are the frailty phenotype (FP, Fried et al., 2001) and the deficit accumulation model (Rockwood & Mitnitski, 2007). According to the categorical FP model, frailty is operationally defined as a physical syndrome consisting of three or more out of five phenotypic criteria: unintentional weight loss, low energy or self-reported exhaustion, low level of physical activity, slowed gait speed, and weakness as determined by low grip strength. A pre-frail stage, in which one or two criteria are fulfilled, represents a stage of high risk of progression to frailty. Subjects meeting none of the criteria are considered to be robust (Fried et al.,

2001). The deficit accumulation model in turn states that the amount of deficits, including disease, symptoms, physical and cognitive impairments, psychosocial risk factors and disability, can predict frailty and that the more deficits a person has, the more likely that person is to be frail (Rockwood & Mitnitski, 2007). To determine the degree of frailty of a person, a quantitative frailty index (FI) is derived by dividing the number of deficits present through the total number of deficits assessed, resulting in a continuous score ranging from 0 to 1, with higher values representing increased frailty. One of the most widely used versions of the FI consists of 40 deficits (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008).

From a conceptual view, these two frailty definitions propose different mechanisms in terms of the underlying pathophysiology of frailty. While the FP represents a biological and physical syndrome, the FI considers frailty as a multidimensional concept and emphasizes the quantity rather than the particular nature of deficits (Theou, Brothers, Mitnitski, & Rockwood, 2013). With respect to the comparability of clinical and scientific properties of the two measures (Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015; Kulminski et al., 2008; Malmstrom, Miller, & Morley, 2014; Theou, Brothers, Peña, Mitnitski, & Rockwood, 2014; Woo, Leung, & Morley, 2012), some studies demonstrated that the two approaches are comparable with respect to the diagnostic characteristics and the frailty scores obtained (Mitnitski, Fallah, Rockwood, & Rockwood, 2011; Woo et al., 2012). However, others have provided evidence that they substantially differ from each other in their content and predictive validity (Hubbard, O'Mahony, & Woodhouse, 2009; Theou et al., 2013) and should not be used interchangeably (Cesari, Gambassi, Van Kan, & Vellas, 2014). For instance, it has been demonstrated that the FI more accurately predicts the risk of all-cause mortality compared to the FP (Theou et al., 2013), likely because it includes deficits that have a causal relationship with adverse clinical outcomes (Rockwood & Mitnitski, 2007). Also, the FI was suggested to be a more sensitive measure of frailty due to its continuous nature and its ability to discriminate better at the lower to middle end of the frailty continuum, thereby allowing to identify individuals who are vulnerable before a state of overt frailty manifests (Blodgett et al., 2015; Kulminski et al., 2008). The continuous scoring system and the fact that the FI contains many more or less stable deficits and diseases also makes it a suitable instrument to discriminate and measure change related to an intervention (de Vries et al., 2011). On the other hand, the FI has been criticized as requiring the recording of several dozen items and therefore being

inapplicable at the first contact with a subject and being too complex for everyday clinical use. The FP may be more feasible and clinically reproducible as it requires fewer items and may therefore serve as an initial indicator for risk stratification of an individual according to different profiles. However, due to its categorical nature, it does not provide information about the severity of frailty. Moreover, since it is only based on physical symptoms, it has been criticized for neglecting other potentially important components of frailty such as mood, cognition and biological markers (Lang, Michel, & Zekry, 2009). Similarly, because it is composed of general symptoms, it does not provide any conclusions about the underlying causes of the vulnerable condition nor does it provide any indication about preventive or therapeutic measures to be taken (Cesari et al., 2014).

Apart from the FP and the FI, the increasing recognition of frailty assessment as a prognostic tool for healthcare outcomes has resulted in the development of more than 50 frailty measures (Buta et al., 2016). A comparative analysis revealed that agreement between many different tools may be low, most likely because the tools differ with respect to the underlying constructs of frailty that are captured, the assumptions made about its etiology, the domains included and the number of items used (Aguayo et al., 2017). Given the heterogeneity of various frailty instruments in identifying the same individuals as frail, the selection of an appropriate frailty instrument should be carefully based on the intended purpose, the domains to be captured and whether the instrument proved to be valid, reliable and feasible in the past (Buta et al., 2016).

1.2.2 Pathogenesis of frailty

While non-pathological aging is also accompanied by a gradual decrease in physiological capacity, this decrease is accelerated and exacerbated in frailty (Ferrucci et al., 2002), affecting multiple physiological systems such as the musculoskeletal, endocrine and cardiovascular system as well as the brain. The complex pathophysiological mechanisms promoting cumulative decline are not fully understood and identification of specific pathways is complicated by the fact that there is overlap between processes related to frailty, aging, and specific diseases (Fulop et al., 2010). Frailty can be associated with a variety of medical conditions, including cardiovascular diseases, musculoskeletal disorders, gastrointestinal diseases, and cognitive impairment (Rockwood et al., 2005). However, it is important to note that frailty is not seen as identical to

physiological comorbidity and disability since frailty may be associated with different symptoms and may even be present in the absence of specific diseases or comorbidities (de Vries et al., 2011; Fulop et al., 2010). As frailty develops with multisystem physiological decline, a key question is whether there is a threshold beyond which physiological reserve in different systems can no longer compensate for the cumulative decline and beyond which frailty manifests itself. It has been shown that there is a nonlinear relationship between the number of impaired physiological systems and frailty, and that the number of impaired systems is more predictive for frailty than any individual impaired system alone (Fried et al., 2009). Such evidence supports theories that frailty is driven by a loss of complexity in physiological systems, as reflected by an increased number of impaired systems, and becomes evident when an aggregate level of physiological decline is reached (Clegg et al., 2013; Fried et al., 2009).

Pathophysiologic mechanisms that seem to be associated with the development of frailty include malnutrition and vitamin D deficit (C. I. Chang, Chan, Kuo, Hsiung, & Chen, 2010), a chronic inflammatory process, impaired immunity as well as neuromuscular, endocrine and metabolic dysregulations (Fulop et al., 2010; Walston et al., 2006). For instance, serum levels of inflammatory markers such as interleukin (IL)-6, tumor necrosis factor (TNF) and C-reactive protein (CRP) were found to increase with age and were found to be associated with cardiovascular disease, diabetes, cancer, and mortality (Lowry et al., 2012; T. Singh & Newman, 2011). Moreover, higher levels of these markers have been related to poorer physical performance, reduced walking speed, impairments of balance and walking, slowing of movement and disability related to mobility (Brinkley et al., 2009; Cesari et al., 2004; Penninx et al., 2004) as well as an increased risk for the development of frailty (Barzilay et al., 2007). It has been suggested that inflammatory markers may be involved in a reduced protein synthesis (Toth, Matthews, Tracy, & Previs, 2005) of skeletal muscle, thereby presumably contributing to the loss of muscle mass and strength and the degradation of muscle function (Roubenoff & Harris, 1997; Visser et al., 2002). However, the reasons for the systemic upregulation of these inflammatory markers are still not known and causal relationships with muscle loss and frailty still need to be demonstrated (Lowry et al., 2012).

Aging is also associated with structural and physiological alterations in the brain. It has been hypothesized that the brain, due to its highly plastic and adaptable nature, could be at the center of a vicious cycle starting with an initial impairment and leading to an accelerated deterioration of physical function (Walston et al., 2006). There is evidence

that older individuals otherwise free of any neurological diagnosis might show signs of neurological impairment (Perrin, Jeandel, Perrin, & Béné, 1997) and that the presence of such neurological signs might be related to reduced lower extremity function, falls, and poor physical activity (Gauchard, Gangloff, Jeandel, & Perrin, 2003). In turn, physical inactivity can promote neurological impairment through its effect on inflammation and insulin resistance (Gauchard et al., 2003). The combination of these declines may contribute to the development of frailty (Walston et al., 2006). While the role of central nervous system changes in the pathogenesis of frailty is still poorly understood (López-Sanz et al., 2018), neurological alterations may determine impairments in gait, balance and strength, all of which are considered major components of frailty (Walston et al., 2006). For instance, structural brain analyses demonstrated that frailty per se was not significantly associated with any brain region, but that weakness and slowness were related to reduced grey matter volumes in brain regions associated with physical mobility, cognitive functioning and social processes (Nishita et al., 2019). Another study reported a positive relationship between reduced cerebellar gray matter and the FP (W. T. Chen et al., 2015). Also, frailty was found to be related to white matter hyperintensities and reduced white matter fractional anisotropy (Avila-Funes et al., 2017), suggesting that disturbances in white matter integrity and connectivity may play a role in the pathophysiology of frailty. Moreover, in postmortem studies, certain Parkinson-like brain pathologies, such as an accumulation of Lewy bodies and neuronal loss in the substantia nigra, have been associated with a more rapid progression of frailty (Buchman, Yu, Wilson, Schneider, & Bennett, 2013). Therefore, a reciprocal mechanism has been postulated, in which reduced physical activity, together with physiological alterations such as inflammatory dysregulation can exacerbate damage to the central nervous system, which in turn aggravates impairments in gait, balance, strength and nutrition, thereby contributing to the multisystem dysregulation observed in frailty (Walston et al., 2006). However, causal relationships within the presumed vicious cycle still need to be clarified.

Moreover, factors other than biological or physiological decline, including behavioral, socio-emotional and environmental factors were shown to contribute to an individual's risk for the development of frailty. For instance, behavioral observations during preclinical phases in older adults suggested that behavioral changes and adaptations made in response to the decreasing physiological capacity might precede the development of an overt state of frailty (Xue, 2011). Such subtle changes may not be observable by

traditional functional and behavioral measures but are more likely to be expressed in real life because of a shift in the balance between physiological capacity and challenges in daily life. Similarly, previous research demonstrated that non-frail individuals who were spatially less mobile at baseline, i.e. who moved less frequently in their daily life, were significantly more likely to become frail within three years (Xue, Fried, Glass, Laffan, & Chaves, 2008). This suggests that maladaptive behavior, such as reduced mobility and physical inactivity, might be a risk factor for the development of frailty.
While an in-depth review of pathogenic mechanisms is beyond the scope of this work, the above-mentioned evidence illustrates that the pathways underlying the development of frailty consist of multiple and complex interrelated physiological, neuronal, environmental and behavioral risk factors, which remain to be clarified (Clegg et al., 2013; Walston et al., 2006).

1.2.3 Sensory and motor decline in frailty

Due to the multisystem degradation processes in frailty, decline in sensory and motor functions has been found to go beyond the extent of decline observed in normal aging. For instance, aging is associated with degenerative and structural changes in muscle and body composition, which promotes the loss of muscle mass and impairs muscle function as executive element of all motor behavior (Buchman et al., 2021; Manini, Hong, & Clark, 2013). Additional dysregulations in the immune system and the associated increase in inflammatory markers are thought to accelerate the degradation of the musculature and loss of muscle strength, resulting in a syndrome known as sarcopenia (Kamel, 2003). Sarcopenia is theorized to affect the entire muscular structure of the body, including upper and lower extremities. Critically, muscle loss and weakness might promote decline in motor abilities, including a reduction in gait speed (Castell et al., 2013), impairment in postural control and balance (Davis, Rockwood, Mitnitski, & Rockwood, 2011; Toosizadeh, Mohler, Wendel, & Najafi, 2015) as well as a decrease in upper extremity dexterity (Brown, Sinacore, Binder, & Kohrt, 2000). Accordingly, physical performance measures such as ambulatory mobility (walking speed and timed up-and-go performance) and muscle endurance were demonstrated to be strong predictors of frailty (Abellan van Kan et al., 2008; Theou, Jones, Jakobi, Mitnitski, & Vandervoort, 2011). Walking in particular has been viewed as a complex task and may be affected by frailty more than other less complex physical tasks (Theou, Jones, et

al., 2011). Muscle dysfunction and motor impairment may in turn exacerbate the symptomatology of frailty by promoting physical inactivity (Xue, 2011), reducing mobility and limiting daily activities (Sakari et al., 2010), thereby increasing the risk for adverse incidents such as falls (Pauelsen, Vikman, Johansson Strandkvist, Larsson, & Röijezon, 2018). In line with such considerations, walking performance was shown to be a valid single indicator of physiological reserve in older adults (Newman, Haggerty, Kritchevsky, Nevitt, & Simonsick, 2003) and a mean gait speed of less than 1 m/s detects persons at high risk for adverse health outcomes (Cesari et al., 2005).

Apart from proper musculoskeletal function, motor performance and mobility rely on the processing of sensory information. With increasing age, peripheral sensory organs deteriorate (e.g., loss of hair cells in the cochlea, loss of photo-receptors in the retina, changes in skin properties), resulting in a degradation of sensory input from all systems (Mahncke, Bronstone, et al., 2006). Sensory systems providing afferent visual, auditory, vestibular and somatosensory information are important for establishing an internal schema of the orientation and motion of the body in relation to the environment, allowing the central nervous system to modulate motor output depending on the congruency between the input and the goals of the intended movement (MacKinnon, 2018). Moreover, successful mobility requires the integration of concurrent multisensory stimulation. Previous studies in fact demonstrated associations between visual-somatosensory integration and quantitative spatial gait parameters, including gait speed, in older adults (Mahoney & Verghese, 2018). In this context, impairments in gait and mobility have been found to be affected by a decline in sensory acuity in the visual (Sakari et al., 2010), auditory (D. S. Chen, Genther, Betz, & Lin, 2014; L. Li, Simonsick, Ferrucci, & Lin, 2013) and somatosensory (Goble, Coxon, Wenderoth, Van Impe, & Swinnen, 2009) domains. Moreover, degradation in sensory systems was found to be a risk factor for age-related cognitive and motor decline that may occur several years before the loss of mobility and independence (Panza et al., 2018; Sakari et al., 2010). Previous studies found positive relationships between the extent of frailty and sensory impairment in vision (Klein et al., 2003; Swenor, Lee, Tian, Varadaraj, & Bandeen-Roche, 2020), hearing (Doba, Tokuda, Goldstein, Kushiro, & Hinohara, 2012; Kamil, Li, & Lin, 2014) and somatosensation (Vieira et al., 2016). However, the mechanisms underlying the relationship between sensory decline and frailty are still poorly understood. For instance, it may be that sensory impairment directly affects physical indicators of frailty such as walking speed and postural control (Swenor et al.,

2020, 2015). Alternatively, it was hypothesized that sensory impairment may promote physical inactivity and a decline of overall fitness as well as communication impairments and social isolation, by which the risk for frailty is increased (L. Li et al., 2013; Swenor et al., 2020). Also, it has been discussed that the same pathophysiological processes, such as hypertension and diabetes mellitus, may underlie both sensory deficits and frailty (Sand et al., 2013; Vieira-Potter, Karamichos, & Lee, 2016).

On the neuronal level, age-related sensory and motor changes were shown to be associated with structural and functional plastic changes in the brain. For instance, age-related reductions in gait performance have been associated with reduced gray matter volume in frontal regions (Callisaya, Beare, Phan, Chen, & Srikanth, 2014; Rosano et al., 2012). A large number of previous studies has provided evidence that in older compared to younger subjects, cognitive, sensory (Cabeza, 2002; Reuter-Lorenz & Lustig, 2005; Zanto & Gazzaley, 2017) and motor processing (Bernard & Seidler, 2012; Heuninckx, Wenderoth, & Swinnen, 2008; Ward, 2006) are associated with greater and more diffuse and increased bilateral brain activity, also including brain regions not directly involved in the actual task. Similarly, increased brain activity has also been found in older subjects suffering from clinical conditions, such as Parkinson's disease (Poston et al., 2016; T. Wu & Hallett, 2005), compared to healthy elderly. Apart from brain imaging, studies using non-invasive brain stimulation such as transcranial magnetic stimulation (TMS) found age-dependent changes in cortical inhibition and excitability in healthy older adults (Bhandari et al., 2016). These studies reported a relationship between reduced motor cortical excitability and motor deficits in older age, such as slowing of motor execution (Fujiyama, Tandonnet, & Summers, 2011) and muscle weakness (Clark, Taylor, Hong, Law, & Russ, 2015). Also, older adults demonstrated significantly higher stimulation thresholds (Bhandari et al., 2016) and reduced motor cortical plasticity (Fathi et al., 2010) compared to young adults, suggesting an age-related hypo-excitability of corticomotor pathways, presumably due to central nervous decline and changes in structural and functional brain integrity.

In the literature, two primary interpretations of the overactivation of brain regions have been discussed: neural dysfunction and neural compensation. Neural dysfunction or neural dedifferentiation refers to a reduced segregation of specialized subregions in sensorimotor brain networks and reduced specificity of motor neural representations, which might result in noisy neuronal processing in sensory and motor systems (Mahncke, Bronstone, et al., 2006). These reductions of neural specificity were related

to impaired sensorimotor performance, such as reduced walking speed and balance as well as declines in mobility in older adults (Bernard & Seidler, 2012; Cassady et al., 2019; Fettrow et al., 2021; Seidler et al., 2010; Sleimen-Malkoun, Temprado, & Hong, 2014). The compensation hypothesis claims that additional neural resources are recruited to compensate for age- or disease-related neural deficits in order to maintain accurate task performance (Fettrow et al., 2021; Reuter-Lorenz, Stanczak, & Miller, 1999). Functional imaging studies in frailty are rare and these mechanisms have only scarcely been reported in frailty, however, preliminary evidence suggests that similar mechanisms may also be present in frailty. For instance, Lammers et al. (2020) found reduced functional connectivity in the supplementary motor area network in pre-frail and frail compared to robust subjects. Functional connectivity positively correlated with motor speed and manual dexterity, suggesting that functional integrity in sensorimotor brain networks may represent an early correlate of frailty-related functional decline (Lammers et al., 2020). Moreover, in a recent functional near-infrared spectroscopy (fNIRS) study (Pelicioni, Lord, Sturnieks, Halmy, & Menant, 2021), older subjects at high versus low fall risk demonstrated significantly higher intra-individual variability in stepping responses and increased brain activity in the dorsolateral prefrontal cortex, suggesting a higher degree of neural inefficiency and/or the recruitment of compensatory processes for postural control deficits in subjects with increased fall risk. Reduced structural and functional integrity of brain areas could be related to inefficient activation of brain circuits resulting in cortical overactivation. However, these results may reflect a compensatory process to overcome sensorimotor impairments and/or declining brain capacity by allocating more attentional resources to cope with task complexity (Pelicioni et al., 2021). With age, both sensory functioning and physical mobility increasingly rely on cognitive resources to compensate for peripheral sensory and motor decline (K. Z. H. Li & Lindenberger, 2002). This suggests that both domains compete for common cognitive resources (Bruce et al., 2019).

In sum, the progressive decline in sensory and motor abilities in aging and particular in frailty may result in an age-associated shift from lower level automatic movement control to higher level cognitive and attentional movement control involving motor imagery, movement planning and controlled processing of sensory feedback (Seidler et al., 2010). Thus, central control mechanisms are hypothesized to gain in importance for postural control and walking with increasing age compared to peripheral sensorimotor systems (C.-C. Lin et al., 2015; Seidler et al., 2010). However, compensatory

resources may be limited, raising the question of how frailty-related physical deficits can be ameliorated.

1.3 Interventions for frailty

Since frailty is a strong risk factor for a certain number of adverse events, a growing interest in the management of frailty has been present, related to its reversible nature (Rolland et al., 2008). More specifically, frailty is seen as a dynamic condition that can improve or worsen over time (Morley et al., 2013) and decline or disability may be slowed down or even reversed through appropriate intervention (De Lepeleire, Iliffe, Mann, & Degryse, 2009). Therefore, it is important to detect frailty at an early stage and to effectively treat initial expressions of frailty before disability sets in (Rolland et al., 2008). Given that frailty is a multidimensional syndrome, interventions aiming at preventing or reversing frailty must simultaneously target several interrelated systems (Clegg et al., 2013).

1.3.1 Overview of interventional approaches in frailty

Frailty is often a consequence of physical disease, hence, the optimal management of any underlying medical illness is the initial goal of treatment (De Lepeleire et al., 2009). In the further course, the treatment of the well-described loss of muscle mass has been considered as a central target for preventing frailty and disability in old age. Therefore, a majority of previous intervention studies in frailty focused on physical exercise to promote muscle strength and physical resistance. These studies included, for instance, aerobic exercises (Jabbour, Iancu, Mauriège, Joanisse, & Martin, 2017), muscular strengthening training (Lazarus, Izquierdo, Higginson, & Harridge, 2018) and multi-component physical activity (Cesari et al., 2015; Ng et al., 2015; Tarazona-Santabalbina et al., 2016). The main objective of these interventions is to maintain or improve components of physical fitness, including muscular strength, muscle mass, flexibility, balance or cardiovascular endurance (Angulo, El Assar, Álvarez-Bustos, & Rodríguez-Mañas, 2020; Caspersen, Powell, & Christenson, 1985). Among those studies, successful reversion rates of frailty ranging from 31.4% (Tarazona-Santabalbina et al., 2016) to 41.3% (Ng et al., 2015) of the cases were reported. With respect to functional performance, studies employing physical exercise reported improvements in weakness (Kwon et al., 2015; Liao, Chen, & Wang, 2019), gait speed and physical inactivity (Liao et al., 2019), chair stand, stair climbing and balance as well as decreases in depression, fear of falling and incidence of falls (Theou, Stathokostas, et al., 2011). Moreover, empirical studies and systematic reviews of

exercise interventions showed that exercise can have a positive impact on outcomes of mobility and functional ability (de Vries et al., 2012; Theou, Stathokostas, et al., 2011), can decrease hospitalizations and nursing home placement (N. A. Singh et al., 2012) and can prevent the progression of frailty and further disability (Yamada, Arai, Sonoda, & Aoyama, 2012). Even relatively low-level resistance training programs including only a few exercise sessions per week were shown to be successful in terms of a lower progression of functional limitations over time (Hunter, McCarthy, & Bamman, 2004). However, the ideal composition and the most effective intensity (duration and frequency) of exercise intervention remains uncertain. Potential mechanisms of benefit of physical exercise on frailty and physical mobility may consist in its effects on multiple physiological systems, including the brain, the endocrine, immune, and musculoskeletal system (Barber, Clegg, & Young, 2012; Clegg et al., 2013; Handschin & Spiegelman, 2008; van Praag, 2009). For instance, physical activity may have a positive effect on downregulating inflammatory markers, as reported in both observational studies (Elosua et al., 2005) and clinical trials (Nicklas et al., 2008).

Apart from physical exercise, beneficial effects of other types of interventions have less consistently been reported and have yielded inconsistent results. For instance, nutritional interventions can counteract impaired nutrition as well as muscle and weight loss in frailty and may act synergistically with physical exercise (Morley et al., 2013). However, other studies reported that nutritional supplementation without an exercise program had no effect on muscle strength, physical performance and mobility in frail elderly (Fiatarone et al., 1994), suggesting that nutritional intervention alone may not be potent enough to reverse the process of physiological and functional decline (Walston, Buta, & Xue, 2018). Also, the use of pharmacological agents is still an understudied topic in the treatment of frailty. For instance, angiotensin-converting enzyme (ACE) inhibitors were found to have the potential to halt or slow decline in muscle strength (Onder et al., 2002) and improve physical capacity and quality of life (Sumukadas, Witham, Struthers, & McMurdo, 2007). Hormone replacement therapies were found to increase muscle mass and improve functional abilities (Morley, Kim, & Haren, 2005), but also to increase the risk for adverse cardiovascular and respiratory outcomes (Basaria et al., 2010). Moreover, low concentrations of vitamin D have been related to frailty (Puts, Visser, Twisk, Deeg, & Lips, 2005) and vitamin D supplementation has been associated with improvements in neuromuscular function and reduction of the risk of falls (Campbell & Szoeke, 2009), however, large-scale clinical trials are still rare.

Despite the close relationship of structural and functional brain changes with age-related decline in cognitive and sensorimotor function, training-induced effects on brain structure and function have rarely been documented in frailty. In persons with Parkinson's disease, balance training was shown to promote structural plasticity and increase gray matter volume of the cerebellum (Sehm et al., 2014). Also, training-induced changes in brain activation reflecting a reduction of neural overactivation after cognitive and sensorimotor training in healthy elderly, older adults with mild cognitive impairment and patients with Parkinson's disease were interpreted to reflect increased neural efficiency and reduced recruitment of compensatory neural processes (Giehl et al., 2020; Iordan et al., 2020; Liao, Tseng, Lin, Wang, & Hsu, 2020; Maidan et al., 2017; Nguyen, Murphy, & Andrews, 2019; Vermeij et al., 2017). In a recent fNIRS study, Liao, Chen, Hsu, Tseng, and Wang (2021) reported that physical exercise training in frailty promoted an improvement in executive function and attention as well as a decrease in activation of the prefrontal cortex during a global cognition test, presumably reflecting a training-induced increase in neural efficiency. However, training-induced structural and/or functional brain changes related to changes in sensorimotor and physical performance have not yet been demonstrated directly in frail individuals.

1.3.2 Principles of neuroplasticity-based training

In the last twenty years, a growing interest has been on ameliorating negative effects of aging based on mechanisms of neuroplasticity, i.e. the principle that the brain is able to adapt to neuronal and cognitive alterations by strengthening existing neuronal connections or creating new ones (Frantzidis, Ladas, Vivas, Tsolaki, & Bamidis, 2014; Mahncke, Bronstone, et al., 2006; Mahncke, Connor, et al., 2006). The basic assumption of this view is that age-related declines are not exclusively a direct consequence of detrimental changes in brain structure and function, but also result, in part, from reduced engagement in cognitively demanding and stimulating tasks, degraded sensory input and/or weakened neuromodulatory control (Cramer et al., 2011; Hertzog, Kramer, Wilson, & Lindenberger, 2008; Mahncke, Bronstone, et al., 2006). Thus, mechanisms of brain plasticity have more recently been considered as an important target for preventive and rehabilitative interventions.

More specifically, processes that control plasticity increase connective strength between all synapses that are activated together at a given moment and that have

contributed to previous behavioral success (Nahum, Lee, & Merzenich, 2013). When behavior engages the brain, simultaneously activated inputs are strengthened together, which increases their cooperativity to generate more reliable responses, which is known as Hebbian network plasticity (Hebb, 1949). On the physiological level, the control of these changes is enabled by changes in the control of the release of neuromodulatory neurotransmitters (e.g. acetylcholine, noradrenaline, dopamine) and in the properties of the associated receptors. The plasticity-driven increase in local neuronal cooperation promotes the improvement of selective, specialized information processing which in turn supports learning-induced progress in behavior (Nahum et al., 2013). That is, when acquiring a new skill or ability by progressive learning and continuous experience, the plastic changes in brain circuitries result in a specialization of the brain supporting these skills and abilities (Merzenich, Van Vleet, & Nahum, 2014). In turn, inputs that were not anticipated and did not contribute to the desired behavior are selectively weakened. By these mechanisms, brain plasticity is enabled by favoring the input strengths for the specific activities that the brain can gain in ability by switching to, and disfavoring the strengths of inputs that do not contribute to behavior (Merzenich et al., 2014). The engagement of competitive processes in brain networks thereby results in a refinement of selective cortical representations, for example, such that they support the processing of sensory inputs and motor actions (Mahncke, Connor, et al., 2006). It is assumed that this sort of enhancement of relevant input into brain systems can counteract age-related neuronal alterations such as neuronal dedifferentiation and noisy neuronal processing. A key mechanism of this learning-induced increase in representational fidelity is likely to be the enhancement of the signal-to-noise ratio of relevant cortical activity (Mahncke, Bronstone, et al., 2006).

Neuroplasticity-based therapeutic tools may exploit these mechanisms by using stimulus features in tasks that are known to elicit more strongly correlated local responses within brain networks. By increasing the coordinated representations of task-relevant stimulus details, the aim is to positively influence all behaviors that emanate from the targeted brain system (Nahum et al., 2013). In this context, a strong engagement of the brain, including extensive repetition, is required in order to promote overlearning of successful performance. This is important to ensure that behaviorally relevant inputs are integrated to promote the creation of robust and complex stimulus-specific and context-specific neuronal responses in the brain (Mahncke, Bronstone, et al., 2006). Continuous practice repetition is seen as critical for inducing stable, enduring

neurological changes and may be supported by the application of positive performance feedback. Success, rather than error feedback, is assumed to upregulate the brain systems related to the processing of reward, which facilitates learning and behavioral improvement (Nahum et al., 2013).

Another core feature of neuroplasticity-oriented approaches is the continuous adaptation of task difficulty using staircase procedures in order to assure both success in training as well as continuous challenge as the subjects' abilities advance (Nahum et al., 2013). Critically, learning has been shown to not occur if task difficulty is too low or too high (Engineer et al., 2012). Rather, task difficulty has to be maintained at the edge of the trainee's abilities in order to evoke sustained close attention and thereby efficiently promote plastic remodeling (Nahum et al., 2013). Neurological improvements are thought to be targeted more efficiently when task demands increase by small challenging steps while still providing sufficient overlap with already mastered ability. These advances in difficulty can be implemented by modulating various task dimensions, such as physical size or presentation time of the stimulus or the extent of cognitive load (Nahum et al., 2013). By modulating training tasks, stimuli and difficulty, the goal is to increase the fidelity and power of neuronal representations of complex, dynamic inputs. For instance, the adaptive decrease of spatial and temporal integration constants shall promote generalization of highly spatially and temporally refined processing to all contexts of lower- and higher-order information processing (Mahncke, Bronstone, et al., 2006).

Finally, to determine success of the intervention, it is important to examine whether training success transfers to non-trained but related abilities (near transfer) and to non-trained abilities that impact on activities of daily living (far transfer). In this vein, apart from targeting mechanisms of neuronal plasticity, therapeutic programs aim to establish new behaviors that positively reinforce the enhanced brain function and restrict negative maladaptive behaviors, such as inactivity and social withdrawal that negatively affect brain health (Mahncke, Bronstone, et al., 2006). In this context, previous promising studies provided evidence for the effectiveness of neuroplasticity-based training programs in enhancing cognitive control in healthy older adults (Anguera et al., 2013), improving cognitive and social behavioral impairments in schizophrenia, as well as increasing resilience against neurodegenerative disease onset by targeting age-related perceptual and cognitive losses (Merzenich et al., 2014; Nahum et al., 2013).

However, studies investigating the usage and effectiveness of a neuroplasticity-oriented training approach in counteracting frailty have not been reported so far.

1.3.3 The role of brain-derived neurotrophic factor (BDNF)

On the molecular level, training-induced plasticity is found to be mediated by neurotrophins, a group of proteins involved in neuroprotection, neurogenesis and neuroplasticity. One extensively studied representative of neurotrophins is brain-derived neurotrophic factor (BDNF). BDNF is released from neurons in the central nervous system as well as various peripheral physiological systems such as the peripheral nervous, musculoskeletal, respiratory and cardiovascular systems (Cardoso et al., 2018). BDNF has been implicated in various aspects of neuronal development and function, including neuronal growth, survival, repair and differentiation as well as synaptic transmission, connectivity and plasticity (E. J. Huang & Reichardt, 2001; Ziegenhorn et al., 2007). There is ample evidence of the important role of BDNF in healthy and pathological aging (Cardoso et al., 2018). For instance, BDNF was suggested to be a modulator of inflammation (Gezen-Ak et al., 2013), have antioxidant effects (C. L. Wu, Chen, Yin, Hwang, & Yang, 2016) and have the potential to mitigate neuronal metabolic defects following injury (Xu, Lv, Dai, Lu, & Jin, 2018). Similarly, high BDNF levels were found to be correlated with successful aging (Lau, Mat Ludin, Rajab, & Shahar, 2017) while reduced BDNF expression, as reflected by decreased BDNF levels, was associated with reduced cognitive performance in mild cognitive impairment (Shimada et al., 2014) and Alzheimer's disease (Siuda et al., 2017) as well as poor outcomes following stroke (Lasek-Bal et al., 2015). Also, reduced BDNF levels were observed in pre-frail compared to robust subjects (F. M. Coelho et al., 2012) and were related to more severe expressions of sarcopenia and frailty and reduced physical performance (Miyazaki, Iino, Koda, Narita, & Kaneko, 2021), suggesting that BDNF may be a key neuromodulatory factor in mediating the syndrome of frailty (F. M. Coelho et al., 2012). In a similar vein, lower BDNF levels were observed in sedentary compared to active people (Szuhany, Bugatti, & Otto, 2015) and regular physical activity was related to higher BDNF concentrations in the brain and enhancement of brain plasticity (Cotman & Berchtold, 2002; Cotman, Berchtold, & Christie, 2007). Together, these studies suggest that peripheral plasma and serum BDNF may partly reflect BDNF released from

the brain and may be significant biomarkers for age- and clinically-relevant brain dysfunction (Voss et al., 2013).

BDNF secretion has been shown to be affected by a single nucleotide polymorphism in the BDNF gene, the Val66Met polymorphism, which represents the valine (Val) to methionine (Met) allele substitution at the BDNF gene. The presence of the Met allele has a frequency of about 30% in healthy Caucasian populations (Egan et al., 2003; Shimizu, Hashimoto, & Iyo, 2004). The Val66Met polymorphism was associated with a reduction of BDNF secretion in response to neuronal stimulation in adults (Egan et al., 2003; Kleim et al., 2006) and may be involved in detrimental effects of brain aging (Canivet et al., 2017; Miyajima et al., 2008). For instance, Val66Met has been related to reduced secretion and activity-dependent release of BDNF, reduced grey matter volume and impaired memory and motor learning (Egan et al., 2003; Kleim et al., 2006; Pearson-Fuhrhop & Cramer, 2010). While BDNF has been suggested to be a key neuromodulatory factor in frailty (F. M. Coelho et al., 2012), the relationship between the BDNF Val66Met polymorphism and frailty is less well understood. Previous studies provided heterogeneous results with respect to the association between BDNF genotype and walking ability, with some studies reporting no relationship (Aljuhni, Cleland, Roth, & Madhavan, 2021; French, Morton, Pohlig, & Reisman, 2018), while others found reduced walking ability in stroke patients carrying the Met allele (Helm, Tyrell, Pohlig, Brady, & Reisman, 2016).

Given the role of BDNF as a mediator of cerebral function and brain plasticity, various interventional approaches have investigated training-related augmentation in BDNF levels as a potential indicator of training effects on brain health. In fact, physical exercise interventions such as aerobic exercise were shown to upregulate BDNF and increase circulating BDNF levels in animals (Neeper, Góauctemez-Pinilla, Choi, & Cotman, 1995) and healthy younger (Szuhany et al., 2015) and older humans (F. G. de M. Coelho et al., 2013; Knaepen, Goekint, Heyman, & Meeusen, 2010; Vaughan et al., 2014). For instance, aerobic exercise was found to increase hippocampal volume in healthy older adults, which in turn, was positively associated with changes in BDNF serum levels and spatial memory performance (Erickson et al., 2011). Moreover, physical exercise may have the potential to improve cognitive impairment by increasing peripheral BDNF levels in patients with mild cognitive impairment and Alzheimer's disease (H. Huang et al., 2021). Similarly, aerobic exercise was demonstrated to augment BDNF plasma levels and improve functional walking ability and pain perception in

musculoskeletal disorders (W. F. Gomes et al., 2014). Thus, it has been hypothesized that physical exercise, by upregulating BDNF and other molecules, promotes the recruitment of use-dependent plasticity mechanisms, which result in a strengthening of neuronal structure and facilitation of synaptic transmission, thereby preparing the brain to encode meaningful information from the environment and activating protective resources against damage and decline (Cotman & Berchtold, 2002).

Apart from physical exercise, BDNF may also be enhanced by external stimulation in the form of cognitive and sensory challenge. Intensive engagement in neuroplasticity-based cognitive interventions was demonstrated to be related to increase in BDNF levels and improvement in cognitive performance in healthy older adults (Ledreux et al., 2019), patients with schizophrenia (Vinogradov et al., 2009) and patients with Parkinson's disease (Angelucci et al., 2015).

Together, evidence from physical exercise and cognitive training studies suggests that BDNF acts as a key neurobiological mediator of training-induced and activity-induced beneficial neuroplasticity.

1.4 Aims and hypotheses

The aim of this dissertation was to further elucidate determinants of sensory and motor decline in frailty with respect to different clinical definitions of frailty, and to evaluate the effectiveness of a neuroplasticity-oriented sensorimotor training in counteracting the frailty syndrome. For this purpose, two research studies were conducted. This chapter presents a summary of the relevant research background and formulates the hypotheses to be investigated, separately for Study 1 and Study 2.

1.4.1 Study 1[1]

1.4.1.1 Summary of the research background[2]

Frailty describes a clinical condition that arises from a decline in multiple physiological systems and manifests in an increased vulnerability to minor stressor events, thereby increasing the risk for adverse health outcomes, including falls, hospitalization, and mortality (Clegg et al., 2013). The two most widely applied approaches to operationalize frailty are the FP model and the cumulative deficit model (Fried et al., 2001; Searle et al., 2008). The phenotype model defines frailty on the basis of five physical criteria: unintentional weight loss, self-reported exhaustion, weak grip strength, slow gait speed and low physical activity level (Fried et al., 2001). A person is classified as frail if three or more criteria are present, pre-frail if one or two criteria are present, or robust if none of the criteria is present. The cumulative deficit model in turn assumes that the more deficits a person has, the more likely that person is frail (Searle et al., 2008). Here, frailty is expressed in terms of the FI, which is determined by computing the ratio between the number of deficits present and the total number of deficits assessed. Both concepts were shown to be moderately correlated (Rockwood, Andrew, & Mitnitski, 2007), and comparison studies revealed substantial diagnostic differences between the two scores (Cesari et al., 2014). For instance, studies using the FP reported lower

[1] This study has already been published: Beier, F., Löffler, M., Nees, F., Hausner, L., Frölich, L., & Flor, H. (2022). Sensory and motor correlates of frailty: dissociation between frailty phenotype and frailty index. *BMC Geriatrics, 22*(1), 755. https://doi.org/10.1186/s12877-022-03416-6.

[2] An adapted version of chapter 1.4.1.1 has already been published as introduction section in Beier et al. (2022).

prevalence of frailty than those using the FI (Collard, Boter, Schoevers, & Oude Voshaar, 2012). Also, associations of frailty with age and mortality were stronger for the FP than the FI (Xue et al., 2020), while female gender, obesity and living alone were more strongly associated with the FI (Thompson et al., 2018). Apart from differences in diagnostic and predictive validity, the two frailty concepts also propose different processes in terms of the assumed underlying pathophysiological mechanisms of frailty. While the FP considers frailty as a biological and physical syndrome, the FI defines frailty as a multidimensional concept by emphasizing the quantity rather than the nature of health deficits (Theou et al., 2013). Information on the characteristic correlates of these two frailty measures is therefore of both scientific and clinical value (Cesari et al., 2014).

Among those critical mechanisms, the decline in motor abilities such as gait speed (Castell et al., 2013), postural control and balance (Davis et al., 2011; Toosizadeh et al., 2015), as well as dexterity (Brown et al., 2000) was shown to greatly reduce mobility and limit daily activities (Sakari et al., 2010), while elevating the risk for adverse events such as falls (Pauelsen et al., 2018). Apart from neuromuscular and musculoskeletal capacity, proper function of the motor system largely relies on the integration of multimodal sensory information. Deterioration of sensory systems is seen as a risk factor for age-related cognitive and motor decline and may precede the loss of mobility and independence by several years (Panza et al., 2018; Sakari et al., 2010). Studies investigating sensory determinants of frailty found positive relationships between frailty and visual impairment (Klein et al., 2003; Swenor et al., 2020), hearing loss (Doba et al., 2012; Kamil et al., 2014) and impairments in tactile discrimination (Vieira et al., 2016). However, sensory impairment is considered in only a small number of frailty indices (Sternberg, Wershof Schwartz, Karunananthan, Bergman, & Mark Clarfield, 2011). Adding the sensory domain to a frailty screening instrument has been demonstrated to change prevalence rates and to modify the risk profile associated with frailty (Linard et al., 2016). These findings suggest that sensory and motor abilities might be differentially associated with frailty depending on the frailty measure used.

1.4.1.2 Objectives and hypotheses

In Study 1, a sample of prefrail and frail older adults (n=44) was examined with regard to the extent of frailty employing two widely used but demonstrably different operationalizations of the concept of frailty, the FP and the FI. In order to determine functional

ability in the sensorimotor system and to perform a physiological characterization of those deficits associated with frailty, various objective measures of sensory acuity in the visual, auditory and tactile system, and of motor performance in relation to upper and lower extremity function were acquired. The relationship of measures of sensory and motor performance with measures of frailty was computed to elaborate independent sensory and motor determinants contributing to frailty. The objectives of Study 1 were to examine the agreement between the FP and the FI in classifying individuals as frail, and to determine sensory and motor correlates of frailty and compare these associations between the two frailty measures. The hypotheses to be investigated were twofold:

1.1. Given that deterioration in sensory and motor systems is implicated in pathological aging, measures of sensory and motor performance are expected to significantly predict frailty.

1.2. Given that different diagnostic and conceptual definitions of frailty have been shown to differ with respect to the proposed pathomechanisms underlying frailty, relationships of sensory and motor abilities with frailty are expected to show differential patterns for the FP and FI.

1.4.2 Study 2

1.4.2.1 Summary of the research background

Frailty is considered as an age-related clinical condition resulting from a decline in multiple physiological systems, by which vulnerability to minor stressor events and risk for adverse health outcomes are considerably increased (Clegg et al., 2013). Despite the heterogeneity of the frailty syndrome (Xue, 2011), it is often associated with a constant decline in motor abilities including gait speed (Castell et al., 2013), postural control and balance (Davis et al., 2011) as well as upper-extremity function (Brown et al., 2000). Additionally, frailty is associated with deterioration in sensory systems (Panza et al., 2018; Swenor et al., 2020; Vieira et al., 2016), which is considered to be a risk factor for age-related cognitive and motor decline. Together, these degradation processes were shown to greatly reduce mobility, limit daily activities and contribute to the loss of independence often associated with aging (Panza et al., 2018; Sakari et al., 2010). While physiological capacity as well as sensory and motor abilities also decline with normal aging, this decline is accelerated and intensified in frailty (Ferrucci et al., 2002).

According to neuroscientific models of dysfunctional aging, the brain may play a major role in determining age-related motor and cognitive decline (Dinse, 2006; Mahncke, Bronstone, et al., 2006). For instance, age-related reductions in gait and memory performance have been associated with structural gray matter reductions in the frontal (Rosano et al., 2012) and medial-temporal (Head, Rodrigue, Kennedy, & Raz, 2008) regions. From a functional perspective, cognitive and sensory (Berlingeri, Danelli, Bottini, Sberna, & Paulesu, 2013; Zanto & Gazzaley, 2017) as well as motor processing (Bernard & Seidler, 2012; Heuninckx et al., 2008; Ward, 2006) are often found to be associated with increased and more diffuse brain activity in older compared to younger adults. This overactivation has been interpreted to reflect compensatory neural mechanisms (Reuter-Lorenz & Cappell, 2008) and/or neural dysfunction in terms of reduced neural differentiation and selectivity of perceptual (Park et al., 2004) and motor (Carp, Park, Hebrank, Park, & Polk, 2011) representations. It is assumed that these altered representations are involved in age-related cognitive (Goh, 2011; Koen, Hauck, & Rugg, 2019) and sensorimotor (Seidler et al., 2010; Sleimen-Malkoun et al., 2014) decline. In this context, the concept of brain “disuse” has been put forth (Mahncke, Bronstone, et al., 2006), reflecting the reduction of perceptual inputs, motor actions,

and cognitive stimulation that are required to refine existing skills and acquire new skills (Mahncke, Bronstone, et al., 2006). For instance, behavior might become more simplified and less complex with increasing age and the brain is thought to adapt to these less complex behaviors by simplifying the underlying cortical representations and reducing their fidelity and reliability (Dinse, 2006; Mahncke, Bronstone, et al., 2006). On the neuronal level, "disuse" of the brain may negatively impact neuronal metabolism and architecture (Beaulieu & Colonnier, 1989), resulting in noisy neuronal processing in sensory and motor systems. In turn, noisy processing in sensorimotor systems might promote maladaptive behaviors such as motor instability, coordination deficits, movement slowing, inactivity, and social isolation. As a result, peripheral and bodily symptoms such as muscle weakness may increase, raising the risk of falls and fractures (Rolland et al., 2008). In combination, these interrelated factors create a downward spiral of impaired brain function, physical disability, and progressive impairment of functional ability, which may ultimately result in frailty.

The optimal procedure of how to prevent or reverse the syndrome of frailty is still a matter of debate (de Labra, Guimaraes-Pinheiro, Maseda, Lorenzo, & Millán-Calenti, 2015; Puts et al., 2017; Theou, Stathokostas, et al., 2011). Despite the evidence for a close link between structural as well as functional brain alterations and sensory, motor and physical decline during aging (Seidler et al., 2010; Sleimen-Malkoun et al., 2014), previous studies have rarely reported treatment effects related to the relationship of brain structure and function with frailty (Liao et al., 2021). Research in healthy adults demonstrated that neuroplasticity-oriented training, including intense sensory, cognitive, or motor stimulation, may have the potential to promote beneficial neuroplasticity in cortical representations, and improve neurocognitive skills that decline with aging (Anguera et al., 2013; Mahncke, Connor, et al., 2006). Computerized neuroplasticity-oriented applications may have the potential to counteract the multi-system decline observed in frailty by stimulating several systems at the same time, providing immediate feedback and promoting everyday activities that are relevant for the participant’s life (Coyle, Traynor, & Solowij, 2015).

1.4.2.2 Objectives and hypotheses

In Study 2, the aim consisted in counteracting the “disuse” of the brain by enhancing relevant input to the sensory and motor brain systems which may have the potential to reverse structural and functional correlates of maladaptive neuroplasticity and neural

inefficiency in cortical representational maps. In turn, the increased fidelity and reliability of cortical representations and the reduction of noisy neural processing may promote cognitive, physical, and sensorimotor function, leading to an improvement in frailty status and frailty-related health indices. Therefore, Study 2 was designed to evaluate the efficacy of a multimodal sensorimotor training in frail elderly, including training of sensory discrimination, multisensory integration and sensorimotor precision. To evaluate the specificity of the sensorimotor approach, a randomized controlled trial was conducted, in which prefrail and frail older adults were randomized to either a neuroplasticity-oriented tablet-based sensorimotor training (n=24) or a tablet-based relaxation control training (n=24). Both training procedures were designed as 90-day interventions encompassing daily 30-minute training sessions performed at home. Primary outcomes consisted of measures of frailty involving the FP and FI. Secondary outcomes consisted of behavioral measures of physical, sensory, motor and cognitive performance as well as clinical characteristics. Moreover, secondary outcomes included measures of sensorimotor brain activity and corticomotor excitability. The potential influence of biomarkers of neuroplasticity was examined. The hypotheses to be investigated were twofold:

2.1. Given the reported positive effects of neuroplasticity-oriented interventions in counteracting pathological aging, engagement in the neuroplasticity-oriented sensorimotor training was expected to have superior effects in improving frailty, compared to the relaxation control training.

2.2. Given that pathological aging has been shown to be associated with maladaptive plastic changes in the brain and given that neuroplasticity-oriented interventions have been demonstrated to have the potential to reverse these maladaptive plastic changes, sensorimotor training-induced improvement in frailty was expected to be accompanied by training-induced plastic alterations in sensorimotor brain systems. These neuroplastic changes were hypothesized to consist in pre-to-post training changes in the extent of sensorimotor brain activation and excitability, reflecting changes in neuronal efficiency and/or compensational neuronal mechanisms.

2 MATERIALS AND METHODS

2.1 Study 1[3]

2.1.1 Participants and procedure

Data are from a randomized controlled interventional study (Beier et al., 2021). The aim of the interventional study was to compare a tablet-based sensorimotor training (experimental group) and a tablet-based relaxation training (control group) in subjects suffering from frailty. Ethics approval was obtained from the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University. For the present cross-sectional analysis, only data from baseline assessments were used.

The present sample consists of N = 52 subjects who were recruited from collaborating geriatric centers, the general population via newspaper advertisements, info leaflets and online announcements and were pre-screened via telephone interviews for medical history, medication intake and activities of daily living to determine general eligibility. Subjects were included in the study if they (a) were aged 65 to 95 years and (b) fulfilled at least one of the five FP criteria, i.e. were classified as being pre-frail or frail, according to the FP model (Fried et al., 2001). Subjects were excluded if they suffered from acute illnesses, severe neurological or mental disorders (i.e. depression), significant cognitive impairment (defined as a Mini Mental State Examination (MMSE) score of ≤ 24), or severe impairments in sensory abilities (i.e. visual acuity of < 0.1; mechanical detection threshold of > 512 mN; mean hearing threshold of > 60 dB; severe tinnitus symptomatology).

2.1.2 Frailty assessment

Frailty was assessed using the FP (Fried et al., 2001) and the FI (Searle et al., 2008). The FP incorporates five different criteria: unintentional weight loss, exhaustion, low levels of physical activity, slow gait speed, and poor grip strength. Unintentional weight loss was evaluated based on self-reports asking the subject if they unintentionally lost 4.5 kg or more in weight within the past year. Exhaustion was assessed using two

[3] An adapted version of chapter 2.1 has already been published as methods section in Beier et al. (2022).

items from the German version of the Center for Epidemiologic Studies Depression Scale (CES-D; Hautzinger, Bailer, Hofmeister, & Keller, 2012; Radloff, 1977): “I could not get going”, and “I felt that everything I did was an effort”. Exhaustion was classified as present if a response of “occasionally” (3-4 days) or “most of the time” (5-7 days) regarding the past week was given to either question. Physical activity was measured asking subjects to state how much time they spent during the past two weeks doing 18 different leisure activities. The amount of time was converted into an estimate of the weekly energy expenditure in kilocalories and low physical activity was classified as present if the kilocalories expended per week fell below a cut-off value, stratified by gender (males: < 383 Kcals/week; females: < 270 Kcals/week). Gait speed was determined by measuring the time taken to walk 4.57 m at usual pace, using walking aids if needed. Cut-off points were stratified by gender and height (males: height ≤ 173 cm: ≥ 7 seconds, height > 173 cm: ≥ 6 seconds; females: height ≤ 159 cm: ≥ 7 seconds, height > 159 cm: ≥ 6 seconds). Grip strength was measured in kg using a Jamar hand dynamometer (Patterson Medical, Cedarburg, WI, USA). Maximal grip strength at the dominant hand was averaged across three trials and cut-off scores were stratified by gender and body mass index (males: BMI ≤ 24: ≤ 29 Kg, BMI 24.1 – 26: ≤ 30 Kg, BMI 26.1 – 28: ≤ 30 Kg, BMI > 28: ≤ 32 Kg; females: BMI ≤ 23: ≤ 17 Kg, BMI 23.1 – 26: ≤ 17.3 Kg, BMI 26.1 – 29: ≤ 18 Kg, BMI > 29: ≤ 21 Kg). Subjects fulfilling three or more FP criteria were classified as frail while subjects fulfilling one or two criteria were classified as pre-frail.

To determine the FI, 40 deficit variables and cut-off points as developed by Searle et al. (2008) were used consisting of physical, psychological, social and cognitive items and reported comorbidity excluding shoulder strength measurement due to feasibility reasons. Each deficit was dichotomized with a score of 0 representing absence of the deficit and 1 representing full presence of the deficit. For some items, intermediate scores were used to allow for a finer grading of the respective deficit. The FI was calculated by summing all deficits and dividing by the total number of deficits, resulting in a total score ranging from 0 (no deficit present) to 1 (all deficits present). Using previously reported cut-off points (Rockwood et al., 2007; Song, Mitnitski, & Rockwood, 2010), individuals with a FI score > 0.25 were considered as frail and those with a score ≤ 0.25 were considered as pre-frail.

2.1.3 Sensory assessment

2.1.3.1 Visual acuity

Binocular visual acuity was assessed using the automated Freiburg Visual Acuity and Contrast Test (FrACT; Bach, 1996, 2007). The test was performed in an artificially lit room and test stimuli were presented on a 15-inch LCD monitor (resolution 1280 x 800) at a distance of 150 cm. All subjects were tested without wearing any visual aids while subjects who used visual aids to correct their vision were additionally tested while wearing their visual aids. For those subjects, the better one of the two scores (with or without visual aids) was considered for the subsequent analyses. In the visual acuity test, 18 black Landolt-C optotypes were successively presented one at a time randomly at one of eight possible orientations against a white background and subjects were to indicate the orientation of the optotype in a forced-choice manner. The size of the optotype was adapted in each trial according to a staircase best-PEST procedure (Lieberman & Pentland, 1982; Treutwein, 1995). Visual acuity was quantified using the logMAR score which is defined as the negative logarithm of the decimal visual acuity score (logMAR = log(VA)). Thus, lower logMAR scores represent higher visual acuity.

2.1.3.2 Auditory perception thresholds

To assess auditory perception thresholds, pure-tone audiometry was performed in a sound-shielded and anechoic booth using a screening audiometer (MA 25, MAICO Diagnostics GmbH, Berlin, Germany). Subjects were tested without wearing any hearing aids and single tones were presented via headphones separately to the right and left ear in a counterbalanced manner. The tones were manually given by the experimenter and subjects were asked to press a button whenever they perceived a tone. For each frequency of 500, 1000, 2000 and 4000 Hz, absolute hearing thresholds in decibel (dB) were determined using a staircase procedure (Carhart & Jerger, 1959). Absolute hearing thresholds were then averaged across the four frequencies separately for the right and left ear. For the subsequent analyses, the hearing threshold of the better hearing ear was considered.

2.1.3.3 Somatosensory perception thresholds

Touch thresholds were determined by stimulating the fingertip of the index finger of the dominant hand using von Frey filaments (Marstocknervtest, Marburg, Germany). Possible touch forces ranged from 0.25 to 512 mN in a logarithmic scale. During the test, subjects were asked to close their eyes and to verbally indicate whenever they perceived a sensation on their skin. The filaments were manually applied by the experimenter perpendicular to the subject's skin. A staircase procedure (Bell-Krotoski, Fess, Figarola, & Hiltz, 1995; Christensen et al., 2020) was applied resulting in five values for upper and lower boundaries, respectively, that were averaged to obtain the touch threshold. Here, lower scores reflect enhanced sensation.

2.1.4 Motor assessment

2.1.4.1 Upper extremity function

To assess upper extremity function, the Purdue Pegboard Test (PPT; Tiffin & Asher, 1948) was used which measures fine and gross motor dexterity and coordination of hands, fingers, and arms (Desrosiers, Hébert, Bravo, & Dutil, 1995). Subjects had to use their dominant hand to place small metal pegs into holes one at a time from top to bottom as fast as possible within a 30-seconds epoch. Three runs were administered and the number of correctly placed metal pegs was averaged across runs.

2.1.4.2 Lower extremity function

Lower extremity function was assessed using the Short Physical Performance Battery (SPPB; Guralnik et al., 1994) comprising timed measures of balance, walking speed, and sit-to-stand ability. For the balance test, subjects had to maintain their feet in side-by-side, semitandem and tandem position for 10 seconds each. For the walking speed test, subjects were asked to walk at their usual speed over a 4-meter distance, using walking aids if needed. For the sit-to-stand test, subjects were asked to stand up from a chair and sit down five times in a row as quickly as possible without using their arms while the time to perform the task was recorded. Performance measures of the individual subtests were then converted into a score ranging from 0 to 4 and were summed up to compute the total SPPB score ranging from 0 to 12.

2.1.5 Additional measures and covariates

Sociodemographic data of each subject were collected through a verbally administered questionnaire requesting information about age, gender, somatic co-morbidities, handedness and use of sensory aids. Height, weight and body mass index were obtained through a physical examination performed by a study physician. The MMSE was used to screen for cognitive impairment. Depressive symptoms were assessed using the German version of the 20-item Center for Epidemiologic Studies Depression Scale (CES-D; Hautzinger et al., 2012; Radloff, 1977).

2.1.6 Statistical analyses

Analyses were carried out using SPSS version 25 (Armonk, NY: IBM Corp.). Continuous variables were checked for normal distribution using Kolmogorov-Smirnov tests. Descriptive characteristics of each variable are reported as mean and standard deviation (SD) for continuous variables and frequency and percentages for categorical variables. Descriptive variables were additionally stratified by gender and gender differences were examined using Student's t-tests for normally distributed variables, Mann-Whitney-U-tests for non-normally distributed variables and Pearson-chi²-tests for categorical variables. Additionally, descriptive variables were contrasted between pre-frail and frail for both frailty measures. Agreement between the two frailty measures was assessed using a kappa statistic and frailty prevalence was compared using the McNemar test. To examine associations of the demographic, sensory and motor variables with frailty as well as between the two frailty measures, correlation coefficients were calculated using Pearson correlations for normally distributed variables and Spearman correlations for non-normally distributed variables. To identify independent determinants of frailty, hierarchical multiple logistic regression models were calculated for each of the two frailty measures, using frailty status (pre-frail, frail) as outcome. In the first block, age and gender were entered into the analyses as covariates to account for the known relationship between age, gender and frailty. In addition, depressive symptoms (CES-D score) were added, which have previously been associated with both sensory impairment and frailty (Buigues et al., 2015; Collard, Comijs, Naarding, & Oude Voshaar, 2014; Liljas et al., 2016; Yu & Liljas, 2019). In the second block, sensory and motor variables were added to the analyses to determine the respective associations with frailty. For the regression models, odds ratio (OR), 95% confidence

intervals (CI) and Nagelkerke's R^2 along with the p-value for the model are reported. A significance level of 0.05 was used for all analyses.

2.2 Study 2

A detailed description of the study procedure and the methods used was previously published in the form of a study protocol (Beier et al., 2021).

2.2.1 Design

Both the tablet-based sensorimotor training (experimental group, EG) and the tablet-based relaxation training (control group, CG) were designed as 90-day home-based interventions. Assessments were conducted (1) before (baseline T0), (2) after 60 days (assessment T1), and (3) after 90 days (assessment T2) at the Institute of Cognitive and Clinical Neuroscience, Central Institute of Mental Health (CIMH), Mannheim.
The study was supported by a grant of the Hector-Stiftung II, Weinheim, Germany, and the funders had no role in study design, data collection and analysis. The study was approved by the local Ethics Committee (Medical Ethics Committee II, Medical Faculty Mannheim, Heidelberg University; 2015-544N-MA) according to the Declaration of Helsinki and has been registered under the trial number NCT03666039 (clinicaltrials.gov). No severe adverse events were reported as a result of the assessments or treatment protocols. The study protocol adheres to the CONSORT guidelines for reporting parallel group randomized trials (see Table 1 for the CONSORT checklist).

Table 1. Materials and Methods Study 2: CONSORT checklist.

Section/Topic	Item No	Checklist item	Reported on page No[4]
Title and abstract			
	1a	Identification as a randomised trial in the title	NA
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	NA
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	26-27
	2b	Specific objectives or hypotheses	27-28
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	35, 39-42
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	39-42
Participants	4a	Eligibility criteria for participants	39-40
	4b	Settings and locations where the data were collected	35, 40-41
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	43-46
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	46-60
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	40-41
	7b	When applicable, explanation of any interim analyses and stopping guidelines	40-41
Randomisation:			
	8a	Method used to generate the random allocation sequence	40

[4] *Note*: The page numbers refer to the pages in the present thesis.

Sequence generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	40
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	40
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	39-42
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	40
	11b	If relevant, description of the similarity of interventions	43-46
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	60-62
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	60-62
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	41-42,
	13b	For each group, losses and exclusions after randomisation, together with reasons	41-42
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	79, 107
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	78-114
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	78-114
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	78-114
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	35

Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	120-121
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	120-121
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	115-121
Other information			
Registration	23	Registration number and name of trial registry	35
Protocol	24	Where the full trial protocol can be accessed, if available	35
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	35

NA, not applicable.

2.2.2 Recruitment and inclusion criteria

Participants were recruited both from the general population and from geriatric hospitals using personal contact, newspaper advertisements, leaflets, and online announcements. Prior to the invitation to the CIMH, telephone interviews were conducted to prescreen potential subjects for general eligibility. Specific eligibility criteria were tested and general eligibility criteria were confirmed during the first examination appointment. Inclusion criteria were age of 65 to 95 years and the presence of at least one of the five FP criteria (Fried et al., 2001) such as self-reported unintentional weight loss of > 5 kg in the prior year, self-reported exhaustion, low level of physical activity specified in kcal/week, muscle weakness as measured by low grip strength using a Jamar hand dynamometer, and slowness as determined by slowed gait speed over 4.57 m. According to the phenotype model, subjects fulfilling one or two criteria were classified as pre-frail while subjects fulfilling three or more criteria were classified as frail (Fried et al., 2001). Apart from frail subjects, pre-frail subjects were included to investigate neuroplasticity mechanisms across a broader range of age-related functional decline, as the pre-frail stage is considered to describe a condition at high risk of progression to frailty (X. Chen, Mao, & Leng, 2014; Gill, Gahbauer, Allore, & Han, 2006) and may be more amenable to change.

Study exclusion criteria consisted of the following: acute bone fractures within the last 3 months, immobility, paralysis or confinement to bed; stroke or neurological disorders with major cognitive or physical impairments; dementia; myocardial infarction within the last 6 months; life-time prevalence of mental disorders such as schizophrenia and other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, drug or alcohol addiction; current severe major depression or other acute axis 1 mental disorders; current intake of benzodiazepines or antipsychotics; vitamin B12-, folate- or thyroid-stimulating hormone deficiency. Specific exclusion criteria included: cognitive impairment defined as a Mini Mental State Examination (MMSE) score of ≤ 24; severe impairments in sensory abilities (i.e. visual acuity of < 0.1; mechanical detection threshold of > 512 mN; severe or profound hearing loss according to the WHO, defined as a mean hearing threshold of > 60 dB; severe tinnitus symptomatology).

2.2.3 Procedure

Prescreened subjects who met the general eligibility criteria were invited for baseline assessments. Subjects gave written consent for participation upon their first visit to the CIMH. Specific eligibility criteria were examined by a trained psychologist and a trained psychiatrist. Individuals who met the diagnostic criteria then underwent behavioral, neuropsychological, and neurophysiological assessments conducted by the psychologist, and a medical and neuropsychiatric examination conducted by the psychiatrist. To analyze BDNF blood levels and genotypes, blood samples were collected and stored. Assessments took place on several consecutive dates. Following baseline assessments, subjects were randomly allocated on a 1:1 ratio to either the experimental or control condition. The randomization schedule was generated electronically by a researcher not involved in the assessments. Group allocations were kept in sequentially numbered sealed opaque envelopes. Participants were informed about the random allocation procedure and were introduced to the respective training procedure by a psychologist. Remote and on-site support during the home-based treatment was provided. After 60 and 90 days, motor, sensory and neurocognitive functioning was reassessed at the CIMH. The neurophysiological assessment as well as the physical examination, including collection of blood samples, was repeated after 60 days. The subjects did not receive payment for their participation, but were compensated for travel expenses. Due to the investigator's involvement in assessments and training procedures, blinding of the investigator was not possible.

2.2.4 Study population

A priori sample size calculation was based on previous studies in healthy older humans using sensory training which have achieved promising results with medium effect sizes and sample sizes of 41 to 53 subjects (Mahncke, Bronstone, et al., 2006; Mahncke, Connor, et al., 2006). Given that the present sensorimotor training approach included a multimodal stimulation approach and focused on motivational enhancement within a virtual training environment, the effect of the experimental training program was expected to exceed a medium effect size (Beier et al., 2021). To estimate sample size, a repeated measures design was used including one between-factor with two groups and one within-factor with three assessment points (Faul, Erdfelder, Lang, & Buchner, 2007). Assuming a medium effect size of Cohen’s f = 0.25, 95% statistical power, a

correlation of 0.50 between the dependent measurements, and a two-sided alpha error level of .05, a priori sample size calculation revealed a sample size of 22 participants in each group (Beier et al., 2021). To account for a drop-out rate of about 25% during the training, a minimum number of 30 subjects per group was aimed at (60 in total).
The detailed flow of participants is depicted in Figure 1. A total of 51 subjects were randomized to the intervention conditions. Twenty-four subjects in each intervention group were reassessed after 60 days of training (T1 assessment). After the interim T1 assessment sessions, subjects continued the respective training procedure for another 30 days. However, due to the fact that the training procedure was not completely finalized yet when the randomization started and because several subjects declined to continue, only a reduced number of 10 subjects in the EG and 7 subjects in the CG continued with the following 30 days of training. Nine subjects in the EG and 7 subjects in the CG underwent the final assessment after a total amount of 90 days of training (T2 assessment). Due to differences in sample sizes, results of the sample completing 60 days and 90 days will be reported separately.

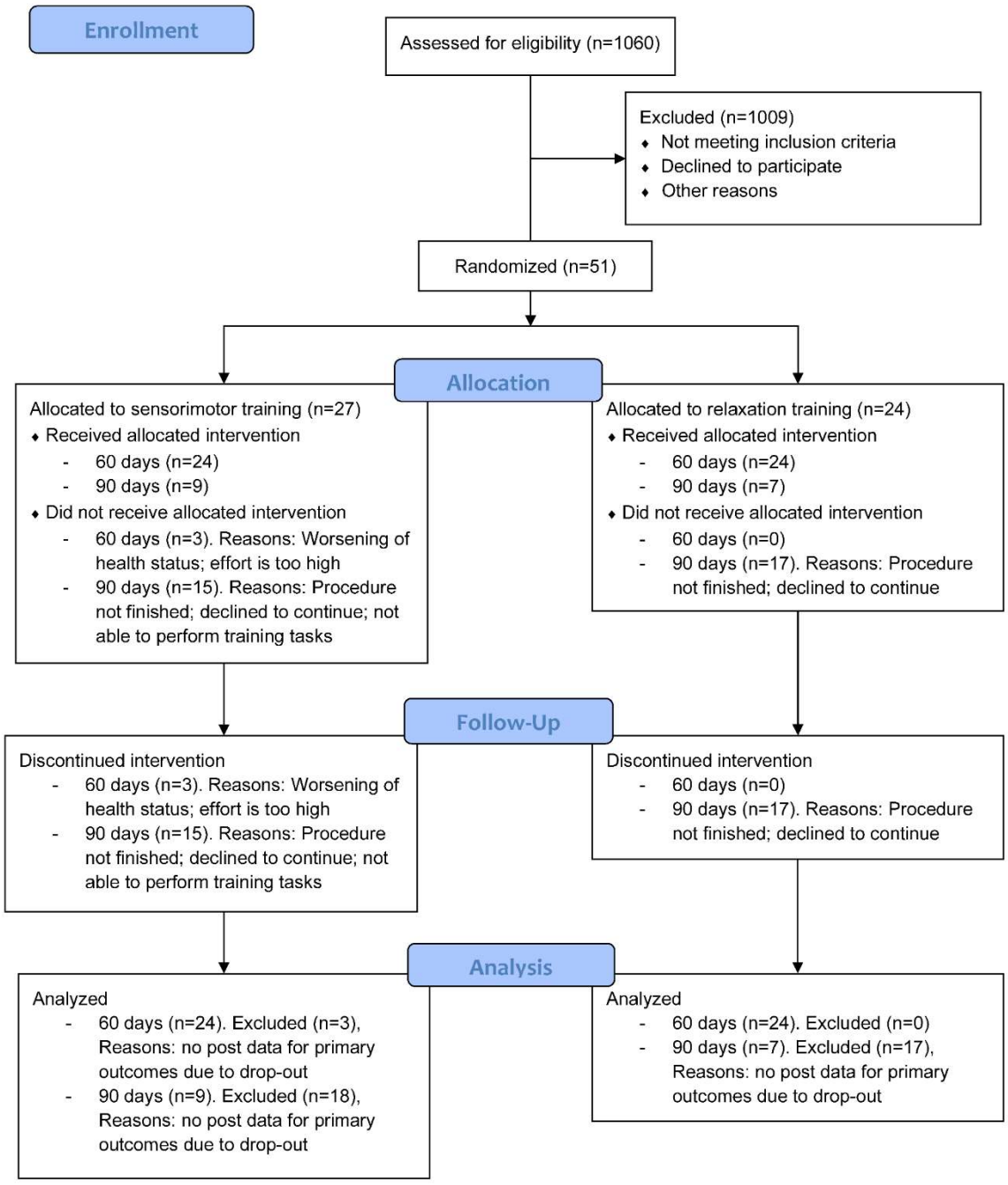

Figure 1. Materials and Methods Study 2: CONSORT flow diagram.

2.2.5 Interventions

2.2.5.1 Experimental condition[5]

The interactive tablet-based sensorimotor training consisted of three successive phases, each lasting 30 days (90 days in total). A detailed description of the training tasks is given in Table 2 (see also Beier et al., 2021, and Bekrater-Bodmann et al., 2019). During the first phase, sensory discrimination tasks were performed in the visual, auditory, and tactile domain to increase sensory acuity. In the second phase, subjects were trained on bimodal sensory integration using visual-auditory, visual-tactile and auditory-tactile tasks requiring subjects to indicate whether two stimuli were synchronous or not. These tasks were designed to improve temporal multisensory integration and to promote plasticity in perceptual integration brain networks (Paraskevopoulos & Herholz, 2013; Wallace & Stevenson, 2014). Unimodal and bimodal stimuli were presented through the tablet requiring explicit answers on the tablet's touch screen. In the third phase, participants were required to process bimodal sensory information in order to control a sensorimotor response in the form of visual-auditory guided cycling, visual-tactile determined grasping, and auditory-visual controlled hand coordination. These tasks aimed at improving motor acuity, i.e. increasing precision and reducing variability of motor actions by increasing the signal-to-noise ratio in sensorimotor brain networks (Censor, Sagi, & Cohen, 2012; Shmuelof, Yang, Caffo, Mazzoni, & Krakauer, 2014). To conduct tactile, cycling, and grasping tasks, external devices were used that were controlled wirelessly by the tablet (i.e. a Braille display device for tactile tasks, a custom ergometer for cycling tasks, and a handgrip dynamometer for grasping tasks).

Each daily training session lasted approximately 30 minutes with about 10 minutes being spent on each of the three respective training tasks. These tasks were embedded in a container application that incorporated a virtual gaming environment including personal reinforcers (Anguera et al., 2013). Performing the daily training tasks, participants were able to earn tickets to progress on a virtual journey throughout European cities. To enhance training motivation and efficacy, the program included a customized

[5] The development of the tablet-based sensorimotor training program took place within the framework of a cross-project collaboration to which the author of this dissertation contributed significantly. For a description of the projects and persons involved, consider Beier et al. (2021) and Bekrater-Bodmann et al. (2019).

application environment as well as personally relevant reinforcers (pictures, sounds) individually embedded in the tasks. In order to maximize motivation during training, task difficulty was dynamically adjusted using various stimulus and task properties to provide a 70-80% positive feedback rate. The adaptive difficulty manipulation aimed at producing sustained sensory and sensorimotor challenges, thereby promoting lasting neural changes and transfer effects (Anguera et al., 2013; Brehmer, Kalpouzos, Wenger, & Lövdén, 2014). The application automatically collected training data including the amount of time spent on the training tasks as well as progress on a daily basis.

Table 2. Materials and Methods Study 2: Overview of the tasks provided in the experimental sensorimotor training.

Domain trained	Description	Properties modulated for difficulty
Phase 1: unimodal sensory discrimination		
Visual discrimination	A visual stimulus (Snellen-E or Landolt-C) is presented and subjects indicate by button press on the screen to which direction the "opening" of the stimulus is pointing	Type (Snellen-E or Landolt-C); Size; Contrast; Presentation time
Auditory discrimination	Acoustic sweeps are presented and subjects indicate by button press on the screen whether the pitch of the sweep increases or decreases. Two tones are presented and subjects indicate by button press which tone has a higher pitch	Type (single-tone or multiple-tone sweeps); Pitch difference; Distance of pitch from lower or upper hearing thresholds; Background noise level; Presentation time
Tactile discrimination	A pattern of dots is presented on a Braille display that subjects have to perceive with their index finger and indicate the correct pattern by button press on the screen	Length of pattern; Size of pattern; Degree of similarity between patterns
Phase 2: bimodal sensory integration		
Visual-auditory discrimination	A word is presented acoustically and the lip movements of the speaker pronouncing the word are presented visually and subjects have to select by button press on the screen the word that was spoken	Background noise level; Visual blurring; Size of visual stimulus; Degree of similarity between response alternatives
Visual-tactile discrimination	A moving pattern of dots is presented visually on the screen and tactilely on the Braille display and subjects have to indicate by button press on the screen whether the two patterns move synchronously or asynchronously	Extent of asynchrony; Speed of moving pattern; Visual contrast; Size of tactile pattern
Auditory-tactile discrimination	A melody is presented acoustically and a moving pattern of dots is presented tactilely on the Braille display and subjects have to indicate by button press on the screen whether the tones of the melody and the dots on the Braille display appear synchronously or asynchronously	Extent of asynchrony; Speed of pattern; Background noise level; Size of tactile pattern
Phase 3: sensorimotor integration		
Visual-auditory guided cycling	By cycling faster or slower on an ergometer, subjects control the height of a visually presented helicopter on the screen. Subjects have to find and maintain the correct cycling speed to match the height of the helicopter with the height of one of two visually presented stimuli, as determined by the increasing or decreasing pitch of an acoustically presented sweep	Degree of similarity between target cycling speeds; Pitch difference; Distance of pitch from lower or upper hearing thresholds; Visual transparency; Extent of the tolerance range for target cycling speed; Background noise level; Duration to maintain the target speed
Visual-tactile determined grasping	A visual pattern of dots is displayed on the screen and subjects have to apply a certain force to a handgrip force measuring dynamometer in order to produce the same pattern of dots on the tactile display	Extent of the tolerance range for target grip force; Visual contrast; Size of tactile pattern; Duration to maintain the target grip force
Auditory-visual controlled hand coordination	Subjects have to direct a visually presented moving ball into either the upper or the lower one of two visually presented holes by tilting the tablet into different directions. The correct hole depends on whether the pitch of an acoustically presented sweep increases or decreases.	Tilt sensitivity; Pitch difference; Distance of pitch from lower or upper hearing thresholds; Distance between visual holes; Visual transparency; Presentation time; Size of visual holes; Use of court edges (yes/no)

2.2.5.2 Control condition

In the control group, a tablet-based relaxation training was used that encompassed 30-minute sessions per day over 90 days. The relaxation training was designed to not include any of the critical features of the sensorimotor training app (multimodal training, adaptive algorithm, personalized feedback). Training sessions consisted of either watching relaxation videos of nature scenes or following verbally guided relaxation exercises, alternating on a regular basis. Relaxation exercises encompassed various relaxation techniques such as autogenic training, breathing meditation, mindfulness practice, or imaginary journeys. At the end of each session, participants were asked to complete a short questionnaire about their affective state including items from the German version of the Positive and Negative Affect Schedule (PANAS; Krohne, Egloff, Kohlmann, & Tausch, 1996; Watson, Clark, & Tellegen, 1988). Training data collected by the app included responses to the post-training questionnaire as well as the total amount of time engaged in the daily training.

2.2.5.3 Training evaluation

To uncover motivational and affective aspects of the training, subjects were asked for treatment expectation and evaluation pre- and post-training using a standard 5 item scale (Borkovec & Nau, 1972; Flor, 1991). Each question was rated on a scale from 1 to 10 and a sum score was computed, with higher scores reflecting more positive expectation/evaluation.

2.2.6 Assessments and outcome measures

The assessments were conducted according to the structure depicted in Table 3.

Table 3. Materials and Methods Study 2: Overview of assessments, measures, instruments and assessment time points, adapted from Beier et al. (2021).

Assessments	Measures	Instruments	Assessment time points
Personal information	• Age, sex, education, clinical history, medication	• Self-report	• T0, T1, T2
Physical and mental characteristics	• Height, weight, BMI • Nutritional status • Depression • Cognitive status	• Standard measures • MNA • GDS • MMSE	• T0, T1, T2 • T0, T1 • T0 • T0, T1, T2
Frailty	• Number of frailty phenotype criteria • Frailty index	• Frailty phenotype • Frailty index	• T0, T1, T2 • T0, T1, T2
Motor function	• Upper extremity function • Lower extremity function • Balance	• PPT • SPPB • CTSIB	• T0, T1, T2 • T0, T1, T2 • T0, T1
Sensory function	• Visual acuity • Visual contrast sensitivity • Hearing thresholds • Fine-touch thresholds • Tactile grating thresholds	• FrACT • FrACT • Audiometer • Von-Frey filaments • JVP domes	• T0, T1, T2 • T0, T1, T2 • T0, T1 • T0, T1 • T0, T1, T2
Cognitive function	• Mental and motor speed • Selective attention • Working memory span • Executive functioning	• CANTAB-RTI • CANTAB-AST • CANTAB-SSP • CANTAB-IED	• T0, T1 • T0, T1, T2 • T0, T1 • T0, T1
Functional level and quality of life	• Functional level in frailty • Depressive symptoms • Health-related quality of life • Functional capacity in everyday activities • Fear of falling	• FEFA • CES-D • SF-36, EQ-5D-5L • MKS • FES-I	• T0, T1 • T0, T1 • T0, T1, T2 • T0, T1 • T0, T1, T2
Brain plasticity in the sensorimotor and somatosensory system	• Structural and functional parameters of cortical sensorimotor and somatosensory maps • MEP peak-to-peak amplitude and latency	• fMRI motor sequence task, fMRI somatosensory mapping task[nr] • TMS at left primary motor cortex	• T0, T1 • T0, T1
Biological markers of neuroplasticity	• BDNF genotypes • BDNF serum blood levels (ng/ml)[nr]	• Collection of blood samples	• T0, T1

AST, Attention Switching Task; BDNF, brain-derived neurotrophic factor; CES-D, Center for Epidemiologic Studies Depression Scale; CTSIB, Clinical Test of Sensory Integration of Balance; EQ-5D-5L, EuroQol-5D-5L; FEFA, Frail Elderly Functional Assessment; FES-I, Falls Efficacy Scale – International Version; fMRI, functional magnetic resonance imaging; FrACT, Freiburg Vision Test; GDS, Geriatric Depression Scale; IED, Intra-Extra Dimensional Set Shift; MEP, motor-evoked potential; MKS, Marburg Competency Scale (Marburger Kompetenz Skala); MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; ng/ml, nanograms per milliliter; PPT, Purdue Pegboard Test; RTI, Reaction Time Test; SF-36, Short Form-36 Health Survey; SPPB, Short Physical Performance Battery; SSP, Spatial Span Test; T0, baseline assessment; T1, assessment 1 after 60 days; T2, assessment 2 after 90 days; TMS, transcranial magnetic stimulation; [nr] not reported in the present thesis.

2.2.6.1 Behavioral and clinical measures

2.2.6.1.1 Sample characteristics

Age, sex, education, clinical history and medication were assessed through self-report. Measurements of height and weight were converted to body mass index (BMI). To screen for nutritional status, the Mini Nutritional Assessment (MNA; Vellas et al., 2006) was used. To screen for clinically relevant depression, the 15-item version of the Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986) was used. To screen for general cognitive status, the mini mental state examination (MMSE; Folstein, Folstein, & McHugh, 1975) was used.

2.2.6.1.2 Frailty

The primary outcomes consisted of the degree of frailty as determined by the FP (Fried et al., 2001) and the FI (Searle et al., 2008).

2.2.6.1.2.1 Frailty phenotype (FP)

For the FP (Fried et al., 2001), five different criteria were taken into account: unintentional weight loss, exhaustion, low level of physical activity, slow gait speed and poor grip strength. Unintentional weight loss was evaluated based on self-reports asking the subject if they unintentionally lost 4.5 kg or more in weight within the past year. Exhaustion was assessed using two items from the German version of the Center for Epidemiologic Studies Depression Scale (CES-D; Hautzinger et al., 2012; Radloff, 1977): “I could not get going”, and “I felt that everything I did was an effort”. If either of the two questions was answered with "occasionally" (3-4 days) or "most of the time" (5-7 days) regarding the past week, exhaustion was classified as present. To determine physical activity, subjects were asked how much time they spent doing 18 different leisure activities during the previous two weeks. The amount of time was converted into an estimate of the weekly energy expenditure in kilocalories and low physical activity was classified as present if the kilocalories expended per week fell below a cut-off value, stratified by gender. Gait speed was determined by measuring the time taken to walk 4.57 m at usual pace, using walking aids if needed. Cut-off points were stratified by gender and height. To measure grip strength in kg, a Jamar hand dynamometer (Patterson Medical, Cedarburg, WI, USA) was used. Maximal grip strength at the dominant hand was averaged across three trials and presence of the criterion was

determined using cut-off scores stratified by gender and body mass index. The number of criteria present were summed up and frailty status was classified as “frail” if three or more FP criteria were present, “pre-frail” if 1 or 2 FP criteria were present, and “robust” if none of the criteria was present.

2.2.6.1.2.2 Frailty index (FI)

The FI was determined by evaluating the presence of deficits out of a total number of 40 deficits assessed. Deficits assessed included previous diseases, disability, psychosocial risk factors as well as physical and cognitive impairments (Searle et al., 2008), excluding shoulder strength measurement due to feasibility reasons. For each deficit, a dichotomous score of 0 and 1 was determined, with 0 representing the absence of the deficit and 1 representing its full presence. For some items, the grading scale included intermediate scores to allow for a finer grading of the respective deficit. To calculate the FI, deficit scores were summed up and divided by the total number of deficits, resulting in a continuous FI score ranging from 0 (no deficit present) to 1 (all deficits present).

2.2.6.1.3 Motor function

2.2.6.1.3.1 Upper extremity function

Upper extremity function was assessed by using the Purdue Pegboard Test (PPT; Tiffin & Asher, 1948), which required participants to place cylindrical metal pegs into holes with either the right, left or both hands simultaneously as fast as possible within 30 seconds. In a fourth condition, participants had to combine pegs, washers and small tubes into a pre-defined assembly as fast as possible within 60 seconds. For each condition, three runs were administered and the number of correctly placed elements was averaged across runs.

2.2.6.1.3.2 Lower extremity function

The Short Physical Performance Battery (SPPB; Guralnik et al., 1994) was used to evaluate lower extremity function based on timed tests of balance, walking speed, and sit-to-stand ability. In the balance test, subjects were required to hold their feet in side-by-side, semitandem, or tandem position for 10 seconds each. In the walking speed test, subjects walked over a distance of four meters at their usual pace, using walking

aids if necessary. In the sit-to-stand test, subjects were asked to get out of a chair and sit down as quickly as possible five times in a row without using their arms, while the time it took to perform the task was recorded. Individual subtest scores were converted into scores ranging from 0 to 4 which were added up to calculate a total SPPB score ranging from 0 to 12.

To determine postural stability, a modified version of the Clinical Test of Sensory Integration of Balance (CTSIB; Shumway-Cook & Horak, 1986) was used. Subjects were required to maintain their feet side-by-side for 30 seconds with eyes open on a firm surface, eyes closed on a firm surface, eyes open on an unstable surface, and eyes closed on an unstable surface. Time scores from different conditions were summed up into a total score.

2.2.6.1.4 Sensory function

2.2.6.1.4.1 Visual perception thresholds

Visual ability testing included visual acuity and visual contrast sensitivity and was carried out using the automated Freiburg Vision Test (FrACT; Bach, 1996, 2007). The tests were performed in an artificially lit room and test stimuli were presented on a 15-inch LCD monitor (resolution 1280 x 800) at a distance of 150 cm. All subjects were tested without wearing any visual aids while subjects who used visual aids to correct their vision were additionally tested while wearing their visual aids. Only scores for non-corrected vision were analyzed. To assess visual acuity, 18 black Landolt-C optotypes were successively presented one at a time randomly at one of eight possible orientations against a white background and subjects were to indicate the orientation of the optotype in a forced-choice manner. A staircase best-PEST procedure (Lieberman & Pentland, 1982; Treutwein, 1995) was used in each trial to adjust optotype size. As a measure of visual acuity, the logMAR score was calculated as the negative logarithm of the decimal visual acuity score (logMAR = -log(VA)). Thus, lower logMAR scores reflect higher visual acuity.

To measure visual contrast sensitivity, 24 grey-scale Landolt-C optotypes of the same size were sequentially displayed one at a time randomly at one of eight possible orientations against a grey-scale background. Again, subjects indicated each optotype's orientation in a forced-choice manner. After each response, luminance of the optotype and the background was automatically adjusted according to the subject's performance. The program reported Weber contrast values (in %) and these were used to

calculate the log contrast sensitivity score logCS using the formula logCS = log(100/Weber%). Here, higher logCS scores reflect enhanced visual contrast sensitivity.

2.2.6.1.4.2 Auditory perception thresholds

Auditory perception thresholds were determined through pure-tone audiometry using a screening audiometer (MA 25, MAICO Diagnostics GmbH, Berlin, Germany). The tests were carried out in a sound-shielded and anechoic booth and subjects were tested without wearing any hearing aids. The experimenter manually presented single tones via headphones separately to the right and left ear in a counterbalanced manner and subjects were instructed to indicate by button press whenever they perceived a tone. Using a staircase procedure (Carhart & Jerger, 1959), absolute hearing thresholds in decibel (dB) were determined for each frequency of 125, 250, 500, 1000, 2000, 4000 and 8000 Hz. Based on the score defined by the WHO for determining hearing loss (WHO, 1991), a composite auditory threshold score was calculated separately for the right and left ear by averaging absolute hearing thresholds (dB) for frequencies of 500, 1000, 2000 and 4000 Hz.

2.2.6.1.4.3 Somatosensory perception thresholds

Mechanical detection thresholds (MDT) were determined by stimulating the fingertip of the index finger of the right and left hand using von Frey filaments (Marstocknervtest, Marburg, Germany). Touch forces ranged from 0.25 to 512 mN in a logarithmic scale. Filaments were manually applied by the experimenter perpendicular to the subject's skin and subjects, while keeping their eyes closed, verbally indicated whenever they perceived a sensation on their skin. Following a staircase procedure (Bell-Krotoski et al., 1995; Christensen et al., 2020), five values for upper and lower boundaries were determined and were averaged to obtain the touch threshold. Here, lower scores reflect enhanced sensation.

Additionally, spatial tactile discrimination was tested in the form of a grating orientation task using hemispherical plastic domes (JVP Domes, Stoelting Europe, Dublin, Ireland). The domes have parallel bars and grooves of equal width on their surface (15 domes with a width range of 0.35 to 12 mm). To determine grating orientation thresholds, the experimenter manually applied the gratings to the subject's right index finger pad and subjects, while keeping their eyes closed, verbally indicated the orientation of

the grating (vertical, horizontal). Testing started at a width of 5 mm and the percentage of correct responses out of 10 trials was recorded. Using a staircase procedure, testing was continued until one width value was obtained for larger (high) and smaller (low) than 75%, respectively. Tactile grating threshold was determined by calculating the width of the hypothetical dome which would be correctly recognized in 75% of the cases. Thus, lower scores reflect enhanced sensation.

2.2.6.1.5 Cognitive function

To assess cognitive function, four subtests of the *Cambridge Neuropsychological Test Automated Battery* (CANTAB; Cambridge Cognition [2019], www.cantab.com) were used. The CANTAB cognition battery was administered using a tablet computer with touch screen and a two-key response pad.

2.2.6.1.5.1 Mental and motor speed

Mental and motor speed were assessed using the *Reaction Time (RTI)* test. Subjects were instructed to hold down a key on a response pad with their right index finger. As soon as a yellow spot appeared, either in the center of the screen (single condition) or at one of five possible locations on the screen (5-choice condition), subjects had to release the key and touch the yellow spot on the screen. Mental speed was defined as the time between the appearance of the spot and release of the key while motor speed was defined as the time between releasing the key and touching the screen.

2.2.6.1.5.2 Attentional control

The *Attention Switching Task (AST)* was used to examine top-down attentional control defined as the ability to flexibly switch attentional resources towards relevant information and inhibit irrelevant information. In each trial, an arrow appeared on either the left or right portion of the screen, pointing in either direction. At the top of the screen, a cue was displayed prompting the subject to press the left or right key on the response pad to evaluate either the position of the arrow on the screen or the direction where the arrow was pointing. Dependent measures included the percentage and reaction time (RT) of correct trials, as well as switch cost (RT switch trials - RT non-switch trials) and congruency cost (RT incongruent trials - RT congruent trials).

2.2.6.1.5.3 Spatial working memory span

Working memory span was assessed using the *Spatial Span (SSP)* test. In each trial, a pattern of white boxes was displayed on the screen. Some of the boxes changed in color, one by one, in a variable sequence. Subjects were instructed to memorize the sequence and reproduce it afterwards by touching the now white boxes on the screen. The maximal span length achieved was taken as a dependent measure to estimate visual working memory capacity.

2.2.6.1.5.4 Executive functioning

Executive functioning and integrity of fronto-striatal pathways was investigated using the *Intra-Extra Dimensional Set Shift (IED)*, which is a computerized version of the Wisconsin Card Sorting test. The test started with the presentation of two color-filled shapes and subjects had to learn which of the stimuli is correct by touching it. After satisfying the criterion of six consecutive correct responses, a new stage began and categorization was reversed. In the following stages, a second dimension consisting of white lines was added to the color-filled shape stimuli and subjects were required to continue to attend to the previously relevant dimension of shape (intradimensional shift). After the criterion to proceed was reached, the relevant dimension was changed and subjects were then required to shift attention to the previously irrelevant dimension, i.e. white lines (extradimensional shift). If at any stage the subject failed to reach the criterion of six consecutive correct responses after 50 trials, the test was automatically terminated. Outcome measures included the number of stages completed and the number of errors committed throughout the task adjusted for the number of stages completed.

2.2.6.1.6 Clinical characteristics

2.2.6.1.6.1 Functional level in frailty

Functional level in frail elderly at a very low activity level was assessed using the Frail Elderly Functional Assessment (FEFA; Gloth, Scheve, Shah, Ashton, & McKinney, 1999; Gloth, Walston, Meyer, & Pearson, 1995). The FEFA is a 19-item questionnaire assessing function in different areas including e.g. mobility, meal preparation, dressing and bathing. Single item scores were summed up resulting in a total score ranging from 0 to 55 with lower scores inferring better function.

2.2.6.1.6.2 Depression

Depressive symptoms experienced in the past week were assessed using the German version of the Center for Epidemiologic Studies Depression Scale (CES-D; Hautzinger et al., 2012; Radloff, 1977). 20 statements were evaluated on a 4-point scale and item scores were added up into a total score with higher values reflecting more pronounced depressive signs.

2.2.6.1.6.3 Quality of life

Health-related quality of life was evaluated using the Short Form-36 Health Survey (SF-36; Ware & Sherbourne, 1992) and the EuroQol-5D-5L (EQ-5D-5L; Brooks, 1996). Data on the 36 items in SF-36 were analyzed and transformed according to the SF-36 algorithm (Ware, Snow, Kosinski, & Gandek, 1993) resulting in eight multi-item health status scales: physical functioning, physical role limitations, bodily pain, general health perception, vitality, social functioning, emotional role limitations and mental health. Additionally, two overall summary scores (physical component summary, PCS; mental component summary, MCS) were computed. Scores on each scale ranged from 0 (worst possible health) to 100 (best possible health).

Using the EQ-5D-5L, impairment in five health dimensions was quantified and individual health profiles were transformed into a standardized index value ranging from < 0 to 1 with higher values reflecting better health status. Additionally, subjects rated their general health status on a visual analogue scale ranging from 0 to 100.

2.2.6.1.6.4 Functional capacity

To assess functional capacity, the self-report version of the Marburg Competency Scale (Marburger Kompetenz Skala [MKS]; Gauggel, Peleska, & Bode, 2000) was used, which consists of 30 questions on competence in typical everyday activities. Single item scores ranging from 0 (very large impairment) to 4 (no impairment) were summed up into a total score with higher total scores indicating higher functional capacity.

2.2.6.1.6.5 Fear of falling

Fear of falling was operationalized using the Falls Efficacy Scale – International Version (FES-I; Tinetti, Richman, & Powell, 1990), a self-report questionnaire assessing

the level of concern regarding the possibility of falling when performing 16 activities of daily living. Items were rated on a scale of 1 (not worried) to 4 (very worried). The sum score ranges from 16 to 64 with higher scores reflecting increased fear of falling.

2.2.6.2 BDNF genotyping

Blood samples were collected by the study psychiatrist and were processed according to standard protocols and stored at -80 °C until analysis (Witt et al., 2016). For genetic analyses, DNA was extracted from blood samples. A genome-wide analysis of single-nucleotide polymorphisms was carried out using Illumina Global Screening Array GSA v3.0 and GenomeStudio 2.0 software (Illumina Inc., San Diego, California, USA) was used to determine BDNF genotypes. Participants were divided into two groups based on their BDNF genotype: Val homozygotes (Val/Val) and Met carriers (Val/Met and Met/Met individuals). Collapsing Val/Met and Met/Met individuals into one group is a common practice in the studies of this polymorphism due to the lower frequency of the Met allele (Petryshen et al., 2010).

2.2.6.3 Functional magnetic resonance imaging (fMRI) assessment

2.2.6.3.1 fMRI motor sequence task

Brain activation in sensorimotor networks was investigated using a motor sequence task adapted from Caproni et al. (2013) and encompassing three different motor exercises of varying complexity. The task was administered using a block design of 12 alternating active and rest blocks, respectively. For each of the three motor exercise conditions, four blocks were administered with the order of the motor exercise conditions being randomized across the entire scan. Each of the 12 active blocks lasted 22 seconds while of the jittered rest blocks, four each lasted 19.5, 22, and 24.5 seconds. During each active block, participants were instructed to perform a sequence of button presses with their right hand using an MRI-compatible keyboard with five keys that were numbered from 1 to 5 corresponding to the thumb, index finger, middle finger, ring finger, and little finger, respectively. The task consisted of three different exercises requiring repetitive tapping of a certain sequence: the “FINGER” condition required repetitive tapping of key no. 2 with the index finger, the “SIMPLE” condition required tapping of the sequence 1-2-3-4-5, and the “COMPLEX” condition required tapping of

the sequence 1-3-5-2-4. Subjects were asked to execute the motor sequences in a self-paced way. Prior to the fMRI measurement, subjects learned the task and practiced the sequences for about 10 to 15 minutes. During the fMRI measurement, subjects looked at a screen outside the scanner via a mirror construction mounted on top of the MR coil. At the beginning of each block, a white cue was displayed on the screen against a grey background for 3 seconds indicating the condition of the upcoming block (i.e. “FINGER”, “SIMPLE”, “COMPLEX”, or “REST”). After the cue disappeared, a grey screen was presented for the rest of the block to minimize the effect of visual processing on cerebral activation. The fMRI measurement lasted approximately 9 to 10 minutes.

2.2.6.3.2 fMRI data acquisition

Functional MR scans on the motor sequence task were recorded using a 3T Magnetom Trio system (Siemens, Erlangen, Germany) and a 32-channel head coil. An EPI gradient echo sequence was used to collect 40 slices with 2.3 mm slice thickness and a 30% gap, using a field of view (FoV) of 220 x 220 mm^2, voxel size 2.3 x 2.3 x 2.3 mm^3, repetition time (TR) 2100 ms, echo time (TE) 22 ms, flip angle 90°. For the 12 active and 12 rest blocks, a total number of 268 volumes was acquired. Visual stimulus presentation and response recording during the task were administered using Presentation software (Neurobehavioral Systems, Albany, New York, USA). Prior to the functional scan, a structural T1-weighted 3D gradient echo sequence was collected using a FoV of 250 x 250 mm^2, voxel size 0.8 x 0.8 x 0.8 mm^3, TR 1900 ms, TE 2.72 ms.

2.2.6.3.3 fMRI preprocessing and analysis

fMRI preprocessing was performed using the SPM12 software (Wellcome Institute of Neurology, University College London, UK, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running under MATLAB R2020a (The MathWorks Inc, Natick, Massachusetts, USA). First, time series of each voxel were temporally realigned to the acquisition of the middle slice. Subsequently, functional images were coregistered and spatially realigned to the first image using a least squares approach and a 6 parameter (rigid body) spatial transformation (Friston et al., 1995). Next, functional images were normalized into the standard Montreal Neurological Institute (MNI) space using a voxel

size of 2.3 x 2.3 x 3 mm^3. The normalized images were then smoothed with a fullwidth-at-half-maximum (FWHM) Gaussian kernel of 4.6 x 4.6 x 6 mm^3.

Prior to statistical analyses, behavioral performance was checked to ensure that performance during blocks corresponded to the given task conditions. For each block, the number of correct sequences was determined with one correct sequence requiring five correct button presses in a row. If the number of correct sequences reflecting another condition was greater than that of the given condition, the block was assigned to the other condition. If the number of button presses during an active block was less than five, the block was assigned to the rest condition. Behavioral measures included the mean number of blocks for each motor condition, the number of correct sequences and mean tapping frequency.

Statistical analysis of brain activation during motor task performance was based on a block design. Single voxel time-series data were modelled with a hemodynamic response function using a general linear model (GLM) approach. In the first level analysis, active blocks in each of the three motor sequence conditions as well as rest blocks were defined as predictors. Additionally, the 6 rigid-body motion parameters obtained from realignment were inserted into the first level GLM model as regressors of no interest to control for head motion. To calculate mean cortical activation during motor performance, three contrasts were calculated for each subject comparing each of the active motor conditions to the rest status (i.e. FINGER > REST, SIMPLE > REST, COMPLEX > REST). Additionally, three contrasts were calculated between active motor conditions of increasing complexity to investigate brain activity associated with increasing motor complexity (i.e. SIMPLE > FINGER, COMPLEX > FINGER, COMPLEX > SIMPLE). First level analyses were identical for scans obtained at baseline (T0) and after 60 days of training (T1).

Group data were analyzed through a second level random-effects analysis based on single subject data. In order to examine differences in brain activity patterns between the two intervention groups, two-sample t-tests were used for each of the six contrasts for brain activity at baseline (T0) and post-training (T1). For each of the comparisons, significant differences in brain activity were identified using an uncorrected significance level of $p<0.001$ at whole-brain level and a family-wise error corrected significance level of $p<0.05$ at cluster level. Due to the small size of the sample, a subsequent analysis of regions of interest (ROIs) was conducted. MNI coordinates (x, y, z) of the ROIs were taken from the literature and referred to brain regions that were previously

associated with motor execution and planning as well as compensational strategies in conditions of sensorimotor impairment. More specifically, ROI coordinates were taken from Jha et al. (2015) including both primary motor cortices (M1; ±37, -25, 62) and the supplementary motor area (SMA; -2, -10, 59), and from T. Wu and Hallett (2005) including both prefrontal cortices (PFC; left: -24, 36, 50; right: 44, 8, 27), both premotor cortices (PMC; left: -38, 7, 48; right: 48, -20, 36), both temporal cortices (TC; left: -46, -62, 4; right: 32, -30, 10), both parietal cortices (PC; left: -24, -56, 51; right: 30, -57, 56), both precunei (left: -8, -76, 40; right: 2, -70, 44) and both cerebella (left: -14, -41, -19; right: 12, -66, -12). Coordinates obtained from T. Wu and Hallett (2005) were converted from Talairach to the MNI space using the transformation implemented in the WFU PickAtlas Tool version 3.0.5 (Maldjian, Laurienti, Kraft, & Burdette, 2003). Using the WFU PickAtlas Tool, 10-mm radius spheres were created around the previously mentioned MNI coordinates (see Figure 2 for the ROI mask locations). For each ROI, mean contrast beta values for each subject were extracted from the data for each contrast at baseline (T0) and after 60 days of training (T1). To examine potential treatment effects and group differences, beta values obtained from ROIs at pre- and post-intervention were then entered into subsequent statistical analyses, as described below.

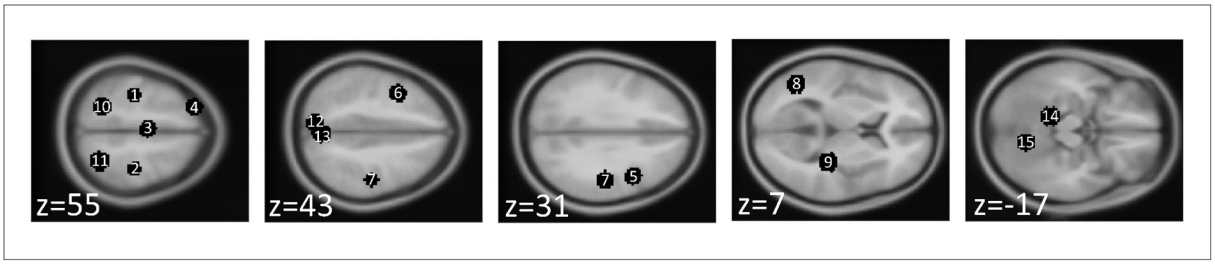

Figure 2. Materials and Methods Study 2: Locations of ROIs used in the analysis of training effects on sensorimotor brain activation.

Numbers refer to the left M1 (1), right M1 (2), SMA (3), left PFC (4), right PFC (5), left PMC (6), right PMC (7), left TC (8), right TC (9), left PC (10), right PC (11), left precuneus (12), right precuneus (13), left cerebellum (14), and right cerebellum (15).

2.2.6.4 Transcranial magnetic stimulation (TMS) assessment

2.2.6.4.1 Experimental setup

To investigate intervention effects on motor cortex excitability, single-pulse transcranial magnetic stimulation (TMS) was performed at the left primary motor cortex to generate motor evoked potentials (MEP) as measure of corticospinal output to the abductor pollicis brevis (APB) of the right hand. TMS assessment was conducted at baseline (T0) and after 60 days of training (T1). During the measurement, subjects sat in a comfortable chair placed within a stereotactic positioning frame and were instructed to let their right hand lie relaxed on an armrest. Single-pulse TMS was performed using a Magstim Super Rapid magnetic stimulator (Magstim Company, Whitland, UK) and a 70-mm figure-of-eight coil. To obtain reproducibility across separate experimental sessions, a TMS neuronavigation system was used (BrainSight software, Rogue-Research, Montreal, QC, Canada) including registration of the coil and subject position. The hand knob of left primary motor cortex was defined as stimulation target, using either an individual structural T1-weighted MR image for subjects who underwent MRI assessment, or a standard MNI152 brain template for subjects for whom an individual structural brain image was not available. During stimulation, the coil was placed tangentially on the scalp and rotated approximately 45° in sagittal direction, with the handle pointing towards the midline. TMS pulses were applied manually using Presentation software (Neurobehavioral Systems, Albany, New York, USA). Stimulation started at subthreshold intensity and was modulated in a stepwise manner until the resting motor threshold (RMT) criterion was achieved. RMT was determined as the lowest stimulation intensity at which at least 6 out of consecutive 10 MEPs reached a peak-to-peak amplitude of ≥ 50 μV (McGregor et al., 2012), with a resolution of 1% of the maximal stimulator output. Following RMT determination, three experimental blocks were administered in a pseudorandomized order with each block consisting of at least 20 consecutive single TMS pulses (one pulse approximately every 4-8 seconds) with an intensity of 100%, 110% and 120% of the RMT intensity, respectively. Stimulation intensities at post-training were determined with respect to both the pre-training RMT and the post-training RMT, resulting in a maximum possible number of six experimental blocks performed during the post-training session, however, only data obtained using the post-training RMT were included in the subsequent analyses. Each experimental session lasted approximately 60-90 min.

2.2.6.4.2 Electromyography recording and data analysis

Electromyography (EMG) was recorded from the right APB with the active electrode being placed on the belly of the muscle and the reference electrode placed over the radiocarpal joint. The EMG signal was acquired using a sampling rate of 5 kHz, a time constant of 10 s and a low-pass filter of 1000 Hz. EMG data were recorded using BrainVision Recorder software and were analyzed offline using BrainVision Analyzer software (Brain Products GmbH, Munich, Germany). Firstly, the continuous EMG signal was filtered using a band-pass filter of 5-1000 Hz and a notch filter of 50 Hz. The EMG signal was then divided into epochs starting 400 ms before and ending 400 ms after each TMS pulse and epochs were baseline-corrected with respect to a 50-ms-baseline preceding the onset of the TMS pulse. Epochs containing artifacts as determined by visual inspection were manually removed. Epochs were then averaged for each experimental block in each subject and the amplitude of the mean MEP was measured peak-to-peak. To examine potential treatment effects and group differences, MEP peak-to-peak amplitudes as well as RMT values at pre- and post-intervention were then entered into subsequent statistical analyses, as described below.

2.2.7 Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics, Version 25 (IBM Corp., Armonk, NY, USA). A two-tailed significance level of $p<0.05$ and a marginal significance level of $p<0.10$ were set for all analyses. Due to differences in sample size, analyses were carried out separately for data obtained after 60 days and after 90 days of training.

Missing data on behavioral and clinical outcomes were analyzed separately for the sample completing 60 days of training (total: n=48; EG: n=24, CG: n=24) who underwent T1 assessment, and the sample completing 90 days of training (total: n=16; EG: n=9, CG: n=7) who completed T2 assessment. There were no missing values for the primary outcomes of FP and FI after 60 days of training. For secondary behavioral and clinical outcomes, the percentage of missing values was low (less than 7% for any given behavioral and clinical variable). Missing data on behavioral and clinical outcomes were reproduced using a multiple imputation approach. Two separate multiple imputation models were computed using the 60-days training sample (n=48) to replace

missing values at T1 and using the 90-days training sample (n=16) to replace missing values at T2, respectively.

Descriptive characteristics of demographic and behavioral variables were calculated as mean and standard deviation (SD) for continuous variables and frequency and percentages for categorical variables. Normality of continuous variables was evaluated using Kolmogorov-Smirnov tests. Baseline differences between groups were assessed using the independent samples t-test or one-way analysis of variance (ANOVA) for normally distributed continuous variables, Mann-Whitney-U-test or Kruskal-Wallis ANOVA for non-normally distributed variables and Pearson-χ^2-test for categorical variables. Pearson and Spearman correlations were performed to evaluate the association between outcomes.

Training effects after 60 days were examined via linear mixed model analyses (LMMs). For each dependent variable of interest, a LMM was constructed with fixed effects of group (EG and CG) and time (T0 and T1), covariates of age and gender, and a random intercept per subject. For LMMs demonstrating a group-by-time interaction effect of $p<0.10$, Bonferroni-corrected post-hoc pairwise comparisons were performed on the estimated marginal means at time points T0 and T1 separately for each treatment group. Dependent variables of interest included primary outcomes of frailty, as well as secondary outcomes of sensory, motor and cognitive abilities, clinical variables, measures of brain activity (ROI beta values) and brain excitability (RMTs and MEPs). For the analysis of MEPs obtained from TMS, LMMs were additionally adjusted for RMTs. For primary outcomes, main effects of time will also be reported. For changes in prevalence of frailty status as determined by the FP and of individual FP criteria, group-wise non-parametric McNemar tests were used. Change scores for individual FP criteria were additionally compared within treatment groups using non-parametric Friedman's ANOVA.

To investigate the potential influence of BDNF genotype on training effects, a separate set of linear mixed models (LMMs) was computed for primary outcomes and frailty-related secondary outcomes on data obtained at T0 and T1. For this analysis, participants were distributed into four groups according to intervention group (EG, CG) and BDNF genotype (Val homozygotes and Met carriers). LMMs included fixed effects of group (EG-Val/Val, EG-Met carrier, CG-Val/Val, CG-Met carrier) and time (T0 and T1), covariates of age and gender, and a random intercept per subject. For models with a

group-by-time interaction effect of $p<0.10$, group-wise post-hoc tests on EMMs were performed.

Data obtained from the subsample of participants who performed the total 90 days of training were additionally analyzed in a separate set of analyses. To investigate whether the additional 30 days of training produces an increase in performance compared to the previous 60 days of training, LMMs were computed on outcomes of interest with fixed effects of group (EG and CG) and time (T1 and T2), covariates of age and gender, and a random intercept per subject. Additionally, a second set of LMMs were computed to examine training effects across the entire training period of 90 days, including fixed effects of group (EG and CG) and time (T0, T1 and T2), covariates of age and gender, and a random intercept per subject.

To assess the robustness of group effects, a secondary set of analyses using multiple regression analyses was conducted. Change in primary and secondary outcome measures was used as dependent variable. Group (EG, CG) was used as predictor of interest and age, gender and baseline performance were used as covariates. Non-matching results are reported at the respective place in the results section.

To estimate the magnitude of treatment effects for outcomes of interest, between-subject effect sizes (ES) reflecting the group difference in change from baseline (interaction) were calculated by subtracting the mean pre-post change in the CG from the mean pre-post change in the EG, and dividing by the pooled pre-training standard deviation (d_{ppc2}, see Morris, 2008). For interpretation of ES, cut-offs of ≥ 0.2, ≥ 0.5 and ≥ 0.8 were applied for small, medium and large effects, respectively (Cohen, 1988; Sawilowsky, 2009).

3 RESULTS

3.1 Study 1

3.1.1 Results[6]

3.1.1.1 Sample characteristics

Of the total number of 52 subjects, 8 subjects were excluded from the analyses because they had incomplete data sets due to study withdrawal. The characteristics of the remaining 44 subjects are presented in Table 4. The mean age was 80.4 (SD: 5.5) years, ranging from 68.6 to 91.9 years, and 72.7% (n=32) were women. Regarding frailty assessment, the mean number of positive FP criteria, averaged across all subjects, was 2.3 (SD: 0.8). Eight (18.2%), 20 (45.5%), 13 (29.5%) and 3 (6.8%) subjects had 1, 2, 3, or 4 positive FP criteria, respectively, while none fulfilled all 5 of the criteria. Thus, 28 (63.6%) subjects were classified as pre-frail and 16 (36.4%) were considered to be frail. The FI had a mean value of 0.23 (SD: 0.09), and ranged from 0.08 to 0.47. Using a cut point of 0.25, 27 (61.4%) subjects were classified as pre-frail and 17 (38.6%) were considered to be frail. With respect to gender differences, the mean FI score was significantly lower for males than females (p=0.005), suggesting that males were classified as less frail, while there was no gender difference in the number of positive FP criteria (p=0.630). The mean value of body mass index, MMSE, and CES-D was 28.5 (SD: 6.4), 28.7 (SD: 1.5), and 16.0 (SD: 8.3), respectively. For the sensory assessment, the mean value of visual acuity (logMAR), hearing threshold (dB), and mechanical detection threshold (mN) was 0.19 (SD: 0.17), 33.3 (SD: 12.0), and 0.74 (SD: 1.04), respectively. Regarding motor function, mean PPT performance was 9.8 (SD: 2.3) and mean SPPB score was 7.4 (SD: 2.3). Males had a significantly lower body mass index (p=0.015) and higher scores of lower extremity function (SPPB; p=0.003) compared to females. When comparing those classified as frail vs. pre-frail using the FP and FI, frail subjects had higher scores of depression and reduced scores of lower extremity function compared to pre-frail subjects (see Table 5). Additionally, frail subjects demonstrated reduced upper motor function (PPT) according to the FP and were older when categorized with the FI.

[6] An adapted version of chapter 3.1.1 has already been published as results section in Beier et al. (2022).

Table 4. Results Study 1: Characteristics of the study sample, stratified by gender.

	All (n=44)	Female (n=32)	Male (n=12)	p-value
Age, years, mean ± SD	80.4 ± 5.5	80.8 ± 5.4	79.4 ± 6.0	0.462
Body mass index, kg/m², mean ± SD	28.5 ± 6.4	30.0 ± 6.7	24.7 ± 3.8	0.015
MMSE, mean ± SD	28.7 ± 1.5	28.9 ± 1.4	28.3 ± 1.7	0.267
CES-D, mean ± SD	16.0 ± 8.3	17.4 ± 8.5	12.4 ± 6.6	0.077
Visual acuity, logMAR, mean ± SD	0.19 ± 0.17	0.22 ± 0.18	0.11 ± 0.13	0.059
Hearing threshold, dB, mean ± SD	33.3 ± 12.0	32.9 ± 11.7	34.5 ± 13.2	0.805
Mechanical detection threshold, mN, mean ± SD	0.74 ± 1.04	0.67 ± 0.80	0.91 ± 1.53	0.490
PPT score, mean ± SD	9.8 ± 2.3	9.8 ± 2.5	9.7 ± 1.8	0.924
SPPB score, mean ± SD	7.4 ± 2.3	6.8 ± 2.2	9.1 ± 1.9	0.003
FP criteria, mean ± SD	2.3 ± 0.8	2.3 ± 0.9	2.2 ± 0.8	0.630
FP criteria (number), n (%)				
1	8 (18.2)	6 (18.8)	2 (16.7)	-
2	20 (45.5)	13 (40.6)	7 (58.3)	-
3	13 (29.5)	11 (34.4)	2 (16.7)	-
4	3 (6.8)	2 (6.3)	1 (8.3)	-
5	0 (0.0)	0 (0.0)	0 (0.0)	-
FP criteria (type), n (%)				
Weight loss	11 (25.0)	6 (18.8)	5 (41.7)	0.118
Exhaustion	23 (52.3)	16 (50.0)	7 (58.3)	0.622
Physical activity	6 (13.6)	5 (15.6)	1 (8.3)	0.530
Slow gait speed	28 (63.6)	21 (65.6)	7 (58.3)	0.654
Low grip strength	31 (70.5)	25 (78.1)	6 (50.0)	0.069
Categories according to the FP, n (%)				
Pre-frail	28 (63.6)	19 (59.4)	9 (75.0)	0.337
Frail	16 (36.4)	13 (40.6)	3 (25.0)	
FI, mean ± SD	0.23 ± 0.09	0.25 ± 0.08	0.17 ± 0.06	0.005
Categories according to the FI, n (%)				
Pre-frail	27 (61.4)	16 (50.0)	11 (91.7)	0.011
Frail	17 (38.6)	16 (50.0)	1 (8.3)	

Data are shown as mean ± standard deviation or n (%). CES-D, Center for Epidemiologic Studies Depression Scale; FI, Frailty index; FP, Frailty phenotype; MMSE, Mini-mental state examination; PPT, Purdue Pegboard Test; SD, standard deviation; SPPB, Short physical performance battery.

Table 5[7]. Results Study 1: Characteristics of the study sample, stratified by frailty status for both frailty measures.

	FP			FI		
	Pre-frail (n=28)	Frail (n=16)	p-value	Pre-frail (n=27)	Frail (n=17)	p-value
Age, years, mean ± SD	79.9 ± 5.6	81.3 ± 5.5	0.412	78.9 ± 5.5	82.8 ± 4.8	0.021
Body mass index, kg/m², mean ± SD	29.1 ± 6.2	27.6 ± 6.8	0.469	27.9 ± 6.5	29.6 ± 6.4	0.403
MMSE, mean ± SD	28.9 ± 1.5	28.5 ± 1.4	0.238	28.8 ± 1.6	28.7 ± 1.3	0.362
CES-D, mean ± SD	13.3 ± 6.7	20.8 ± 8.9	0.003	13.3 ± 6.3	20.3 ± 9.4	0.012
Visual acuity, logMAR, mean ± SD	0.20 ± 0.17	0.18 ± 0.18	0.816	0.16 ± 0.13	0.24 ± 0.22	0.161
Hearing threshold, dB, mean ± SD	34.0 ± 12.4	32.0 ± 11.4	0.855	30.7 ± 11.2	37.4 ± 12.4	0.058
Mechanical detection threshold, mN, mean ± SD	0.69 ± 1.12	0.82 ± 0.91	0.486	0.79 ± 1.21	0.66 ± 0.71	0.621
PPT score, mean ± SD	10.6 ± 1.9	8.3 ± 2.3	0.001	10.2 ± 2.2	9.0 ± 2.5	0.075
SPPB score, mean ± SD	8.1 ± 1.7	6.2 ± 2.7	0.017	8.4 ± 1.7	5.8 ± 2.3	<0.001

Data are shown as mean ± standard deviation. CES-D, Center for Epidemiologic Studies Depression Scale; FI, Frailty index; FP, Frailty phenotype; MMSE, Mini-mental state examination; PPT, Purdue Pegboard Test; SD, standard deviation; SPPB, Short physical performance battery.

3.1.1.2 Relationship between frailty measures and demographic, sensory and motor variables

Observed agreement between the two frailty measures in classifying individuals as pre-frail or frail was 75.0% (see Table 6) with a Kappa statistic of 0.467 (p=0.002). Frailty prevalence (FP: 36.4%; FI: 38.6%) did not significantly differ between the two measures (p=1). Table 7 displays the correlations among the two frailty measures and demographic, sensory and motor variables. There was a moderate positive correlation between the mean FI score and the number of positive FP criteria (0.497, p=0.001; see Figure 3). Frailty as determined by both the FP criteria and the FI was significantly negatively associated with upper (PPT; FP: -0.417, p=0.005; FI: 0.430, p=0.004) and

[7] Height, weight and body mass index were obtained through a physical examination performed by a study physician. Subsequent processing of subject data including statistical analyses were performed by the author of the present dissertation.

lower extremity function (SPPB; FP: 0.392, p=0.009; FI: 0.645, p<0.001). Unlike the FP, the FI significantly positively correlated with depression (0.532, p<0.001). None of the two frailty measures was significantly associated with measures of visual, auditory, or somatosensory abilities (all p≥0.155). For the demographic, sensory and motor variables, there were significant associations between visual acuity and age (0.434, p=0.003), visual acuity and hearing threshold (0.313, p=0.039), hearing threshold and age (0.452, p=0.002), mechanical detection threshold and upper motor function (-0.323, p=0.032) and between upper and lower motor function (0.329, p=0.029).

Table 6. Results Study 1: Proportion of participants within the FP and FI categories, n (%).

		FI		Total
		Pre-frail	Frail	
FP	Pre-frail	22 (50.0)	6 (13.6)	28 (63.6)
	Frail	5 (11.4)	11 (25.0)	16 (36.4)
		27 (61.4)	17 (38.6)	44 (100)

FI, Frailty index; FP, Frailty phenotype.

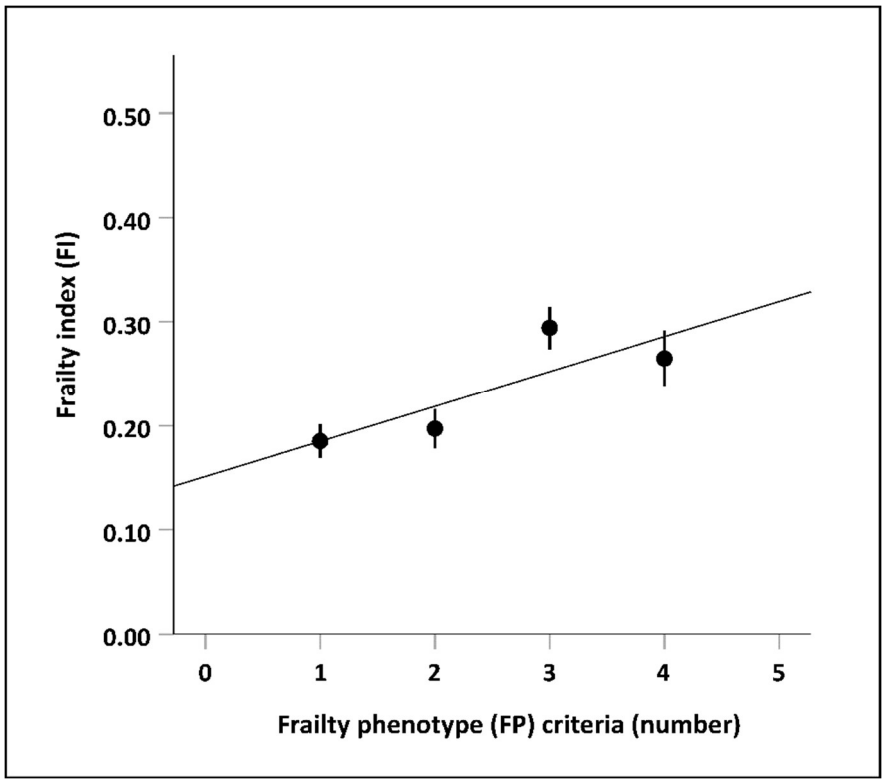

Figure 3. Results Study 1: Relationship between FP (number of deficits) and FI (mean score).

Error bars represent standard errors of the mean FI. Note that subjects had at least one positive FP criterion due to study inclusion criteria. None of the subjects had five FP criteria.

Table 7[8]. Results Study 1: Correlations between frailty and demographic, sensory and motor variables.

	FP criteria (number)	FI	Age (years)	Body mass index	MMSE	CES-D	Visual acuity	Hearing threshold	Mechanical detection threshold	Purdue Pegboard score	SPPB score
FP criteria (number)	1.000										
FI	0.497**	1.000									
Age (years)	0.242	0.269	1.000								
Body mass index	-0.104	0.250	-0.120	1.000							
MMSE	-0.147	-0.032	-0.377*	0.232	1.000						
CES-D	0.293	0.532**	0.149	0.077	-0.122	1.000					
Visual acuity	-0.017	0.218	0.434**	0.205	-0.220	-0.007	1.000				
Hearing threshold	0.000	0.130	0.452**	0.030	-0.140	0.011	0.313*	1.000			
Mechanical detection threshold	0.168	-0.030	0.144	-0.103	-0.278	0.087	-0.078	0.288	1.000		
PPT score	-0.417**	-0.430**	-0.282	-0.021	0.534**	-0.225	-0.143	-0.095	-0.323*	1.000	
SPPB score	-0.392**	-0.645**	-0.229	-0.094	-0.012	-0.356*	-0.196	0.002	-0.142	0.329*	1.000

CES-D, Center for Epidemiologic Studies Depression Scale; FI, Frailty index; FP, Frailty phenotype; MMSE, Mini-mental state examination; PPT, Purdue Pegboard Test; SPPB, Short physical performance battery; * $p \leq 0.05$; ** $p \leq 0.01$.

[8] Height, weight and body mass index were obtained through a physical examination performed by a study physician. Subsequent processing of subject data including statistical analyses were performed by the author of the present dissertation.

3.1.1.3 Hierarchical multiple logistic regression models

The results of the hierarchical multiple logistic regression analyses of covariates and sensory and motor variables on frailty are depicted in Table 8.

Frailty phenotype

In the first block, only depression (OR=1.13, 95% CI 1.03-1.24, p=0.013) was significantly associated with pre-frail vs. frail as classified by the FP, with the covariate model explaining 25.4% of the variance (p=0.029). In the second block, upper extremity function as assessed by the PPT score (OR=0.50, 95% CI 0.29-0.87, p=0.014) was independently associated with frailty and the total amount of variance explained by the model was significantly increased to 54.2% (p=0.005).

Frailty index

Regarding the FI, the covariate model explained 44.7% of variance (p=0.001) and age (OR=1.18, 95% CI 1.01-1.38, p=0.042) and depression (OR=1.11, 95% CI 1.00-1.23, p=0.044) were independently associated with frailty. In the second block, frailty was significantly associated with depression (OR=1.20, 95% CI 1.01-1.44, p=0.040), hearing threshold (OR=1.21, 95% CI 1.02-1.43, p=0.027) and lower extremity function as determined by the SPPB score (OR=0.32, 95% CI 0.13-0.77, p=0.012). Adding the sensory and motor variables significantly improved the predictive value of the model (p=0.003) compared to the covariate model and raised the amount of explained variance to 74.8% (p<0.001).

Table 8. Results Study 1: Results of the hierarchical multiple logistic regression analyses for relationships of demographic, sensory and motor variables with FP and FI.

	FP		FI	
Independent variables	OR (95% CI)	p-value	OR (95% CI)	p-value
Block 1				
Age	1.03 (0.90-1.17)	0.666	1.18 (1.01-1.38)	0.042
Gender	1.19 (0.23-6.10)	0.838	9.76 (0.94-101.33)	0.056
CES-D	1.13 (1.03-1.24)	0.013	1.11 (1.00-1.23)	0.044
	R^2 = 0.254	0.029	R^2 = 0.447	0.001
Block 2				
Age	0.94 (0.77-1.16)	0.583	1.07 (0.81-1.40)	0.649
Gender	1.36 (0.15-12.28)	0.785	56.89 (0.88-3660.12)	0.057
CES-D	1.11 (0.99-1.25)	0.087	1.20 (1.01-1.44)	0.040
Visual acuity	0.22 (0.00-84.65)	0.614	0.01 (0.00-275.16)	0.397
Hearing threshold	1.00 (0.91-1.09)	0.928	1.21 (1.02-1.43)	0.027
Mechanical detection threshold	0.96 (0.28-3.28)	0.951	0.11 (0.01-1.49)	0.096
PPT score	0.50 (0.29-0.87)	0.014	0.64 (0.32-1.31)	0.223
SPPB score	0.69 (0.44-1.07)	0.100	0.32 (0.13-0.77)	0.012
	R^2 = 0.542	0.005	R^2 = 0.748	<0.001
	R^2 change	0.022	R^2 change	0.003

CES-D, Center for Epidemiologic Studies Depression Scale; FI, Frailty index; FP, Frailty phenotype; PPT, Purdue Pegboard Test; SPPB, Short physical performance battery.

3.1.2 Interim discussion[9]

The objectives of Study 1 were to examine the agreement between the FP and the FI in classifying individuals as frail and to identify sensory and motor correlates of frailty and compare these associations between the two frailty measures. The findings demonstrate that the FP and the FI moderately agree in classifying the same individuals as either pre-frail or frail, but that there is heterogeneity when determining sensory and motor correlates of frailty. Given that frailty is a potentially reversible state (Gill et al., 2006), the identification of characteristic correlates and knowledge about the underlying deficits is necessary for offering timely and appropriate interventions.

3.1.2.1 Diagnostic agreement between frailty phenotype (FP) and frailty index (FI)

In Study 1, there was a moderate Kappa agreement of 0.467 between the two frailty measures, which is consistent with previous literature reporting agreement ranging from 0.428 (Zhu et al., 2016) to 0.51 (Theou et al., 2013) when dichotomized frailty measures and a cut point of 0.25 for the FI are used. There was also a significant moderate correlation in continuous scores of 0.497 which is in accordance with earlier studies reporting correlations ranging from 0.361 (Arakawa Martins et al., 2019) to 0.76 (Thompson et al., 2018). In the cross-sectional analysis performed in Study 1, agreement between measures was potentially strengthened by the fact that subjects had to fulfill at least one FP criterion to be included in the primary training study while previous cross-sectional studies also considered robust non-frail individuals (Blodgett et al., 2015; Theou et al., 2013; Thompson et al., 2018; Zhu et al., 2016). There is evidence that the FI compared to the FP discriminates better at the lower end of the frailty continuum (Blodgett et al., 2015; Rockwood & Mitnitski, 2007; Theou et al., 2013) and classifies a larger number of individuals as frail, resulting in higher prevalence rates (Arakawa Martins et al., 2019; Blodgett et al., 2015; García-Peña, Ávila-Funes, Dent, Gutiérrez-Robledo, & Pérez-Zepeda, 2016; Thompson et al., 2018). Therefore, reducing variability at the lower end of the frailty continuum by including subjects that are at

[9] An adapted version of chapter 3.1.2 has already been published as discussion section in Beier et al. (2022).

least pre-frail might also be a possible explanation why frailty prevalence did not substantially differ between the two measures in Study 1.

The results with the FI correspond to studies which demonstrated that at the same age, women have significantly greater frailty than men (Collard et al., 2012; Gordon et al., 2017; Shamliyan, Talley, Ramakrishnan, & Kane, 2013; Theou et al., 2014; Zhang, Guo, Gu, & Zhao, 2018). Various explanations for increased frailty in females have been discussed and tested in the literature, including biological, behavioral and social factors (García-Peña et al., 2016; Gordon & Hubbard, 2020; Hubbard, 2015; Theou et al., 2014), indicating that females compared to males are likely to acquire more health deficits overall and have these deficits for a longer period of time (Gordon et al., 2017). While greater frailty in women compared to men has been consistently demonstrated across various frailty measures (Alexandre et al., 2018; Gordon et al., 2017; Theou et al., 2014), results of Study 1 demonstrated gender differences in frailty only for the FI, but not for the FP. There might be several possible explanations for this finding. First, it might be that the higher FI in women compared to men represents an increased vulnerability of women, which however is not captured by the FP. In line with that, previous studies found associations between the FI and adverse health measures even in subjects who were classified as non-frail by the FP (Theou et al., 2013). Thus, one might argue that the higher FI scores in women result from the fact that, due to its continuous nature, the FI captures an increased subclinical vulnerability before the full picture of frailty becomes manifested in the FP (Blodgett et al., 2015; Mitnitski et al., 2015). Second, it might be that gender-specific differences in the underlying pathological mechanisms of frailty are captured in different ways by the two frailty measures. More specifically, the FP considers frailty as a biological and physical syndrome whereas the FI defines frailty by the quantity rather than the nature of health deficits (Theou et al., 2013). Cross-sectional analyses suggested that the underlying determinants of frailty are more complex and interrelated in women compared to men (Alexandre et al., 2018, 2014). Given that the FI includes mental health, medical conditions as well as indicators of disability while the FP does not, it might be that the FI, compared to the FP, superiorly detects the multidimensional risk and vulnerability in women that underlies the physical expression of frailty (Lim et al., 2020; Theou et al., 2013; Xue et al., 2020).

Together, the results observed in Study 1 support the perspective that both frailty instruments share some common characteristics but also slightly differ from each other

in detecting frailty in the same population (Arakawa Martins et al., 2019; Theou et al., 2013; Thompson et al., 2018), raising the question as to the characteristic correlates of the two frailty concepts.

3.1.2.2 Sensory and motor correlates of frailty depending on frailty measure

The multiple regression analyses revealed overlapping as well as non-overlapping associations of demographic, sensory and motor variables with frailty vs. pre-frailty as a function of the frailty measure. There were strong associations of reduced physical and motor performance with greater frailty for both frailty approaches. The total regression model for the FP demonstrated a significant relationship between frailty and dexterity performance whereas the FI was associated with lower extremity performance. Previous evidence demonstrated that upper limb dexterity performance might differentiate robust from pre-frail/frail individuals (Tay et al., 2019). In the descriptive analyses in Study 1, there was also a significantly lower dexterity performance in frail vs. pre-frail subjects as determined by the FP suggesting that also within the group of pre-frail and frail subjects, upper extremity function is related to the degree of frailty. These results fit well with earlier research showing that reduced upper extremity control might be a marker of an increased risk for frailty and dependency (Falconer et al., 1991; Ho, Williams, & Hardwick, 2002). Likewise, the observed relationship between SPPB performance and frailty as determined by the FI is consistent with prior evidence stating that impaired lower extremity performance is a key indicator of frailty and SPPB performance has previously been shown to reliably identify frail individuals (Abizanda et al., 2012; Lim et al., 2020; Pritchard et al., 2017).

However, while both PPT and SPPB performance demonstrated strong linear associations with both frailty measures in the bivariate correlation analyses, only PPT performance was found to be an independent predictor of the FP, and only SPPB performance was independently associated with the FI in the multiple regression models. This finding seems to indicate that there are common factors and mechanisms shared among upper and lower extremity motor performance as well as with the other domains inspected in the models (e.g. sensory abilities, depression, gender) that are associated with frailty. Thus, there is more to motor decline in frailty than motor variables alone and further factors should be taken into account to map the complex and interacting mechanisms that underlie physical and motor decline in frailty (Brown et al., 2000).

There was a significant independent association between hearing threshold and the FI. Previous cross-sectional studies found that perceived hearing impairment was independently associated with frailty in older women (Kamil et al., 2014) and helped to predict frailty risk in community-living older persons (Ng, Feng, Nyunt, Larbi, & Yap, 2014). Similarly, hearing impairment has been independently associated with frailty-related deficits, including gait speed (L. Li et al., 2013), increased falls (Kamil et al., 2016; F. R. Lin & Ferrucci, 2012), depression (Brewster et al., 2018), hospitalizations and mortality (Genther, Frick, Chen, Betz, & Lin, 2013). The mechanisms that could underlie an association between hearing impairment and frailty are still not fully understood. Degradation of shared neurophysiological pathways, including neurodegeneration, microvascular disease and systemic inflammation might contribute to both hearing disability and frailty (Dinarello, Simon, & van der Meer, 2012; Gates, Cobb, D'Agostino, & Wolf, 1993; Kamil et al., 2016; Liew et al., 2007). Alternatively, hearing impairment might potentially affect frailty through mediating effects of cognitive impairment (Ávila-Funes et al., 2009; Panza et al., 2015), social isolation (Dalton et al., 2003), and depression (Mener, Betz, Genther, Chen, & Lin, 2013; Win et al., 2011). Notably, in Study 1 there was an association between hearing ability and frailty with the FI, but not the FP. This is not necessarily in contrast to prior findings, given the methodological heterogeneity in previous studies. While some studies assessed hearing impairment through self-report (Kamil et al., 2014; Ng et al., 2014), in Study 1 behavioral fine-grained sensory measures were obtained by using pure-tone audiometry. This reduced the impact of potential self-report bias which might depend on the individuals' insight regarding chronic disease (Kriegsman, Penninx, van Eijk, Boeke, & Deeg, 1996) and on the tendency to generalize the rating from a diminished function in one sense to the other senses as well (Cavazzana et al., 2018). Moreover, some studies used non-traditional definitions of frailty (Kamil et al., 2016) whereas in Study 1 two well established frailty measures were used that are also most widely used in geriatric practice. This observation suggests that the FI might be more sensitive than the FP in capturing sensory decline that is associated with frailty. For instance, the FI contains items that might reflect direct or indirect effects of hearing disability on frailty, such as everyday function, mood, cognitive abilities and previous diseases. In this regard, the observed relationship might also be a function of increased comorbidities and accumulation of multidimensional deficits as assessed by the FI. However, despite the fact that age-related sensory impairments are strongly associated with physical decline (D. S. Chen

et al., 2015; Swenor et al., 2015), the lack of associations between sensory performance and the FP in the above analyses suggests that the precise mechanisms underlying the sensory impairment – physical frailty relationship may be more complex than those reflected by the physical FP. Assuming that traditional frailty measures might be more or less sensitive in capturing the contribution of sensory impairment to frailty, the results of Study 1 support previous proposals that the evaluation of sensory abilities should be included in frailty assessment protocols (Linard et al., 2016; Tan et al., 2020; Vieira et al., 2016).

Depression as assessed by the CES-D was identified as a significant covariate for FI. There is ample evidence about the association of depression with frailty in older age suggesting that associations between depression and frailty might be driven by various common characteristics, such as exhaustion, slowness and weight loss (Buigues et al., 2015; Collard et al., 2014). For instance, in Study 1 there was a significant negative correlation between depression and SPPB scores which is consistent with earlier findings reporting a relationship between depression and lower-extremity performance and mobility (Yanagita et al., 2006). However, it has been argued that physical symptoms and functional impairment in elderly may inflate scores on depression measures including somatic items, such as the CES-D, compared to other measures such as the Geriatric Depression Scale (GDS), which contains no somatic items (Mui, Burnette, & Chen, 2001). When replacing the CES-D score with the GDS score[10] in the above analyses, depression is no longer found to be independently related to frailty status for either frailty measure, but the pattern of independent relationships between sensory and motor determinants and frailty as well as the differences observed between the two frailty indicators does not substantially change (data not shown). This implies that the relationship between depression and frailty in the above analyses might be driven by the overlap of somatic symptoms in the measures, which however did not bias the main findings. Importantly, associations of depression with frailty were also found when the measures used to determine one syndrome were adjusted for the characteristics of the other syndrome (Collard et al., 2014), suggesting that it is not the shared characteristics alone that explain the increased severity of depression in frail compared to non-frail depressed older individuals (Collard et al., 2014). Previous reviews suggested

[10] GDS data for each subject were acquired by a study physician using a standard questionnaire. Subsequent processing of subject data including statistical analyses were performed by the author of the present dissertation.

a bidirectional relationship between depression and frailty (Buigues et al., 2015; Mezuk, Edwards, Lohman, Choi, & Lapane, 2012) and evidence pointed to common pathophysiological mechanisms, such as low-grade inflammation (Bremmer et al., 2008; Leng, Xue, Tian, Walston, & Fried, 2007), that might underlie the relationship between depression and frailty. The fact that the above results revealed a significant independent association only between depression and frailty as assessed with the FI but not the FP might be surprising given that higher scores of depression were found in frail vs. pre-frail individuals as determined by either frailty measure. However, it should be noted that, given that the independent association between depression and the FP in the multivariate analysis almost reached significance (p=0.087), it could be possible that the results in Study 1 failed to demonstrate an existing effect due to insufficient statistical power.

3.1.2.3 Strengths and limitations

Study 1 has several strengths. First, Study 1 included validated behavioral measures to assess sensory, motor and physical performance, thereby reducing the impact of potential self-report bias. Second, Study 1 demonstrated that conclusions about the underlying impairments of a person classified as frail should be made with caution because the identification of frailty and potentially modifiable determinants, particularly physical performance, sensory impairment and depression, is influenced by the frailty measure and construct employed. The findings provide further evidence that frailty measures should not be used interchangeably (Cesari et al., 2014) and that multiple dimensions should be taken into account when diagnosing and treating the frailty syndrome.

Study 1 is also subject to limitations. Due to the cross-sectional nature of the analyses, the results cannot determine the temporal relationship and causal or mechanistic pathways underlying the relationship of sensory and motor abilities with frailty. Taking into account the small number of subjects in the sample, the results should therefore be considered as preliminary. Moreover, the fact that the analyses were performed on baseline data from individuals participating in a frailty intervention study might have promoted selection and exclusion bias in the sample. For instance, inclusion criteria required subjects not to have significant cognitive impairment (MMSE > 24) while frailty and cognitive dysfunction were demonstrated to be significantly associated in the population (Kiiti Borges et al., 2019; Kulmala, Nykänen, Mänty, & Hartikainen, 2014). Also,

the fact that subjects had to fulfil at least one positive FP criterion excluded robust (i.e. non-frail) individuals from the sample while the need for willingness and ability to participate in a multi-month intervention program might have favored the inclusion of less frail individuals (Gordon et al., 2017). Thus, the relationships that were found in a sample presumably located in the lower to middle range of the frailty continuum still need to be examined in robust elderly individuals and individuals located at the upper end of the frailty continuum. Therefore, generalizability of the results may be limited, and it will still have to be examined whether the results apply to other frailty measures, to the use of different cutoffs for frailty and pre-frailty, to the use of different measures of sensory and motor performance or to different subject populations.

3.1.2.4 Conclusion

Based on the results, it can be assumed that the differences by which the FP and FI capture frailty-related sensory, motor and psychological impairment could provide an explanation for the frequently observed discordance in identifying frailty. These differences in diagnostic properties have implications for researchers and clinicians, since the choice of the instrument may influence the accurate identification of frailty and the planning of interventions in individuals suffering from different impairments. Therefore, the objectives of the use should be taken into account in order to select the appropriate instrument. The above cross-sectional analyses indicate that frailty is a multidimensional and complex syndrome and future representative studies involving large-scale longitudinal data of objective sensory and motor performance in community-dwelling as well as institutionalized robust, pre-frail and frail individuals will be needed to identify the temporal and causal mechanisms underlying the relationship of sensory and motor impairment with frailty. The understanding of mechanistic pathways is imperative for considering the heterogeneity of changes in function, for refining existing diagnostic systems and measures of frailty and for developing individualized treatment plans. In this context, sensory and motor determinants of frailty, which are potentially modifiable, might represent useful targets for the development of effective prevention and treatment strategies to maintain function and independence in old age.

3.2 Study 2

3.2.1 Results

The following section consists of two separate chapters describing the results of the 60-day and 90-day training, respectively.

3.2.1.1 Results of the 60-day training

3.2.1.1.1 Sample characteristics

Baseline characteristics and training-related data of the 60-day training sample are summarized in Table 9. Age ranged from 68.6 to 92.8 years with a mean age of 80.4 (5.9) years and the majority of subjects (72.9 %) was female. There were no significant differences between treatment groups in any sample characteristics at baseline (all $p \geq 0.270$).

Total time of training tasks in the EG (mean 26.7, SD 4.9 hours) and total time engaged in the daily training in the CG (mean 27.9, SD 8.8 hours) did not significantly differ ($p=0.167$) suggesting that training adherence was comparable in both intervention groups. With respect to motivational aspects, training motivation (maximum value: 50) before the training period was rated comparably high in both groups (EG: mean 41.0, SD 6.9; CG: mean 39.1, SD 8.3; $p=0.381$), however, the control intervention was evaluated less positively compared to the experimental intervention at post-training (EG: mean 38.5, SD 8.3; CG: mean 32.1, SD 8.7; $p=0.015$).

Table 9[11]. Results Study 2: Baseline (T0) characteristics and training-related data of the 60-day training sample.

Characteristic	Total		EG		CG		p-value
	n	48	n	24	n	24	
Baseline characteristics							
Age, years (mean, SD)	80.4	5.9	79.5	5.9	81.3	5.7	0.279
Female (n, %)	35	72.9	16	66.7	19	79.2	0.330
Education, years (mean, SD)	12.7	2.8	13.0	2.9	12.5	2.7	0.574
BMI, kg/m² (mean, SD)	28.1	6.3	29.5	7.1	26.8	5.1	0.270
MMSE (mean, SD)	28.8	1.5	28.9	1.5	28.8	1.5	0.895
GDS (mean, SD)	0.7	1.3	0.8	1.7	0.6	0.9	0.990
MNA (mean, SD)	25.4	2.7	25.7	3.1	25.0	2.1	0.334
Training-related data							
Total training time, hours (mean, SD)			26.7	4.9	27.9	8.8	0.167
Training motivation pre-training (mean, SD)			41.0	6.9	39.1	8.3	0.381
Training evaluation post-training (mean, SD)			38.5[1]	8.3	32.1[1]	8.7	0.015

P-values refer to the between-group comparison. BMI, body mass index; CG, control group; EG, experimental group; GDS, Geriatric depression scale; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; [1]n=23.

3.2.1.1.2 Frailty

Results of primary outcomes including frailty measured by the FP and FI are summarized in Table 10 and displayed in Figure 4. With respect to the number of positive FP criteria, there was a significant main effect of time ($F_{1,46.176}$=24.51, p<0.001) and a marginally significant group-by-time interaction ($F_{1,46.000}$=3.78, p=0.058). Post-hoc group-wise comparisons revealed that the number of FP criteria decreased after 60 days of training in both the EG (p<0.001) and CG (p=0.039) with the tendency of a stronger

[11] Height, weight, and body mass index were obtained through a physical examination performed by a study physician. GDS data for each subject were acquired by a study physician using a standard questionnaire. Raw data obtained from the experimental sensorimotor training were analyzed and mean values for each subject were computed by a fellow researcher involved in the cross-project collaboration. Subsequent processing of subject data including statistical analyses were performed by the author of the present dissertation.

decrease in the EG compared to the CG. The magnitude of the intervention effect was medium (d=-0.63).

For the FI, there was a marginally significant main effect of time ($F_{1,46.622}$=3.32, p=0.075) but no significant group-by-time interaction ($F_{1,45.995}$=1.48, p=0.231) and the interaction effect size was small (d=-0.21).

With respect to frailty prevalence, Pearson-χ^2-test showed that both intervention groups were comparable at baseline (p=0.330, see Table 11). However, in the EG, the prevalence of robust individuals significantly increased from 0% at baseline to 29.2% post-training (p=0.016) suggesting that frailty status was improved, while no significant change in prevalence rates was found for the CG (all p≥0.453). Prevalence of individual FP criteria at baseline did not significantly differ between the two groups, however, there was a slight imbalance for distribution of the grip strength criterion (p=0.057), with a higher prevalence rate in the CG compared to the EG. In order to further elucidate the nature of the intervention effect on FP, prevalence rates on individual FP criteria pre- and post-training were compared, separately for both groups using McNemar tests. In the EG, prevalence of the gait speed criterion significantly decreased from 54.2% at baseline to 16.7% post-training (p=0.004), while the change for other FP criteria was not significant (p≥0.109). For the CG, no significant changes in prevalence of FP criteria were found (p≥0.125). With respect to prevalence rates post-training, there was a marginally higher number of robust individuals (p=0.064) and a marginally lower number of frail individuals (p=0.081) in the EG compared to the CG. Prevalence rates for individual FP criteria post-training did not significantly differ between the groups except for a lower prevalence of the grip strength criterion (p=0.019) in the EG compared to the CG, which, however, might be overestimated due to the imbalance in the criterion observed at baseline. Additionally, the change scores (-1, 0 or 1) on individual FP criteria were statistically compared, separately for both groups (see Figure 5). Group-wise non-parametric Friedman's analysis of variance revealed a marginally significant effect in the EG ($\chi^2(4)$=9.17, p=0.057) and the strongest numerical change values were found for the gait speed criterion, however, Bonferroni-corrected post-hoc tests did not reveal significant differences in change scores between FP criteria (all p>0.10). For the CG, no significant overall effect was found ($\chi^2(4)$=0.97, p=0.915).

With respect to performance scores of individual FP criteria (see Table 12), there was no significant group-by-time interaction for physical activity ($F_{1,45.999}$=1.03, p=0.315) and gait speed ($F_{1,46.000}$=1.38, p=0.247), but there was a marginally significant group-

by-time interaction for grip strength ($F_{1,46.000}$=3.02, p=0.089). Post-hoc group-wise comparisons revealed a marginal significant increase of grip strength in the EG (p=0.056) while there was no significant effect in the CG (p=0.624). Effect sizes of treatment effects on FP criteria were small (all d≤0.42).

Correlational analyses (see Figure 6) revealed that both frailty measures moderately correlated with respect to baseline scores (ρ=0.461, p=0.001) and change scores after 60 days of training (ρ=0.462, p=0.001).

Table 10. Results Study 2: Frailty scores at baseline (T0) and after 60 days (T1), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG			CG					
Measure	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	p-value (T0)	Interaction effect (F_{df}- and p-value)	ES
FP (number)*	1.96 (0.17)	1.00 (0.17)	-0.96 (0.21)	2.21 (0.18)	1.79 (0.22)	-0.42 (0.18)	0.313	$F_{1,46.000}$=3.78, p=0.058	-0.63
FI*	0.198 (0.016)	0.177 (0.017)	-0.022 (0.007)	0.237 (0.018)	0.233 (0.018)	-0.004 (0.012)	0.111	$F_{1,45.995}$=1.48, p=0.231	-0.21

CG, control group; EG, experimental group; ES, effect size; FI, frailty index; FP, frailty phenotype; SE, standard error of the mean; * lower scores represent better performance.

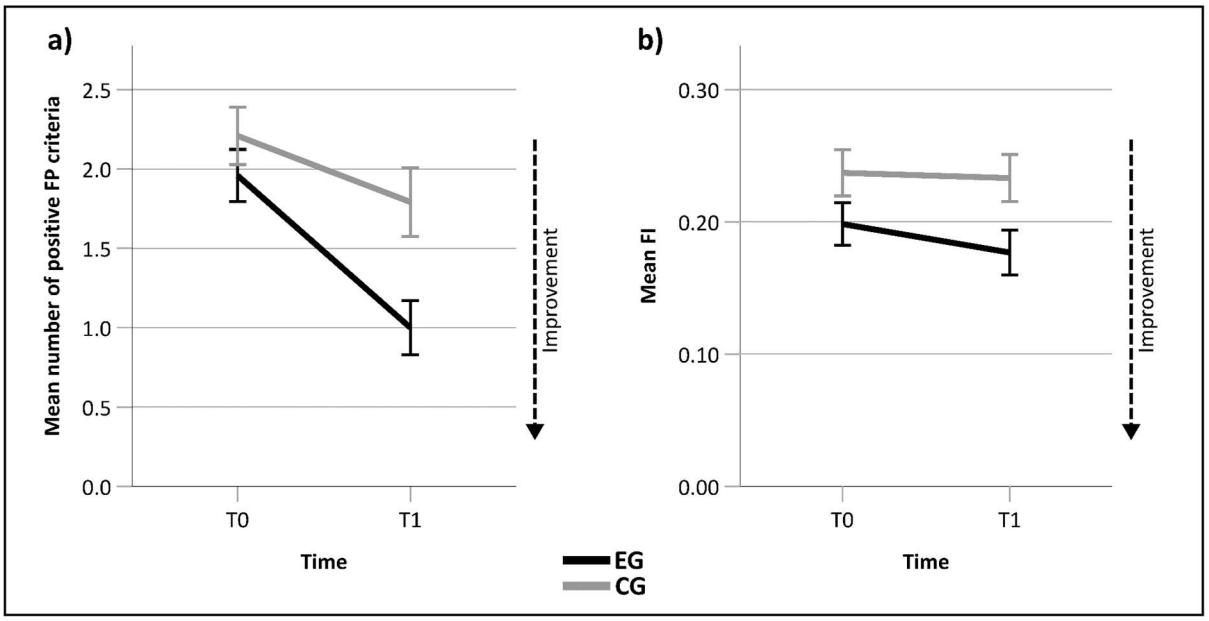

Figure 4. Results Study 2: Illustration of frailty scores for the (a) FP and (b) FI at baseline (T0) and after 60 days of training (T1) for the experimental group (EG) and control group (CG).

Error bars represent standard errors of the mean.

Table 11. Results Study 2: Prevalence of FP status and FP criteria at baseline (T0) and after 60 days (T1).

	EG			CG				
Measure	T0, n (%)	T1, n (%)	p-value change	T0, n (%)	T1, n (%)	p-value change	p-value (T0)	p-value (T1)
FP status								
Robust	0 (0)	7 (29.2)	0.016	0 (0)	2 (8.3)	0.500	-	0.064
Pre-frail	19 (79.2)	16 (66.7)	0.453	16 (66.7)	17 (70.8)	1	0.330	0.755
Frail	5 (20.8)	1 (4.2)	0.125	8 (33.3)	5 (20.8)	0.453	0.330	0.081
FP criteria								
Weight loss	6 (25)	3 (12.5)	0.250	4 (16.7)	3 (12.5)	1	0.477	1
Exhaustion	12 (50.0)	6 (25.0)	0.109	13 (54.2)	11 (45.8)	0.754	0.773	0.131
Physical inactivity	2 (8.3)	1 (4.2)	1	3 (12.5)	2 (8.3)	1	0.637	0.551
Gait speed	13 (54.2)	4 (16.7)	0.004	13 (54.2)	9 (37.5)	0.125	1	0.104
Grip strength	14 (58.3)	10 (41.7)	0.125	20 (83.3)	18 (75.0)	0.625	0.057	0.019

P-values change refer to the intra-group pre-post comparison using McNemar test. P-values (T0) and p-values (T1) refer to between-group comparisons of frequencies at baseline and post-training, respectively. CG, control group; EG, experimental group; FP, frailty phenotype.

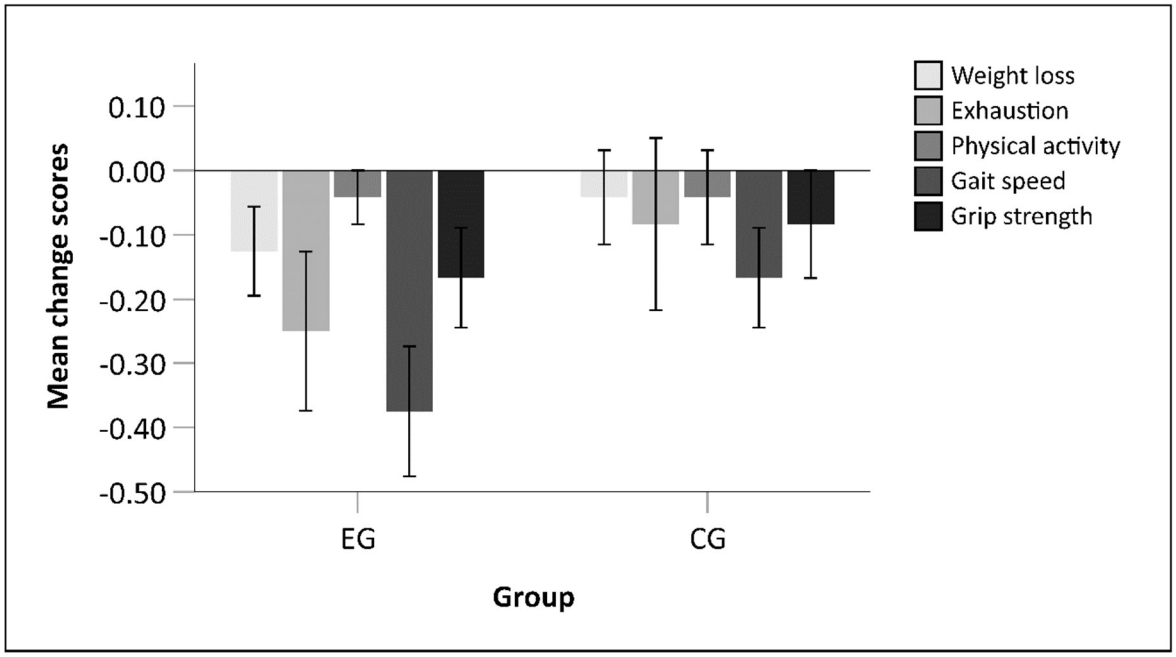

Figure 5. Results Study 2: Mean change scores in individual FP criteria, separately for the experimental group (EG) and control group (CG).

Error bars represent standard errors of the mean.

Table 12. Results Study 2: Performance scores of FP criteria at baseline (T0) and after 60 days (T1), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG			CG					
Measure	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	p-value (T0)	Interaction effect (F_{df}- and p-value)	ES
Physical activity (kcal/week)	2625 (390.6)	3693 (409.2)	1068 (620.6)	2304 (301.1)	2636 (366.8)	332 (375.6)	0.519	$F_{1,45.999}$=1.03, p=0.315	0.42
Gait speed (m/s)	0.811 (0.036)	0.895 (0.044)	0.084 (0.040)	0.776 (0.042)	0.806 (0.359)	0.029 (0.023)	0.536	$F_{1,46.000}$=1.38, p=0.247	0.28
Grip strength (kg)	21.85 (2.02)	23.27 (1.82)	1.41 (0.80)	17.73 (1.88)	17.27 (1.81)	-0.46 (0.72)	0.080	$F_{1,46.000}$=3.02, p=0.089	0.19

CG, control group; EG, experimental group; ES, effect size; SE, standard error of the mean.

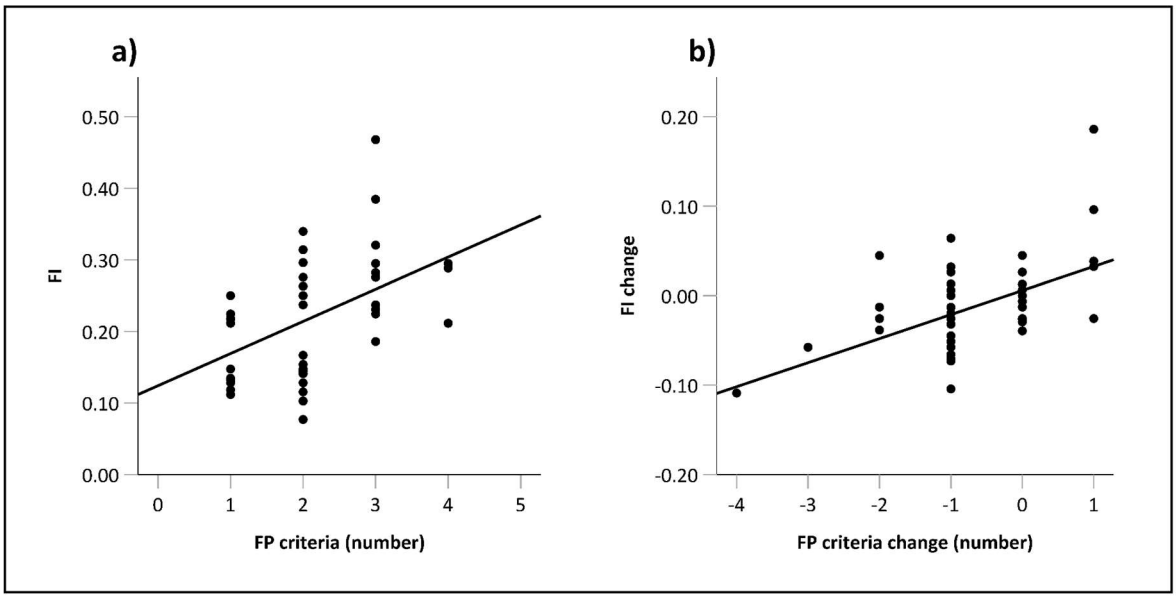

Figure 6. Results Study 2: Correlation of baseline (a) and change scores (b) between FP and FI.

3.2.1.1.3 Behavioral and clinical measures

3.2.1.1.3.1 Motor function

Results on measures of motor function are summarized in Table 13. There were no significant group-by-time interaction effects for upper or lower extremity function scores (all $p \geq 0.164$) and effect sizes were small (all $d \leq 0.19$). Baseline scores differed for SPPB scores ($p=0.006$) and marginally differed for CTSIB scores ($p=0.065$), suggesting that the CG had considerably reduced lower extremity function compared to the EG.

Table 13. Results Study 2: Motor performance scores at baseline (T0) and after 60 days (T1), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG			CG					
Measure	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	p-value (T0)	Interaction effect (F_{df}- and p-value)	ES
PPT right hand (score)	10.35 (0.36)	10.50 (0.37)	0.15 (0.24)	9.69 (0.56)	10.28 (0.52)	0.59 (0.20)	0.502	$F_{1,46.001}$=2.00, p=0.164	-0.19
PPT left hand (score)	9.69 (0.33)	9.57 (0.39)	-0.13 (0.23)	9.35 (0.51)	9.32 (0.51)	-0.02 (0.31)	0.571	$F_{1,45.999}$=0.07, p=0.792	-0.05
PPT both hands (score)	7.65 (0.32)	7.60 (0.34)	-0.06 (0.20)	7.43 (0.44)	7.17 (0.45)	-0.26 (0.15)	0.901	$F_{1,46.001}$=0.67, p=0.417	0.11
PPT assem-blies (score)	19.22 (0.93)	19.60 (0.97)	0.38 (0.55)	17.92 (0.94)	17.66 (0.82)	-0.25 (0.51)	0.330	$F_{1,45.998}$=0.69, p=0.409	0.13
SPPB (score)	8.50 (0.34)	8.29 (0.39)	-0.21 (0.22)	6.71 (0.52)	6.71 (0.54)	<0.01 (0.36)	0.006	$F_{1,45.999}$=0.25, p=0.616	-0.10
CTSIB score (sec)	96.5 (7.2)	100.1 (6.9)	3.5 (2.9)	77.5 (8.3)	83.9 (8.6)	6.3 (3.1)	0.065	$F_{1,46.001}$=0.46, p=0.501	-0.07

CG, control group; CTSIB; Clinical Test of Sensory Integration of Balance; EG, experimental group; ES, effect size; FI, frailty index; FP, frailty phenotype; PPT, Purdue Pegboard Test; SE, standard error of the mean; SPPB, Short Physical Performance Battery.

3.2.1.1.3.2 Sensory function

Results on measures of sensory function are summarized in Table 14. With respect to visual acuity, there was a significant group-by-time interaction ($F_{1,46.001}$=4.83, p=0.033), however, post-hoc group-wise comparisons revealed no significant changes after 60 days in the EG (p=0.106) and CG (p=0.151). With regard to other measures of visual, auditory and somatosensory ability, there were no significant group-by-time interaction effects (all p≥0.281) and effect sizes were small (all d≤0.46).

Table 14. Results Study 2: Sensory performance scores at baseline (T0) and after 60 days (T1), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG			CG					
Measure	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	p-value (T0)	Interaction effect (F_{df}- and p-value)	ES
Visual acuity (logMAR)*	0.40 (0.07)	0.33 (0.06)	-0.07 (0.04)	0.27 (0.05)	0.33 (0.04)	0.07 (0.05)	0.110	$F_{1,46.001}$=4.83, p=0.033	-0.46
Visual contrast sensitivity (logCS)	1.39 (0.09)	1.38 (0.10)	-0.02 (0.08)	1.51 (0.08)	1.47 (0.08)	-0.03 (0.06)	0.347	$F_{1,46.000}$=0.02, p=0.889	0.04
Hearing threshold right ear (dB)*	36.0 (3.1)	35.1 (3.1)	-1.0 (0.6)	36.1 (2.7)	35.6 (2.7)	-0.5 (0.5)	0.845	$F_{1,46.004}$=0.31, p=0.583	-0.03
Hearing threshold left ear (dB)*	37.8 (3.8)	38.3 (3.9)	0.5 (0.8)	36.2 (2.7)	35.8 (2.6)	-0.4 (1.1)	0.721	$F_{1,45.999}$=0.49, p=0.490	0.06
MDT right hand (mN)*	0.92 (0.28)	0.91 (0.26)	-0.01 (0.34)	0.75 (0.16)	0.75 (0.17)	<0.01 (0.09)	0.516	$F_{1,46.000}$<0.01, p=0.968	-0.01
MDT left hand (mN)*	1.22 (0.58)	0.93 (0.32)	-0.29 (0.44)	0.40 (0.08)	0.62 (0.17)	0.23 (0.17)	0.868	$F_{1,45.999}$=1.19, p=0.281	-0.25
Spatial tactile discrimination right hand (mm)*	3.62 (0.29)	3.89 (0.37)	0.27 (0.31)	4.07 (0.30)	3.94 (0.29)	-0.13 (0.32)	0.327	$F_{1,45.998}$=0.83, p=0.368	0.28

CG, control group; EG, experimental group; ES, effect size; MDT, mechanical detection threshold; SE, standard error of the mean; * lower scores represent better performance.

3.2.1.1.3.3 Cognitive function

Results on measures of cognitive function are summarized in Table 15. There were no significant group-by-time interaction effects for performance in any cognitive domain (all p≥0.140) and effect sizes were small (all d≤0.48).

Table 15. Results Study 2: Cognitive performance scores at baseline (T0) and after 60 days (T1), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG			CG					
Measure	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	p-value (T0)	Interaction effect (F_{df}- and p-value)	ES
RTI mental speed single choice (ms)*	360.0 (10.4)	342.1 (11.7)	-17.9 (9.8)	352.4 (11.4)	341.0 (12.4)	-11.4 (12.0)	0.625	$F_{1,46.000}$=0.18, p=0.677	-0.12
RTI mental speed five choice (ms)*	394.6 (10.2)	380.3 (10.9)	-14.3 (8.8)	416.2 (16.1)	383.6 (10.3)	-32.6 (15.7)	0.263	$F_{1,46.000}$=1.04, p=0.314	0.27
RTI motor speed single choice (ms)*	563.8 (39.4)	526.4 (27.6)	-37.4 (34.2)	529.3 (30.4)	483.6 (24.8)	-45.8 (29.6)	0.492	$F_{1,46.000}$=0.03, p=0.854	0.05
RTI motor speed five choice (ms)*	494.4 (24.1)	536.5 (24.6)	42.1 (17.5)	515.2 (32.7)	533.5 (19.8)	18.3 (29.0)	0.610	$F_{1,45.999}$=0.49, p=0.486	0.17
AST correct trials (%)	76.6 (3.5)	77.4 (4.3)	0.9 (1.9)	74.5 (3.4)	75.3 (3.5)	0.8 (2.6)	0.673	$F_{1,45.999}$<0.01, p=0.982	0.01
AST RT correct trials (ms)*	1107.5 (40.8)	1153.7 (42.5)	46.1 (35.5)	1170.5 (43.2)	1174.1 (45.6)	3.6 (44.9)	0.295	$F_{1,45.999}$=0.55, p=0.461	0.20
AST switch cost (ms)*	-38.0 (19.2)	-45.2 (22.1)	-7.1 (21.6)	-45.4 (27.7)	-57.4 (29.5)	-12.0 (20.4)	0.828	$F_{1,46.000}$=0.03, p=0.870	0.04
AST congruency cost (ms)*	100.8 (19.1)	93.3 (30.0)	-7.5 (21.5)	148.8 (16.2)	106.8 (21.0)	-42.0 (20.2)	0.061	$F_{1,46.000}$=1.37 p=0.248	0.39
SSP working memory span (score)	5.1 (0.2)	4.8 (0.2)	-0.3 (0.3)	4.9 (0.2)	5.1 (0.1)	0.2 (0.2)	0.380	$F_{1,46.000}$=2.26, p=0.140	-0.48
IED stages completed (number)	7.2 (0.4)	7.7 (0.4)	0.5 (0.5)	7.5 (0.4)	7.6 (0.3)	0.1 (0.5)	0.495	$F_{1,46.000}$=0.41, p=0.525	0.22
IED total errors (number)*	59.5 (9.4)	54.0 (9.3)	-5.5 (11.2)	55.0 (9.0)	52.9 (6.5)	-2.1 (11.8)	0.650	$F_{1,46.000}$=0.04, p=0.837	-0.07

AST, Attention Switching Task; CG, control group; EG, experimental group; ES, effect size; IED, Intra-Extra Dimensional Set Shift; RT, reaction time; RTI, Reaction Time Test; SE, standard error of the mean; SSP, Spatial Span Test; * lower scores represent better performance.

3.2.1.1.3.4 Clinical characteristics

Results on measures of clinical characteristics are summarized in Table 16. There was a significant group-by-time interaction effect for the SF-36 subscale measuring the extent of bodily pain ($F_{1,46.000}$=8.90, p=0.005) and group-wise post-hoc tests showed that bodily pain significantly decreased in the EG (p=0.005) compared to the CG (p=0.209). The magnitude of the effect was medium (d=0.60). Additionally, there was a significant group-by-time interaction effect for the SF-36 subscale measuring emotional role limitations ($F_{1,46.000}$=4.19, p=0.046) and group-wise post-hoc tests showed that there was a reduction in role limitations due to emotional problems in the CG (p=0.001) compared to the EG (p=0.425). The magnitude of the effect was medium (d=-0.56). However, the effect did not persist in the multiple regression analysis when adjusting for baseline value (group effect: β=0.156, p=0.238; see Table 24). Baseline scores for clinical measures did not significantly differ between the groups except for the EQ-5D-5L health status (p=0.001) suggesting that the CG rated their perceived current overall health status significantly lower compared to the EG.

Table 16. Results Study 2: Measures of clinical characteristics at baseline (T0) and after 60 days (T1), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG			CG					
Measure	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	p-value (T0)	Interaction effect (F_{df}- and p-value)	ES
FEFA score*	3.2 (0.9)	2.5 (0.8)	-0.6 (0.4)	3.0 (0.7)	2.5 (0.6)	-0.5 (0.4)	0.712	$F_{1,46.000}$=0.06, p=0.804	-0.04
CES-D score*	13.8 (1.4)	14.2 (2.2)	0.3 (1.3)	17.2 (1.7)	16.0 (1.5)	-1.3 (1.5)	0.109	$F_{1,46.000}$=0.64, p=0.428	0.20
SF-36 physical functioning	50.8 (5.7)	49.3 (5.9)	-1.5 (5.1)	37.7 (5.4)	37.1 (5.8)	-0.6 (2.7)	0.099	$F_{1,46.000}$=0.03, p=0.870	-0.03
SF-36 physical role limitations	36.5 (8.5)	47.1 (8.7)	10.7 (6.0)	27.1 (7.8)	31.7 (7.6)	4.6 (8.4)	0.408	$F_{1,46.000}$=0.35, p=0.560	0.15
SF-36 bodily pain	54.9 (5.3)	64.8 (4.8)	9.9 (2.8)	53.9 (4.5)	49.2 (5.5)	-4.7 (4.1)	0.825	$F_{1,46.000}$=8.90, p=0.005	0.60
SF-36 general health perception	52.2 (3.8)	57.7 (3.6)	5.6 (2.1)	44.2 (3.8)	46.5 (3.5)	2.2 (3.2)	0.148	$F_{1,45.998}$=0.75, p=0.393	0.17
SF-36 vitality	52.3 (4.4)	54.8 (3.9)	2.5 (3.2)	42.3 (3.6)	43.3 (3.5)	1.0 (2.3)	0.073	$F_{1,45.997}$=0.16, p=0.692	0.08
SF-36 social functioning	79.2 (4.7)	79.9 (4.2)	0.7 (4.1)	69.3 (5.5)	70.1 (6.6)	0.8 (4.5)	0.168	$F_{1,46.000}$<0.01, p=0.990	<0.01
SF-36 emotional role limitations	61.1 (8.7)	67.9 (8.4)	6.7 (7.2)	37.5 (8.8)	68.7 (8.4)	31.2 (9.5)	0.063	$F_{1,46.000}$=4.19, p=0.046	-0.56
SF-36 mental health	73.8 (3.5)	76.9 (3.2)	3.1 (2.5)	68.0 (2.7)	66.4 (3.5)	-1.6 (3.1)	0.197	$F_{1,46.000}$=1.36, p=0.250	0.30
SF-36 PCS	35.4 (1.9)	37.5 (2.0)	2.1 (1.2)	33.3 (1.8)	32.3 (2.1)	-1.1 (1.6)	0.432	$F_{1,46.000}$=2.30, p=0.136	0.34
SF-36 MCS	48.9 (2.8)	50.6 (2.4)	1.6 (2.0)	42.3 (2.2)	46.4 (2.9)	4.0 (2.2)	0.053	$F_{1,46.000}$=0.65, p=0.426	-0.19

CES-D, Center for Epidemiologic Studies Depression Scale; CG, control group; EG, experimental group; EQ-5D-5L, EuroQol-5D-5L; ES, effect size; FEFA, Frail Elderly Functional Assessment; FES-I, Falls Efficacy Scale – International Version; MCS, mental component summary; MKS, Marburg Competency Scale (Marburger Kompetenz Skala); PCS, physical component summary; SF-36, Short Form-36; * lower scores represent better performance.

Table 16 (continued).

Measure	EG T0 Mean (SE)	EG T1 Mean (SE)	EG Change Mean (SE)	CG T0 Mean (SE)	CG T1 Mean (SE)	CG Change Mean (SE)	p-value (T0)	Interaction effect (F_{df}- and p-value)	ES
EQ-5D-5L index	0.797 (0.031)	0.778 (0.044)	-0.019 (0.024)	0.726 (0.043)	0.697 (0.048)	-0.029 (0.036)	0.134	$F_{1,46.001}$=0.05, p=0.819	0.05
EQ-5D-5L health status	70.0 (3.4)	66.9 (3.1)	-3.1 (2.7)	53.8 (3.2)	53.0 (3.3)	-0.8 (3.7)	0.001	$F_{1,46.000}$=0.27, p=0.606	-0.14
MKS score	93.9 (3.8)	93.6 (3.7)	-0.3 (1.8)	91.0 (2.4)	90.0 (2.7)	-1.0 (1.8)	0.523	$F_{1,46.000}$=0.07, p=0.794	0.04
FES score*	28.3 (2.3)	28.3 (2.1)	0.0 (1.0)	31.6 (1.8)	31.4 (2.0)	-0.3 (1.2)	0.101	$F_{1,45.999}$=0.03, p=0.875	0.02

3.2.1.1.4 BDNF genotype

After genetic analyses of blood samples, 32 subjects (66.7 %) out of the total number of 48 subjects were identified as Val/Val homozygotes and 16 subjects (33.3 %) were identified as Met carriers. Despite randomized allocation to the treatment groups, the distribution of BDNF genotype significantly differed between the two intervention groups ($\chi^2(1)=6.00$, p=0.014). 4 subjects in the EG (16.7 %) and 12 subjects in the CG (50.0 %) were identified as Met carriers. The four groups (EG-Val/Val, EG-Met carrier, CG-Val/Val and CG-Met carrier) did not significantly differ at baseline with respect to sample characteristics and measures of frailty (all p≥0.196; see Table 17) as well as values of single FP criteria (physical activity: p=0.564; gait speed: p=0.245; grip strength: p=0.117).

Results of LMMs with respect to BDNF genotype are summarized in Table 18 and displayed in Figure 7. With respect to the number of positive FP criteria, there was a significant main effect of time ($F_{1,44.137}$=18.34, p<0.001) and a marginally significant group-by-time interaction ($F_{3,44.000}$=2.26, p=0.094) and post-hoc group-wise comparisons showed that the number of FP criteria decreased after 60 days of training in the EG-Val/Val (p<0.001), EG-Met carrier (p=0.041) and CG-Val/Val group (p=0.009), but not the CG-Met carrier group (p=0.755). No significant group-by-time interaction effects were found for FP criteria of physical activity, gait speed and grip strength as well as for the FI (all p≥0.381).

With respect to individual FP criteria, statistical within-groups comparison of prevalence rates pre- and post-training were not possible due to the low number of cases in some groups (e.g. n=4 for EG-Met carrier). However, descriptive comparisons of change scores (-1, 0 or 1) on individual FP criteria (see Figure 8) indicated that in both the EG-Val/Val and EG-Met carrier group, the most pronounced pre-to-post improvement was found for the gait speed criterion. In the CG, Val/Val homozygotes demonstrated the most pronounced reduction for the exhaustion criterion, while the Met carriers instead showed an increase in exhaustion.

Table 17[12]. Results Study 2: Baseline (T0) characteristics in the two intervention groups, separated by BDNF genotype (Val/Val homozygotes and Met carriers).

Characteristic	EG		CG		p-value
	Val/Val	Met carrier	Val/Val	Met carrier	
N (% in treatment group)	20 (83.3)	4 (16.7)	12 (50.0)	12 (50.0)	0.014
Age, years (mean, SD)	79.7 (6.5)	78.3 (2.1)	83.1 (6.4)	79.6 (4.6)	0.299
Female (n, %)	12 (60.0)	4 (100.0)	9 (75.0)	10 (83.3)	0.277
Education, years (mean, SD)	13.3 (3.0)	11.3 (1.9)	12.2 (2.8)	12.8 (2.7)	0.341
BMI, kg/m² (mean, SD)	28.2 (6.0)	35.6 (9.8)	25.7 (3.0)	28.0 (6.5)	0.196
MMSE (mean, SD)	28.8 (1.6)	29.5 (0.6)	28.6 (1.5)	29.0 (1.5)	0.694
GDS (mean, SD)	1.0 (1.8)	0.0 (0.0)	0.3 (0.7)	0.8 (1.0)	0.214
MNA (mean, SD)	25.9 (3.0)	25.1 (3.8)	24.9 (2.3)	25.0 (2.1)	0.389
FP (mean, SD)	1.95 (0.83)	2.00 (0.82)	2.25 (0.87)	2.17 (0.94)	0.770
FI (mean, SD)	0.196 (0.074)	0.210 (0.117)	0.220 (0.080)	0.255 (0.091)	0.385

P-values refer to the comparison between the four groups. BMI, body mass index; CG, control group; EG, experimental group; GDS, Geriatric depression scale; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment.

[12] Height, weight and body mass index were obtained through a physical examination performed by a study physician. GDS data for each subject were acquired by a study physician using a standard questionnaire. Subsequent processing of subject data including statistical analyses were performed by the author of the present dissertation.

Table 18. Results Study 2: Frailty scores at baseline (T0) and after 60 days (T1) and group-by-time interaction effects from linear mixed model analyses for subjects with different BDNF genotypes.

Measure	Group	BDNF geno-type	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	Interaction effect (F_{df}- and p-value)
FP (number)*	EG	Val/Val	1.95 (0.19)	1.00 (0.16)	-0.95 (0.23)	$F_{3,44.000}$=2.26, p=0.094
		Met	2.00 (0.41)	1.00 (0.71)	-1.00 (0.58)	
	CG	Val/Val	2.25 (0.25)	1.50 (0.23)	-0.75 (0.22)	
		Met	2.17 (0.27)	2.08 (0.36)	-0.08 (0.26)	
FI*	EG	Val/Val	0.196 (0.016)	0.172 (0.018)	-0.024 (0.008)	$F_{3,43.995}$=0.61, p=0.614
		Met	0.210 (0.059)	0.203 (0.055)	-0.007 (0.019)	
	CG	Val/Val	0.220 (0.023)	0.214 (0.023)	-0.006 (0.020)	
		Met	0.255 (0.026)	0.252 (0.027)	-0.002 (0.016)	
Physical activity (kcal/week)	EG	Val/Val	2742.5 (459.9)	3822.0 (463.8)	1079.5 (730.7)	$F_{3,43.999}$=0.53, p=0.662
		Met	2038.1 (424.7)	3049.4 (852.7)	1011.3 (899.7)	
	CG	Val/Val	2686.3 (359.0)	2615.0 (576.4)	-71.3 (560.5)	
		Met	1922.5 (473.1)	2657.7 (479.9)	735.2 (496.2)	
Gait speed (m/s)	EG	Val/Val	0.839 (0.041)	0.928 (0.049)	0.089 (0.048)	$F_{3,44.000}$=0.49, p=0.690
		Met	0.672 (0.028)	0.726 (0.029)	0.054 (0.026)	
	CG	Val/Val	0.826 (0.064)	0.854 (0.045)	0.028 (0.042)	
		Met	0.726 (0.055)	0.757 (0.054)	0.031 (0.021)	
Grip strength (kg)	EG	Val/Val	22.80 (2.34)	24.12 (2.09)	1.32 (0.90)	$F_{3,44.000}$=1.05, p=0.381
		Met	17.12 (2.27)	18.99 (2.65)	1.88 (1.87)	
	CG	Val/Val	18.73 (1.78)	18.60 (1.74)	-0.14 (1.23)	
		Met	16.72 (3.39)	15.94 (3.22)	-0.78 (0.82)	

CG, control group; EG, experimental group; FI, frailty index; FP, frailty phenotype; SE, standard error of the mean; * lower scores represent better performance.

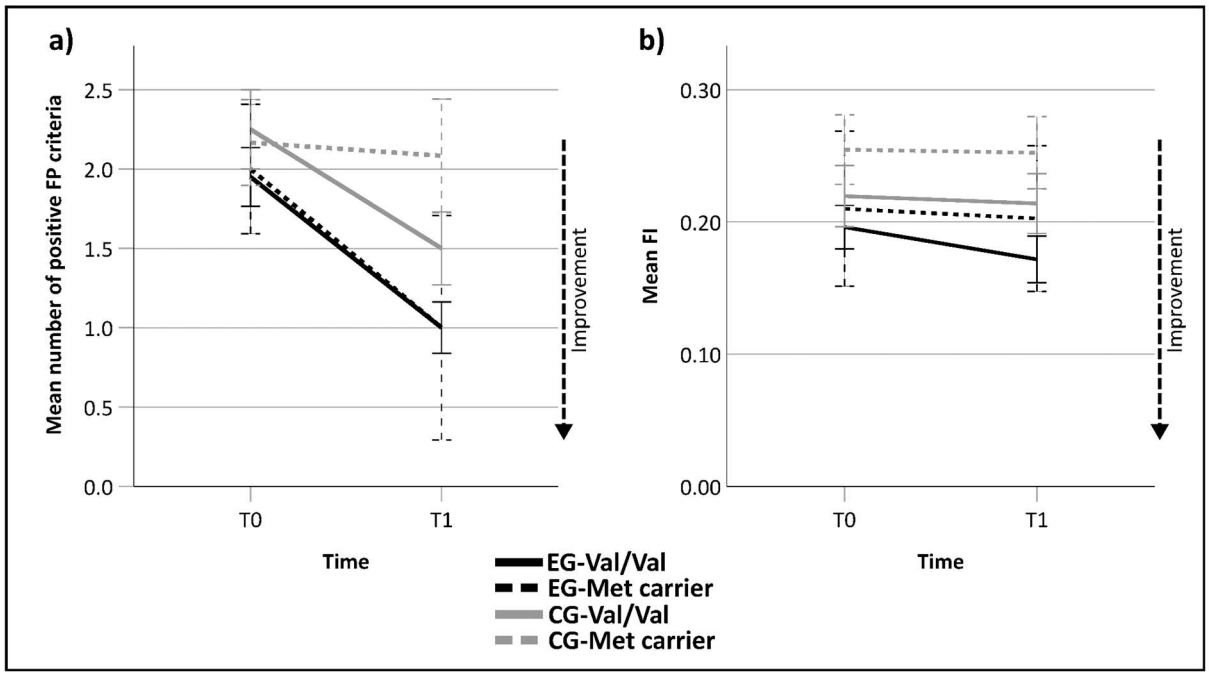

Figure 7. Results Study 2: Illustration of frailty scores for the FP (a) and FI (b) at baseline (T0) and after 60 days of training (T1), stratified by intervention group and BDNF genotype.

Error bars represent standard errors of the mean.

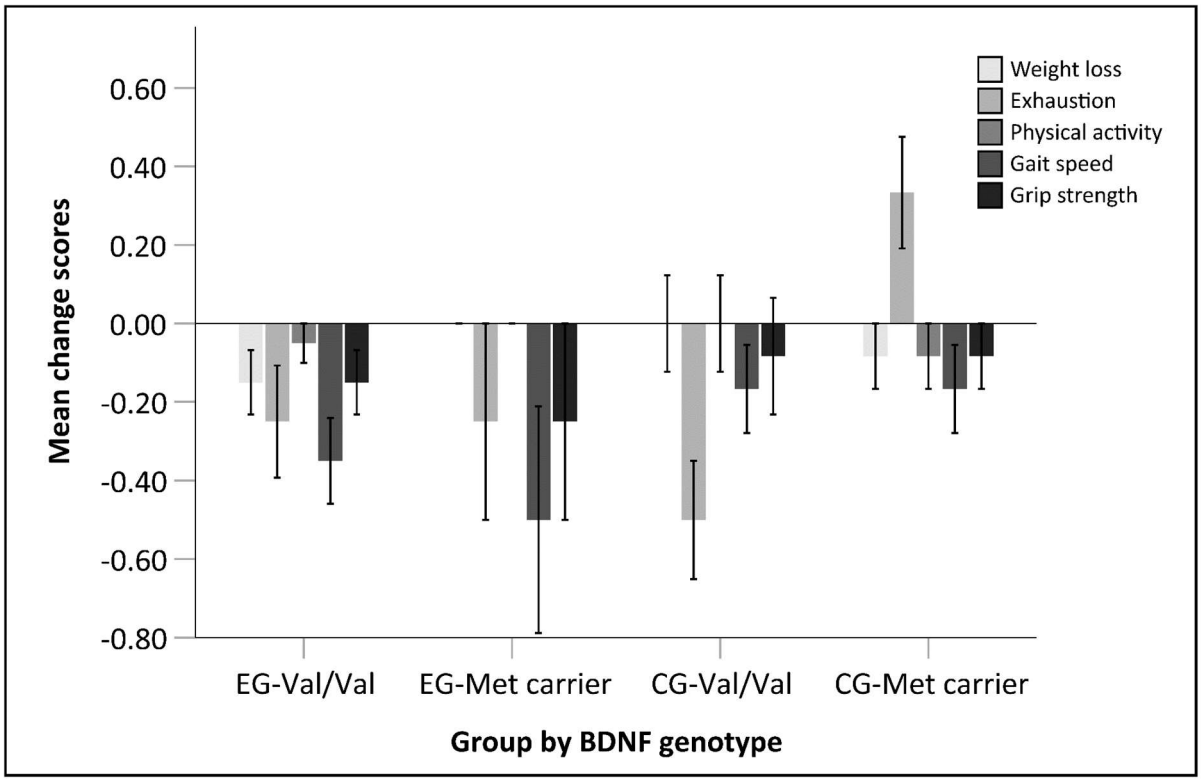

Figure 8. Results Study 2: Mean change scores in individual FP criteria, stratified by experimental group (EG) and control group (CG) and BDNF genotype.

Error bars represent standard errors of the mean.

3.2.1.1.5 Functional magnetic resonance imaging (fMRI) results

3.2.1.1.5.1 fMRI sample characteristics

A total of 25 subjects out of 48 subjects completing T0 and T1 assessments underwent fMRI measurement at baseline (T0). Reasons for non-execution of fMRI included medical contraindications, such as pacemakers (2 subjects), artificial heart valve (1 subject), MRI-incompatible implants (17 subjects), as well as claustrophobia (3 subjects). Of these 25 subjects (EG: n=13; CG: n=12), 22 underwent fMRI measurement after 60 days of training (T1), with one subject refusing fMRI measurement at T1 and two subjects not being measured due to Covid-19 safety regulations (all three in the CG). The 22 subjects consisted of 13 subjects in the EG and 9 subjects in the CG. One dataset in the CG had to be excluded during analysis due to extensive motion during measurement (more than 3 mm and more than 2 degrees in any direction). Thus, the fMRI sample consisted of 21 complete pre-post datasets, 13 in the EG and 8 in the CG. An overview of the baseline characteristics of the fMRI sample can be found in Table 19. The two intervention groups did not significantly differ in sample characteristics and

measures of frailty (all p≥0.201). Similarly, the fMRI sample did not differ from the rest of the total sample with respect to baseline sample characteristics and measures of frailty (all p>0.05; data not shown) suggesting that the fMRI sample analyzed represents a comparable subsample to the total sample.

Table 19[13]. Results Study 2: Baseline (T0) characteristics of the fMRI sample.

Characteristic	Total		EG		CG		p-value
	n	21	n	13	n	8	
Age, years (mean, SD)	80.9	7.0	79.9	6.7	82.4	7.6	0.435
Female (n, %)	15	71.4	8	61.5	7	87.5	0.201
Education, years (mean, SD)	13.1	3.1	13.7	3.6	12.1	2.1	0.276
BMI, kg/m² (mean, SD)	27.4	5.9	28.2	6.5	26.1	5.0	0.450
MMSE (mean, SD)	28.8	1.5	29.1	1.2	28.4	2.0	0.697
GDS (mean, SD)	0.3	0.6	0.5	0.7	0.1	0.4	0.336
MNA (mean, SD)	25.4	3.0	26.0	3.6	24.4	1.6	0.247
FP (mean, SD)	1.95	0.74	1.92	0.86	2.00	0.54	0.645
FI (mean, SD)	0.195	0.074	0.181	0.071	0.218	0.077	0.276

P values refer to the between-group comparison. BMI, body mass index; CG, control group; EG, experimental group; FI, frailty index; FP, frailty phenotype; GDS, Geriatric depression scale; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment.

3.2.1.1.5.2 fMRI behavioral results

Behavioral parameters of the fMRI motor sequence task are summarized in Table 20. Recording of subjects' responses during fMRI assessment revealed that subjects were able to correctly carrying out the motor task and only a minor portion of the blocks had to be recoded or excluded during data analysis. No statistical differences between interventional groups were observed at any point (all p>0.05) with respect to the number of active blocks entering the analysis, the number of correctly performed sequences and the mean tapping frequency in each task.

[13] Height, weight and body mass index were obtained through a physical examination performed by a study physician. GDS data for each subject were acquired by a study physician using a standard questionnaire. Subsequent processing of subject data including statistical analyses were performed by the author of the present dissertation.

Table 20. Results Study 2: Behavioral performance of each motor sequence task during fMRI measurement at baseline (T0) and after 60 days of training (T1).

	EG		CG	
Condition	T0	T1	T0	T1
FINGER				
No. of blocks (mean, SD)	4.0 (0.0)	4.1 (0.3)	3.8 (1.8)	4.1 (0.4)
No. of sequences (mean, SD)	23.2 (7.8)	23.3 (8.0)	20.1 (10.9)	23.0 (6.0)
Tapping frequency in Hz (mean, SD)	1.42 (0.45)	1.40 (0.41)	1.29 (0.24)	1.38 (0.32)
SIMPLE				
No. of blocks (mean, SD)	4.2 (0.6)	3.9 (0.3)	3.8 (0.5)	3.9 (0.8)
No. of sequences (mean, SD)	20.2 (5.2)	18.1 (3.7)	17.6 (5.4)	20.0 (8.1)
Tapping frequency in Hz (mean, SD)	1.29 (0.29)	1.23 (0.27)	1.25 (0.37)	1.38 (0.42)
COMPLEX				
No. of blocks (mean, SD)	4.2 (0.4)	4.2 (0.4)	4.5 (1.5)	3.9 (0.4)
No. of sequences (mean, SD)	15.2 (7.1)	14.2 (7.3)	14.0 (10.7)	12.8 (9.5)
Tapping frequency in Hz (mean, SD)	1.08 (0.32)	1.03 (0.33)	0.98 (0.48)	1.04 (0.44)
Total blocks recoded/excluded (mean %, SD)	0.04 (0.09)	0.01 (0.02)	0.06 (0.08)	0.04 (0.09)

3.2.1.1.5.3 Effects of training on sensorimotor brain activation

At baseline (T0), brain activation patterns for all six contrasts did not significantly differ on cluster level between the two intervention groups (all cluster level familywise error-corrected [FWEcorr] p≥0.320). At post-training (T1), no whole-brain differences in brain activation patterns were found between the two intervention groups for any one of the six contrasts (all cluster level familywise error-corrected [FWEcorr] p≥0.125).

In the ROI analyses, there was a significant or marginally significant interaction effect between group and time in five of the ROIs for the FINGER > REST contrast (see Table 21 and Figure 9). More specifically, there was a significant group-by-time interaction effect for the left M1 ROI ($F_{1,18.000}$=5.92, p=0.026), the right M1 ROI ($F_{1,18.000}$=8.64, p=0.009), the left PFC ROI ($F_{1,18.000}$=3.14, p=0.093), the right PFC ROI ($F_{1,18.000}$=3.88, p=0.065) and the left PMC ROI ($F_{1,18.000}$=5.50, p=0.031). Group-wise post-hoc tests in these ROIs showed that brain activity (beta values) significantly or marginally significantly decreased in the CG compared to the EG for the left M1 (EG: p=0.355, CG: p=0.032), right M1 (EG: p=0.188, CG: p=0.017), left PFC (EG: p=0.881,

CG: p=0.051) and right PFC (EG: p=0.430, CG: p=0.081) while for the left PMC, brain activity (beta values) marginally significantly increased in the EG compared to the CG (EG: p=0.065, CG: p=0.161). However, these effects were not robust as they were not confirmed in the multiple regression analysis (see Table 24), suggesting that these effects might be biased by differences in baseline brain activity. No interaction effects were found for any other ROI in any other contrast (all p≥0.109).

Table 21. Results Study 2: Mean beta values for five different ROIs for the FINGER > REST contrast at baseline (T0) and after 60 days (T1), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG			CG					
ROI	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	p-value (T0)	Interaction effect (F_{df}- and p-value)	ES
FINGER > REST									
Left M1	0.387 (0.113)	0.468 (0.097)	0.081 (0.063)	0.674 (0.132)	0.384 (0.216)	-0.290 (0.174)	0.132	$F_{1,18.000}$=5.92, p=0.026	0.92
Right M1	-0.190 (0.097)	-0.077 (0.069)	0.113 (0.055)	0.190 (0.091)	-0.108 (0.154)	-0.298 (0.164)	0.011	$F_{1,18.000}$=8.64, p=0.009	1.24
Left PFC	-0.002 (0.102)	0.030 (0.142)	0.032 (0.187)	0.265 (0.194)	-0.329 (0.175)	-0.594 (0.338)	0.757	$F_{1,18.000}$=3.14, p=0.093	1.42
Right PFC	-0.021 (0.091)	0.060 (0.067)	0.080 (0.101)	0.380 (0.099)	0.131 (0.083)	-0.249 (0.129)	0.013	$F_{1,18.000}$=3.88, p=0.065	1.02
Left PMC	-0.079 (0.062)	0.097 (0.059)	0.175 (0.098)	0.148 (0.092)	-0.028 (0.102)	-0.176 (0.090)	0.050	$F_{1,18.000}$=5.50, p=0.031	1.46

CG, control group; EG, experimental group; ES, effect size; M1, primary motor cortex; PFC, prefrontal cortex; PMC, premotor cortex; ROI, region of interest; SE, standard error of the mean.

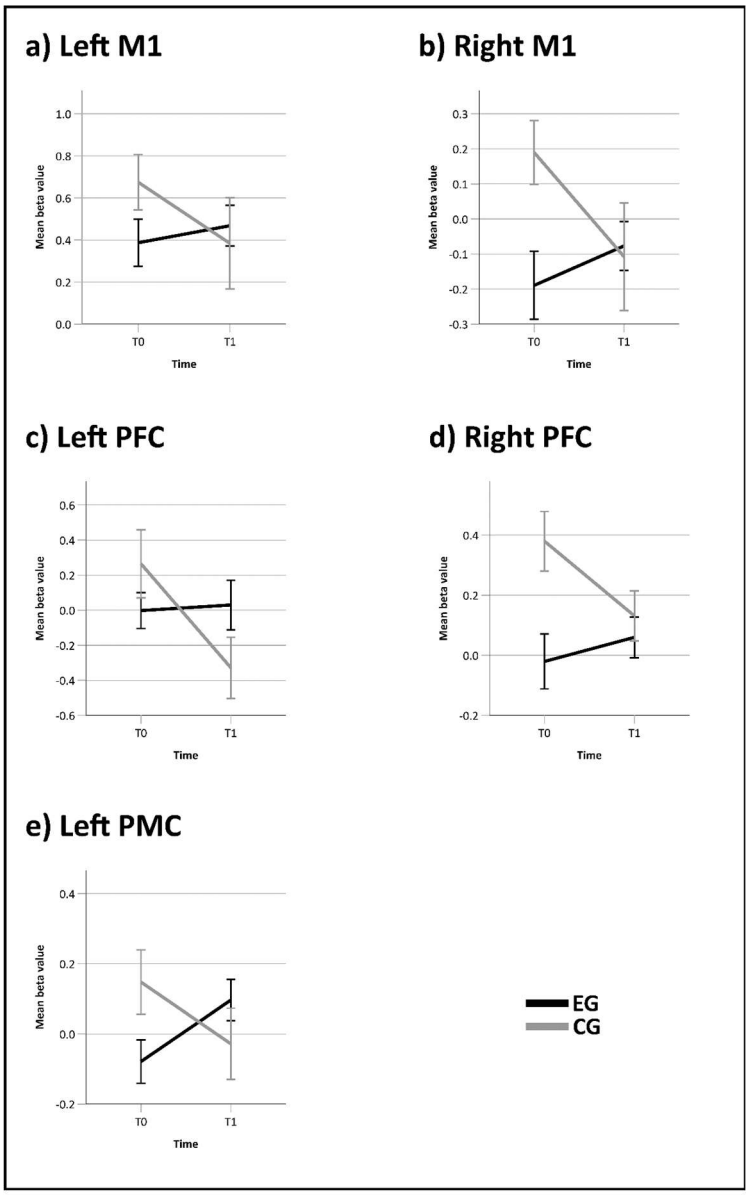

Figure 9. Results Study 2: Illustration of brain activity (beta values) for the FINGER > REST contrast at baseline (T0) and after 60 days of training (T1) for the experimental group (EG) and control group (CG).

Values refer to 5 different ROIs in a) left primary motor cortex (M1), b) right primary motor cortex (M1), c) left prefrontal cortex (PFC), d) right prefrontal cortex (PFC), and e) left premotor cortex (PMC). Error bars represent standard errors of the mean.

3.2.1.1.6 Transcranial magnetic stimulation (TMS) results

3.2.1.1.6.1 TMS sample characteristics

Twenty-four subjects out of the total number of 48 subjects completing T0 and T1 assessments underwent TMS measurement at baseline (T0). Reasons for non-execution of TMS included TMS not being part of the initial procedure (7 subjects), medical contraindications, such as pacemakers (2 subjects), TMS-incompatible implants in head-chest area (9 subjects), a history of stroke or suspected stroke (3 subjects), current intake of medication lowering the convulsive threshold (1 subject), refusal of assessment (1 subject) as well as technical issues during assessment (1 subject). Of these 24 subjects (EG: n=13; CG: n=11), 21 underwent TMS measurement after 60 days of training (T1), with three subjects not being measured due to Covid-19 safety regulations (all three in the CG). The post-treatment assessment of one additional subject in the CG was aborted due to technical issues. Thus, the TMS sample consisted of 20 complete pre-post datasets, 13 in the EG and 7 in the CG. An overview of the baseline characteristics of the TMS sample can be found in Table 22. The two intervention groups did not significantly differ in sample characteristics and measures of frailty (all $p \geq 0.311$). Similarly, the TMS sample did not differ from the rest of the total sample with respect to baseline sample characteristics and measures of frailty (all $p > 0.05$; data not shown).

3.2.1.1.6.2 Effects of training on sensorimotor brain excitability

RMTs and MEP amplitudes did not significantly differ between the EG and CG at baseline (see Table 23). There were no significant group-by-time interaction effects for RMTs or MEP amplitudes (all $p \geq 0.569$) and effect sizes were small (all $d \leq 0.38$).

Table 22[14]. Results Study 2: Baseline (T0) characteristics of the TMS sample.

Characteristic	Total		EG		CG		p-value
	n	20	n	13	n	7	
Age, years (mean, SD)	80.8	7.2	80.0	6.6	82.3	8.6	0.516
Female (n, %)	16	80.0	11	84.6	5	71.4	0.482
Education, years (mean, SD)	13.1	3.1	13.2	3.3	12.9	2.7	0.802
BMI, kg/m² (mean, SD)	29.8	6.1	29.7	7.1	29.8	3.8	0.817
MMSE (mean, SD)	29.0	1.4	29.2	1.2	28.4	1.7	0.311
GDS (mean, SD)	0.8	1.9	0.9	2.2	0.4	1.1	0.643
MNA (mean, SD)	25.7	2.9	25.7	3.4	25.6	1.4	0.438
FP (mean, SD)	1.80	0.52	1.77	0.44	1.86	0.69	0.877
FI (mean, SD)	0.200	0.083	0.184	0.083	0.230	0.030	0.536

P-values refer to the between-group comparison. BMI, body mass index; CG, control group; EG, experimental group; FI, frailty index; FP, frailty phenotype; GDS, Geriatric depression scale; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment.

[14] Height, weight and body mass index were obtained through a physical examination performed by a study physician. GDS data for each subject were acquired by a study physician using a standard questionnaire. Subsequent processing of subject data including statistical analyses were performed by the author of the present dissertation.

Table 23. Results Study 2: Measures of motor cortex excitability obtained through TMS at baseline (T0) and after 60 days (T1), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG			CG					
Measure	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	T0 Mean (SE)	T1 Mean (SE)	Change Mean (SE)	p-value (T0)	Interaction effect (F_{df}- and p-value)	ES
RMT (% stimulator output)	58.3 (2.2)	58.6 (3.6)	0.3 (2.3)	57.9 (4.2)	59.0 (3.5)	1.1 (3.0)	0.918	$F_{1,18.000}$=0.05, p=0.832	-0.09
MEP amplitude at 100 % RMT stimulation (µV)	56.5 (10.7)	61.7 (13.7)	5.1 (19.9)	48.0 (22.2)	34.9 (5.4)	-13.1 (21.4)	0.393	$F_{1,18.000}$=0.38, p=0.546	0.38
MEP amplitude at 110 % RMT stimulation (µV)	185.3 (32.0)	146.2 (32.4)	-39.1 (44.3)	209.3 (97.1)	166.9 (59.7)	-42.4 (100.3)	0.757	$F_{1,18.000}$<0.01, p=0.969	0.02
MEP amplitude at 120 % RMT stimulation (µV)	323.9 (80.5)	441.7 (88.1)	117.9 (80.0)	179.7 (47.7)	281. 5 (79.8)	101.8 (68.4)	0.231	$F_{1,18.000}$=0.03, p=0.861	0.06

CG, control group; EG, experimental group; ES, effect size; MEP, motor evoked potential; RMT, resting motor threshold; SE, standard error of the mean.

3.2.1.1.7 Regression analyses

Results of additional regression analyses are summarized in Table 24.

Table 24. Results Study 2: Intervention effects after 60 days of training as determined by multiple regression analyses, adjusted for age, gender, and baseline performance.

	Group effect		
Measure	β	t (df)	p-value
Frailty measures			
FP (number)	0.318	2.45 (43)	0.018
FI	0.207	1.41 (43)	0.167
Physical activity (kcal/week)	-0.202	-1.80 (43)	0.078
Gait speed (m/s)	-0.128	-1.10 (43)	0.299
Grip strength (kg)	-0.312	-2.26 (43)	0.029
Motor function			
PPT right hand (score)	0.170	1.19 (43)	0.242
PPT left hand (score)	0.030	0.20 (43)	0.839
PPT both hands (score)	-0.087	-0.59 (43)	0.561
PPT assemblies (score)	-0.162	-1.14 (43)	0.262
SPPB (score)	-0.005	-0.03 (43)	0.974
CTSIB	0.068	0.45 (43)	0.657
Sensory function			
Visual acuity (logMAR)	0.204	1.68 (43)	0.099
Visual contrast sensitivity (logCS)	0.042	0.29 (43)	0.774
Hearing threshold right ear (dB)	0.056	0.36 (43)	0.718
Hearing threshold left ear (dB)	-0.087	-0.56 (43)	0.576

AST, Attention Switching Task; CES-D, Center for Epidemiologic Studies Depression Scale; CG, control group; CTSIB; Clinical Test of Sensory Integration of Balance; EG, experimental group; EQ-5D-5L, EuroQol-5D-5L; ES, effect size; FEFA, Frail Elderly Functional Assessment; FES-I, Falls Efficacy Scale – International Version; FI, frailty index; FP, frailty phenotype; IED, Intra-Extra Dimensional Set Shift; M1, primary motor cortex; MCS, mental component summary; MEP, motor evoked potential; MDT, mechanical detection threshold; MKS, Marburg Competency Scale (Marburger Kompetenz Skala); PFC, prefrontal cortex; PMC, premotor cortex; PPT, Purdue Pegboard Test; PCS, physical component summary; RMT, resting motor threshold; ROI, region of interest; RT, reaction time; RTI, Reaction Time Test; SF-36, Short Form-36; SPPB, Short Physical Performance Battery; SSP, Spatial Span Test; [1]Regression analyses of TMS MEP data were additionally adjusted for the pre-post difference in RMT.

Table 24 (continued).

	Group effect		
Measure	β	t (df)	p-value
MDT right hand (mN)	-0.041	-0.32 (43)	0.750
MDT left hand (mN)	0.000	0.00 (43)	0.998
Spatial tactile discrimination right hand (mm)	-0.080	-0.58 (43)	0.566
Cognitive function			
RTI mental speed single choice (ms)	0.022	0.15 (43)	0.879
RTI mental speed five choice (ms)	-0.051	-0.45 (43)	0.657
RTI motor speed single choice (ms)	-0.097	-0.89 (43)	0.377
RTI motor speed five choice (ms)	-0.039	-0.34 (43)	0.734
AST correct trials (%)	-0.001	-0.05 (43)	0.957
AST RT correct trials (ms)	-0.052	-0.37 (43)	0.713
AST switch cost (ms)	-0.039	-0.27 (43)	0.790
AST congruency cost (ms)	-0.144	-0.90 (43)	0.372
SSP working memory span (score)	0.151	1.66 (43)	0.104
IED stages completed (number)	-0.051	-0.49 (43)	0.624
IED total errors (number)	0.001	0.01 (43)	0.992
Clinical characteristics			
FEFA score	-0.026	-0.21 (43)	0.838
CES-D score	-0.075	-0.49 (43)	0.624
SF-36 physical functioning	-0.012	-0.08 (43)	0.933
SF-36 physical role limitations	-0.135	-0.98 (43)	0.333
SF-36 bodily pain	-0.395	-2.94 (43)	0.005
SF-36 general health perception	-0.223	-1.62 (43)	0.112
SF-36 vitality	-0.179	-1.26 (43)	0.216
SF-36 social functioning	-0.057	-0.39 (43)	0.700
SF-36 emotional role limitations	0.156	1.20 (43)	0.238
SF-36 mental health	-0.254	-1.77 (43)	0.083

Table 24 (continued).

	Group effect		
Measure	β	t (df)	p-value
SF-36 PCS	-0.216	-1.49 (43)	0.144
SF-36 MCS	0.015	0.10 (43)	0.922
EQ-5D-5L index	-0.017	-0.11 (43)	0.911
EQ-5D-5L health status	-0.196	-1.35 (43)	0.184
MKS score	-0.037	-0.25 (43)	0.806
FES score	-0.019	-0.13 (43)	0.895
Analysis by BDNF genotype			
FP (number)	0.343	2.67 (43)	0.011
FI	0.249	1.70 (43)	0.096
Physical activity (kcal/week)	-0.182	-1.60 (43)	0.117
Gait speed (m/s)	-0.158	-1.29 (43)	0.204
Grip strength (kg)	-0.333	-2.42 (43)	0.020
fMRI ROI analysis (FINGER > REST)			
Left M1	-0.400	-1.71 (15)	0.108
Right M1	-0.370	-1.72 (15)	0.106
Left PFC	-0.117	-0.75 (15)	0.464
Right PFC	0.010	0.05 (15)	0.958
Left PMC	-0.214	-1.17 (15)	0.261
TMS analysis			
RMT (% stimulator output)	0.104	0.40 (15)	0.697
MEP amplitude at 100 % RMT stimulation (μV)[1]	-0.209	-1.47 (14)	0.164
MEP amplitude at 110 % RMT stimulation (μV)[1]	0.012	0.07 (14)	0.944
MEP amplitude at 120 % RMT stimulation (μV)[1]	-0.284	-1.25 (14)	0.231

3.2.1.2 Results of the 90-day training

3.2.1.2.1 Sample characteristics

Out of the total number of 48 subjects completing T0 and T1 assessments, a number of 17 subjects (EG: n=10; CG: n=9) were able and agreed to continue the last 30 days of the training. One subject in the EG aborted the intervention because the subject was not able to perform the training tasks due to physical issues. Thus, the subsample of subjects completing 90 days of training consisted of 16 datasets, 9 in the EG and 7 in the CG. Table 25 provides an overview of the baseline characteristics of the 90-days sample. The two intervention groups did not significantly differ in sample characteristics (all $p \geq 0.375$) but subjects in the CG engaged for a significantly longer time in the training compared to the EG ($p=0.042$).

Table 25[15]. Results Study 2: Baseline (T0) characteristics and training-related data of the 90-days sample.

Characteristic	Total		EG		CG		p-value
	n	16	n	9	n	7	
Baseline characteristics							
Age, years (mean, SD)	80.8	6.5	80.4	5.4	81.3	8.2	0.790
Female (n, %)	13	81.3	8	88.9	5	71.4	0.375
Education, years (mean, SD)	13.1	3.1	13.2	3.6	13.0	2.7	1
BMI, kg/m² (mean, SD)	29.4	7.6	30.8	9.6	27.7	3.9	0.397
MMSE (mean, SD)	28.9	1.5	28.9	1.6	29.0	1.4	0.918
GDS (mean, SD)	0.3	0.6	0.3	0.7	0.1	0.4	0.758
MNA (mean, SD)	25.3	3.1	25.2	4.0	25.4	1.6	0.872
Training-related data							
Total training time, hours (mean, SD)			38.8	7.7	46.1	3.2	0.042

P-values refer to the between-group comparison. BMI, body mass index; CG, control group; EG, experimental group; GDS, Geriatric depression scale; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment.

[15] Height, weight and body mass index were obtained through a physical examination performed by a study physician. GDS data for each subject were acquired by a study physician using a standard questionnaire. Raw data obtained from the experimental sensorimotor training were analyzed and mean values for each subject were computed by a fellow researcher involved in the cross-project collaboration. Subsequent processing of subject data including statistical analyses were performed by the author of the present dissertation.

3.2.1.2.2 Frailty

For the comparison between T1 and T2, analyses of frailty measures did not show significant main effects of time for the number of FP ($F_{1,14.025}$=0.10, p=0.758) and the FI ($F_{1,14.064}$=0.73, p=0.407) and no significant group-by-time interaction effects were found for frailty measures and FP criteria (all p≥0.124; see Table 26 and Figure 10). When including all three assessments in the model, the main effect of time collapsed across both groups was significant for the FP ($F_{1,14.057}$=7.94, p=0.005) with post-hoc tests showing a decrease in frailty from T0 to T1 (p=0.004) and a marginal decrease from T0 to T2 (p=0.070) but no significant change from T1 to T2 (p=1). The main effect of time was marginally significant for the FI ($F_{1,14.470}$=3.00, p=0.081) and post-hoc tests showed a marginal decrease in frailty across the whole 90-days period from T0 to T2 (p=0.091) while no significant changes were found from T0 to T1 (p=0.538) and T1 to T2 (p=1). Apart from that, no significant time-by-group interactions were found (p≥0.219), except for physical activity ($F_{1,13.999}$=5.19, p=0.021). Post-hoc group-wise comparisons revealed that in the EG, physical activity tended to increase from T0 to T1 (p=0.072) and T0 to T2 (p=0.092) but not from T1 to T2 (p=0.620), while for the CG, no differences were found between T0 and T1 (p=1) and T0 and T2 (p=0.884), but activity decreased from T1 to T2 (p=0.014).

Table 26. Results Study 2: Frailty scores at baseline (T0), after 60 days (T1), and after 90 days of training (T2), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG						CG								ES		
Measure	T0 Mean (SE)	T1 Mean (SE)	T2 Mean (SE)	Change Mean T1-T0 (SE)	Change Mean T2-T0 (SE)	Change Mean T2-T1 (SE)	T0 Mean (SE)	T1 Mean (SE)	T2 Mean (SE)	Change Mean T1-T0 (SE)	Change Mean T2-T0 (SE)	Change Mean T2-T1 (SE)	p-value (T0)	Interaction effect T1-T2 (F_{df}- and p-value)	Interaction effect T0-T1-T2 (F_{df}- and p-value)	T0-T1	T0-T2	T1-T2
FP (number)*	1.78 (0.22)	1.22 (0.32)	1.33 (0.37)	-0.56 (0.24)	-0.44 (0.34)	0.11 (0.26)	2.00 (0.31)	1.29 (0.29)	1.29 (0.42)	-0.71 (0.18)	-0.71 (0.29)	0.00 (0.22)	0.606	$F_{1,14.000}$=0.10, p=0.758	$F_{2,14.000}$=0.18, p=0.835	0.20	0.35	0.12
FI*	0.192 (0.031)	0.181 (0.032)	0.166 (0.034)	-0.011 (0.010)	-0.026 (0.011)	-0.015 (0.011)	0.255 (0.027)	0.243 (0.027)	0.243 (0.033)	-0.012 (0.013)	-0.012 (0.010)	0.000 (0.013)	0.252	$F_{1,14.000}$=0.71, p=0.414	$F_{2,13.999}$=0.49, p=0.623	0.01	-0.15	-0.16
Physical activity (kcal/week)	1981 (372.0)	4020 (835.7)	3507 (634.8)	2039 (931.0)	1525 (760.4)	-513 (412.2)	3203 (518.0)	3877 (376.2)	2406 (399.0)	673 (684.7)	-796 (482.0)	-1470 (394.5)	0.069	$F_{1,13.999}$=2.68, p=0.124	$F_{2,13.999}$=5.19, p=0.021	1.05	1.78	0.45
Gait speed (m/s)	0.821 (0.073)	0.934 (0.104)	0.929 (0.090)	0.113 (0.069)	0.108 (0.049)	-0.005 (0.022)	0.812 (0.082)	0.847 (0.077)	0.859 (0.085)	0.035 (0.025)	0.048 (0.051)	0.012 (0.028)	1	$F_{1,13.997}$=0.23, p=0.636	$F_{2,13.999}$=0.46, p=0.642	0.34	0.26	-0.06
Grip strength (kg)	18.84 (3.19)	20.55 (3.17)	20.84 (2.73)	1.70 (1.05)	2.00 (0.90)	0.30 (0.76)	22.82 (5.03)	22.12 (4.77)	21.70 (2.82)	-0.70 (0.69)	-1.12 (2.56)	-0.42 (2.22)	0.681	$F_{1,14.000}$=0.11, p=0.741	$F_{2,14.000}$=1.70, p=0.219	0.20	0.26	0.06

CG, control group; EG, experimental group; ES, effect size; FI, frailty index; FP, frailty phenotype; SE, standard error of the mean; * lower scores represent better performance.

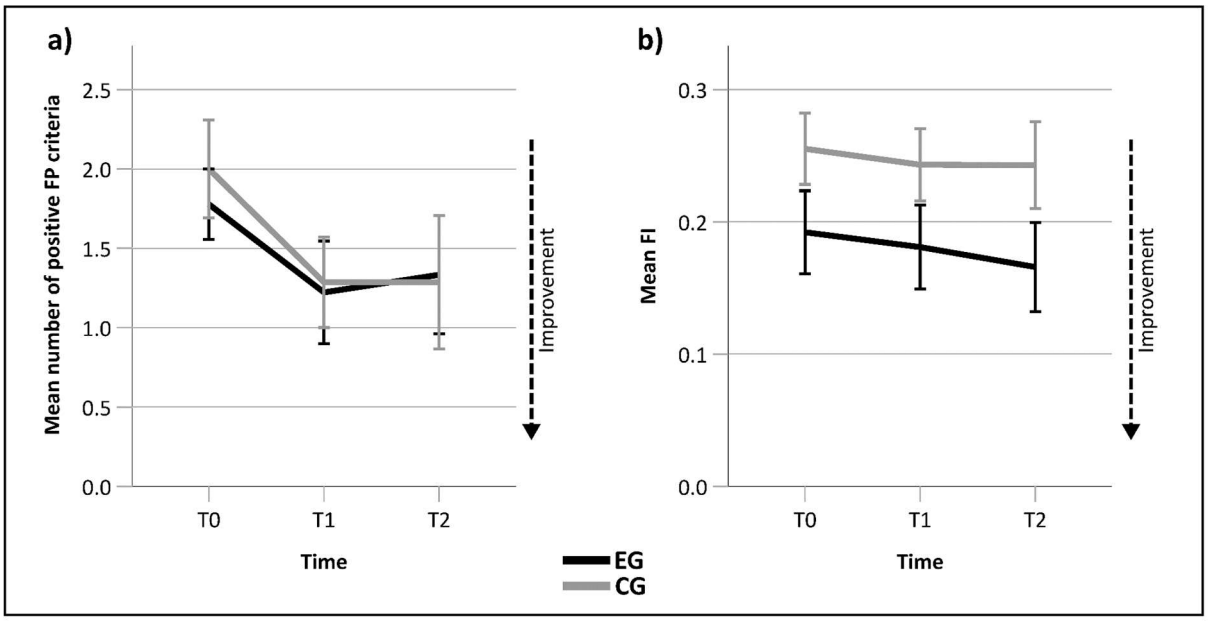

Figure 10. Results Study 2: Illustration of frailty scores for the (a) FP and (b) FI at baseline (T0), after 60 days of training (T1) and after 90 days of training (T2) for the experimental group (EG) and control group (CG).

Error bars represent standard errors of the mean.

3.2.1.2.3 Behavioral and clinical measures

Results on measures of sensory, motor and cognitive ability as well as clinical characteristics are summarized in Table 27. There was an increase in upper extremity motor function in the CG, compared to the EG. More specifically, there was a significant time-by-group interaction effect for right-hand dexterity ($F_{1,14.000}$=4.14, p=0.039). Post-hoc group-wise comparisons showed that in the CG, dexterity increased from T0 to T1 (p=0.011) and T0 to T2 (p=0.013) but not from T1 to T2 (p=1), while for the EG, no differences were found between T0 and T1 (p=1), T0 and T2 (p=1), and T1 and T2 (p=0.786). Additionally, there was a marginally significant time-by-group interaction effect for left-hand dexterity ($F_{1,13.999}$=2.84, p=0.093) and post-hoc group-wise comparisons showed that in the CG, dexterity increased from T0 to T2 (p=0.011), but not from T0 to T1 (p=0.290) or from T1 to T2 (p=1). No significant differences were found for the EG (all p=1). Apart from that, no significant time-by-group interactions were found for other sensory, motor and cognitive variables (all p≥0.119). In the analysis of clinical outcomes, there was a marginally significant time-by-group interaction effect for the SF-36 subscale measuring general health perception across all three assessments ($F_{1,14.001}$=2.98, p=0.083) and post-hoc group-wise comparisons showed that in the CG, general health perception increased from T0 to T2 (p=0.013), but not from T0 to T1

(p=0.211) or from T1 to T2 (p=1). No significant differences were found for the EG (all p=1). No significant time-by-group interactions were found for other clinical variables (all p≥0.140).

Table 27. Results Study 2: Motor, sensory and cognitive performance scores as well as clinical characteristics at baseline (T0), after 60 days (T1), and after 90 days of training (T2), group comparisons of baseline values (p-values) and group-by-time interaction effects from linear mixed model analyses.

	EG						CG								ES		
Measure	T0 Mean (SE)	T1 Mean (SE)	T2 Mean (SE)	Change Mean T1-T0 (SE)	Change Mean T2-T0 (SE)	Change Mean T2-T1 (SE)	T0 Mean (SE)	T1 Mean (SE)	T2 Mean (SE)	Change Mean T1-T0 (SE)	Change Mean T2-T0 (SE)	Change Mean T2-T1 (SE)	p-value (T0)	Interaction effect T1-T2 (F_{df}- and p-value)	Interaction effect T0-T1-T2 (F_{df}- and p-value)	T0-T1	T0-T2	T1-T2
Motor function																		
PPT right hand (score)	10.74 (0.59)	10.96 (0.41)	10.56 (0.59)	0.22 (0.42)	-0.19 (0.22)	-0.41 (0.31)	9.95 (0.83)	11.33 (0.76)	11.48 (0.57)	1.38 (0.28)	1.52 (0.63)	0.14 (0.42)	0.681	$F_{1,13.999}$=1.14, p=0.304	$F_{2,14.000}$=4.14, p=0.039	-0.56	-0.82	-0.32
PPT left hand (score)	9.85 (0.57)	9.52 (0.62)	10.04 (0.60)	-0.33 (0.27)	0.19 (0.31)	0.52 (0.26)	9.14 (0.68)	9.90 (0.68)	10.24 (0.66)	0.76 (0.53)	1.10 (0.23)	0.333 (0.40)	0.435	$F_{1,14.000}$=0.16, p=0.694	$F_{2,13.999}$=2.84, p=0.093	-0.59	-0.49	0.10
PPT both hands (score)	7.89 (0.51)	7.26 (0.51)	7.93 (0.48)	-0.63 (0.27)	0.04 (0.24)	0.67 (0.33)	7.76 (0.73)	7.95 (0.73)	8.05 (0.76)	0.19 (0.27)	0.29 (0.38)	0.10 (0.21)	0.885	$F_{1,14.000}$=1.81, p=0.200	$F_{2,14.001}$=2.28, p=0.139	-0.45	-0.14	0.32
PPT assemblies (score)	18.81 (1.50)	18.44 (1.47)	18.74 (1.39)	-0.37 (1.26)	-0.07 (0.72)	0.30 (0.79)	19.14 (1.16)	19.14 (1.08)	19.33 (1.53)	0.00 (0.69)	0.19 (1.23)	0.19 (0.76)	0.871	$F_{1,14.000}$=0.01, p=0.925	$F_{2,14.000}$=0.03, p=0.972	-0.09	-0.06	0.03
SPPB (score)	8.00 (0.58)	8.00 (0.67)	8.22 (0.80)	0.00 (0.33)	0.22 (0.40)	0.22 (0.28)	7.29 (1.13)	7.43 (1.31)	7.29 (1.25)	0.14 (0.34)	0.00 (0.38)	-0.14 (0.26)	1	$F_{1,14.000}$=0.89, p=0.363	$F_{2,14.000}$=0.45, p=0.647	-0.06	0.09	0.13
Sensory function																		
Visual acuity (logMAR)*	0.45 (0.13)	0.36 (0.11)	0.34 (0.12)	-0.09 (0.06)	-0.11 (0.04)	-0.02 (0.04)	0.29 (0.08)	0.29 (0.07)	0.25 (0.05)	0.00 (0.03)	-0.03 (0.05)	-0.03 (0.03)	0.291	$F_{1,13.996}$=0.07, p=0.802	$F_{2,14.000}$=0.95, p=0.411	-0.27	-0.23	0.05
Visual contrast sensitivity (logCS)	1.20 (0.14)	1.34 (0.21)	1.25 (0.16)	0.14 (0.12)	0.04 (0.09)	-0.10 (0.10)	1.62 (0.18)	1.54 (0.13)	1.56 (0.11)	-0.08 (0.13)	-0.06 (0.12)	0.02 (0.08)	0.082	$F_{1,14.000}$=0.79, p=0.388	$F_{2,14.000}$=0.85, p=0.449	0.48	0.23	-0.21

AST, Attention Switching Task; CG, control group; EG, experimental group; ES, effect size; FES-I, Falls Efficacy Scale – International Version; MCS, mental component summary; PCS, physical component summary; RT, reaction time; SF-36, Short Form-36; SE, standard error of the mean; * lower scores represent better performance.

Table 27 (continued).

Measure	EG						CG						p-value (T0)	Interaction effect T1-T2 (F_{df}- and p-value)	Interaction effect T0-T1-T2 (F_{df}- and p-value)	ES		
	T0 Mean (SE)	T1 Mean (SE)	T2 Mean (SE)	Change Mean T1-T0 (SE)	Change Mean T2-T0 (SE)	Change Mean T2-T1 (SE)	T0 Mean (SE)	T1 Mean (SE)	T2 Mean (SE)	Change Mean T1-T0 (SE)	Change Mean T2-T0 (SE)	Change Mean T2-T1 (SE)				T0-T1	T0-T2	T1-T2
Spatial tactile discrimination right hand (mm)*	3.65 (0.50)	4.28 (0.78)	3.52 (0.43)	0.63 (0.72)	-0.13 (0.40)	-0.76 (0.49)	3.93 (0.40)	3.74 (0.50)	3.58 (0.41)	-0.18 (0.70)	-0.35 (0.42)	-0.17 (0.46)	0.691	$F_{1,14.000}$=0.74, p=0.406	$F_{2,14.000}$=0.38, p=0.694	0.58	0.15	-0.28
Cognitive function																		
AST correct trials (%)	76.4 (6.2)	79.2 (7.2)	82.9 (6.1)	2.8 (2.7)	6.5 (2.3)	3.8 (2.4)	77.2 (8.2)	82.8 (6.4)	79.8 (5.1)	5.5 (5.2)	2.6 (6.5)	-3.0 (3.5)	0.935	$F_{1,14.000}$=2.65, p=0.126	$F_{2,14.000}$=1.34, p=0.293	-0.13	0.19	0.32
AST RT correct trials (ms)*	1156.9 (54.9)	1107.8 (67.6)	1139.5 (79.8)	-49.1 (42.5)	-17.4 (30.6)	31.7 (40.8)	1250.2 (74.8)	1267.1 (93.4)	1198.8 (88.4)	17.0 (39.5)	-51.4 (27.3)	-68.4 (43.5)	0.321	$F_{1,14.000}$=2.76, p=0.119	$F_{2,14.000}$=1.40, p=0.279	-0.35	0.18	0.42
AST switch cost (ms)*	-53.7 (47.9)	-79.0 (39.7)	-92.6 (36.5)	-25.3 (28.5)	-39.0 (26.8)	-13.6 (37.2)	-81.8 (40.0)	-85.4 (38.1)	-139.0 (37.5)	-3.6 (26.0)	-57.2 (39.9)	-53.6 (17.3)	0.672	$F_{1,14.000}$=0.78, p=0.391	$F_{2,14.000}$=0.41, p=0.669	-0.16	0.13	0.34
AST congruency cost (ms)*	125.7 (34.9)	107.8 (36.9)	123.7 (24.7)	-18.0 (28.3)	-2.0 (28.5)	15.9 (29.8)	131.4 (31.8)	100.5 (26.8)	140.5 (26.4)	-31.0 (27.1)	9.1 (34.3)	40.0 (23.8)	0.908	$F_{1,14.000}$=0.37, p=0.555	$F_{2,14.000}$=0.19, p=0.831	0.13	-0.11	-0.24
Clinical characteristics																		
SF-36 physical functioning	40.6 (8.3)	46.1 (9.2)	52.2 (8.4)	5.6 (5.7)	11.7 (3.6)	6.1 (4.9)	38.6 (11.3)	36.4 (12.5)	53.6 (9.6)	-2.1 (2.9)	15.0 (3.8)	17.1 (5.8)	0.887	$F_{1,14.000}$=2.14, p=0.166	$F_{2,13.999}$=1.07, p=0.370	0.27	-0.12	-0.35
SF-36 physical role limitations	25.0 (11.0)	33.3 (11.0)	38.9 (11.9)	8.3 (12.5)	13.9 (8.4)	5.6 (15.5)	17.9 (14.1)	42.9 (16.1)	35.7 (15.3)	25.0 (18.9)	17.9 (11.8)	-7.1 (25.4)	0.681	$F_{1,14.000}$=0.20, p=0.661	$F_{2,14.000}$=0.39, p=0.684	-0.45	-0.11	0.32
SF-36 bodily pain	55.2 (9.8)	56.3 (9.5)	55.9 (8.1)	1.1 (4.0)	0.7 (5.4)	-0.4 (3.9)	47.7 (7.7)	41.1 (7.8)	52.1 (9.2)	-6.6 (3.9)	4.4 (5.0)	11.0 (7.2)	0.575	$F_{1,13.999}$=2.17, p=0.163	$F_{2,13.998}$=1.44, p=0.271	0.28	-0.14	-0.43

Table 27 (continued).

Measure	EG						CG						p-value (T0)	Interaction effect T1-T2 (F_{df}- and p-value)	Interaction effect T0-T1-T2 (F_{df}- and p-value)	ES		
	T0 Mean (SE)	T1 Mean (SE)	T2 Mean (SE)	Change Mean T1-T0 (SE)	Change Mean T2-T0 (SE)	Change Mean T2-T1 (SE)	T0 Mean (SE)	T1 Mean (SE)	T2 Mean (SE)	Change Mean T1-T0 (SE)	Change Mean T2-T0 (SE)	Change Mean T2-T1 (SE)				T0-T1	T0-T2	T1-T2
SF-36 general health perception	51.6 (6.7)	55.0 (5.4)	52.4 (6.6)	3.4 (2.8)	0.9 (2.7)	-2.6 (4.3)	27.9 (4.3)	39.9 (7.0)	40.6 (5.3)	12.0 (8.4)	12.7 (4.3)	0.7 (5.3)	0.015	$F_{1,14.000}$=0.24, p=0.635	$F_{2,14.001}$=2.98, p=0.083	-0.48	-0.66	-0.18
SF-36 vitality	48.9 (6.6)	46.7 (6.9)	48.9 (6.8)	-2.2 (4.5)	0.0 (3.3)	2.2 (4.8)	36.4 (6.2)	35.0 (6.6)	37.9 (6.3)	-1.4 (4.2)	1.4 (3.0)	2.9 (4.1)	0.351	$F_{1,14.000}$=0.01, p=0.923	$F_{2,14.000}$=0.05, p=0.951	-0.04	-0.07	-0.03
SF-36 social functioning	73.6 (9.6)	70.8 (8.1)	81.9 (5.9)	-2.8 (6.5)	8.3 (10.0)	11.1 (8.7)	60.7 (13.5)	62.5 (16.8)	66.1 (9.7)	1.8 (9.2)	5.4 (10.5)	3.6 (13.0)	0.437	$F_{1,14.000}$=0.25, p=0.624	$F_{2,14.000}$=0.15, p=0.861	-0.13	0.09	0.21
SF-36 emotional role limitations	59.3 (15.5)	74.1 (12.1)	77.8 (14.7)	14.8 (13.7)	18.5 (11.3)	3.7 (11.7)	52.4 (16.0)	66.7 (16.3)	52.4 (14.3)	14.3 (16.0)	0.0 (10.3)	-14.3 (14.3)	0.765	$F_{1,14.000}$=0.97, p=0.343	$F_{2,13.999}$=0.95, p=0.412	0.01	0.39	0.43
SF-36 mental health	70.2 (5.8)	72.9 (5.5)	71.1 (6.2)	2.7 (6.0)	0.9 (4.5)	-1.8 (5.5)	66.3 (2.4)	60.6 (8.2)	60.6 (4.8)	-5.7 (6.6)	-5.7 (4.4)	0.0 (5.6)	0.174	$F_{1,14.000}$=0.05, p=0.827	$F_{2,14.000}$=0.64, p=0.541	0.57	0.45	-0.09
SF-36 PCS	33.2 (3.1)	34.6 (3.6)	35.5 (2.5)	1.5 (2.0)	2.3 (1.7)	0.8 (2.5)	29.5 (3.3)	32.4 (2.2)	36.9 (3.0)	2.9 (3.1)	7.4 (1.7)	4.5 (3.6)	0.429	$F_{1,14.000}$=0.75, p=0.401	$F_{2,14.000}$=2.27, p=0.140	-0.15	-0.54	-0.38
SF-36 MCS	47.4 (5.7)	48.5 (5.2)	50.2 (4.2)	1.1 (4.2)	2.8 (3.7)	1.7 (3.7)	42.2 (4.3)	42.1 (7.0)	39.3 (4.3)	-0.1 (4.3)	-2.8 (2.8)	-2.7 (5.4)	0.408	$F_{1,14.000}$=0.48, p=0.499	$F_{2,14.000}$=0.68, p=0.523	0.08	0.36	0.25
FES score*	31.6 (3.9)	31.8 (2.9)	28.8 (2.6)	0.2 (1.5)	-2.8 (1.9)	-3.0 (1.1)	29.3 (3.8)	30.9 (4.9)	29.9 (4.3)	1.6 (1.7)	0.6 (1.3)	-1.0 (1.8)	0.687	$F_{1,14.000}$=0.99, p=0.337	$F_{2,13.996}$=1.05, p=0.375	-0.12	-0.29	-0.18

3.2.2 Interim discussion

The randomized controlled trial described in Study 2 evaluated the effects of an intervention specifically targeted at reversing maladaptive neuroplasticity to promote physical and neuropsychological functioning in frail older adults. In this trial, a sensorimotor training embedded in an app-based at-home training approach was employed and efficacy was compared to an app-based relaxation training. The results after 60 days of training suggest that it might be useful in counteracting frailty. However, the vast majority of secondary behavioral and neurophysiological outcomes did not reveal any significant training effects, thereby not providing insights into potentially underlying neuroplasticity mechanisms.

3.2.2.1 Training effects on frailty and frailty components

First, the results showed that in both groups, frailty as determined by the number of positive FP criteria significantly decreased after the 60-day intervention, with a marginally significant interaction effect suggesting that the decrease tended to be stronger in the EG compared to the CG. Also, the results demonstrated that nearly 30% of subjects in the EG recovered to a condition of robustness, compared to 8% in the CG, and 80% of frail subjects in the EG returned to a pre-frail or robust level after the intervention, compared to 38% in the CG. These findings imply that the use of a sensorimotor training may be useful in addressing physical frailty. These results are comparable with the effects of physical exercise interventions where the frailty reversion rates were 31.4% (Tarazona-Santabalbina et al., 2016) and 41.3% (Ng et al., 2015), respectively. Thus, the present results are consistent with previous findings demonstrating that pre-frailty and frailty are potentially reversible conditions and add knowledge on the utility of a focus on sensory rather than motor tasks.

With respect to individual FP criteria, the strongest improvement in the EG was found for the gait speed criterion. More specifically, prevalence of the gait speed criterion decreased from 54% to 17% in the EG and from 54% to 38% in the CG. With respect to performance values, gait speed improved by 0.084 m/s in the EG suggesting a clinically meaningful change of more than 0.05 m/s (Perera, Mody, Woodman, & Studenski, 2006) compared to 0.029 m/s in the CG. Gait speed has previously been associated with transitions in an individual's frailty status (Fallah et al., 2011). Apart

from proper musculoskeletal and cardio-pulmonary function, maintaining effective gait requires the integrity and complex interaction of distributed brain cortical networks important for initiating and executing movements, processing of sensory information as well as serving attention and cognitive control (Callisaya et al., 2014; K. L. Martin et al., 2013; Wang, Wai, Kuo, Yeh, & Wang, 2008). Correspondingly, previous research demonstrated associations between sensory acuity (Sturnieks, St George, & Lord, 2008) and multisensory integration (Mahoney & Verghese, 2018) with gait.

One potential explanation for the present findings is that the sensorimotor training approach, due to increasing central and peripheral sensory input, promoted subjects to improve their ability to integrate multisensory inputs by which multisensory integration became more efficient in controlling complex motor actions such as posture and gait (Cattaneo, Jonsdottir, Zocchi, & Regola, 2007; Gandolfi et al., 2014). A possible mechanism is the improvement in attentional control (Talsma, Senkowski, Soto-Faraco, & Woldorff, 2010), which, however, was not found in the present cognitive measures. Alternatively, it has been shown that the training-induced narrowing of the temporal binding window, within which concurrent multisensory information is integrated, may increase accuracy and efficiency of multisensory integration and reduce sensory distractibility (Setti, Burke, Kenny, & Newell, 2011). However, these mechanistic interpretations remain hypothetical since the outcome measures used did not include measures of multisensory integration.

There was also a trend towards an increase of hand grip strength for the EG compared to the CG. Grip strength measures have been shown to be predictive of health outcomes (Dodds et al., 2016) and have been extensively used as outcomes in physical exercise interventions in frailty (Liao et al., 2019). However, the low pre-to-post change value of 1.41 kg in the EG is below a clinically meaningful change of 5.0 to 6.5 kg (Bohannon, 2019). In sum, the fact that the EG showed improvements in gait speed and grip strength but not other frailty criteria suggests that the sensorimotor training approach specifically targets mechanisms related to complex motor actions (Cesari et al., 2015).

With respect to clinical outcomes, the treatment-related improvement of bodily pain suggests that the sensorimotor training may also have positive effects on pain. In fact, sensory discrimination training has previously been shown to have the potential of reducing pain by improving sensory discrimination ability and reducing maladaptive cortical reorganization in the somatosensory cortex (Flor, Denke, Schaefer, & Grüsser,

2001). Given that chronic pain seems to be associated with a slower gait in older adults (Ogawa et al., 2020), intense sensory discrimination training can possibly improve pain-related physical impairment in frailty (Nakai et al., 2020).

Notably, there was also an - although much smaller - improvement in frailty after the relaxation control training. Thus, to some degree, improvement in both groups may rely on unspecific treatment effects affecting physical parameters, possibly related to the novelty of actively participating in a trial which is accompanied by increased social contacts and operating on an electronic device among these usually inactive prefrail and frail individuals (Meissner, Distel, & Mitzdorf, 2007; Petrie & Rief, 2019). However, particular properties of the sensorimotor training such as massed sensory and sensorimotor stimulation induced additional treatment effects, as treatment effects in the EG were higher than in the CG. On the other hand, it is conceivable that the effect observed in the CG is due to the specific properties of the relaxation training. Previous research provided evidence for the efficacy of various relaxation, mindfulness and meditation approaches in promoting physical and emotional wellbeing (Geiger et al., 2016), reducing psychological symptoms (Klainin-Yobas, Oo, Suzanne Yew, & Lau, 2015) and promoting neuroplasticity (Tang, Hölzel, & Posner, 2015), though the underlying mechanisms are not fully understood. In fact, the intervention effect in the CG was not related to a particular improvement in one or a few specific FP components indicating that the reduction in frailty in the CG comes from a more general effect on frailty criteria.

The treatment effect that was found for the FP was not reflected in the FI. Regarding agreement of the two frailty measures, there was a moderate correlation of 0.461 for baseline scores and of 0.462 for change scores which is in accordance with earlier studies reporting correlations ranging from 0.361 (Arakawa Martins et al., 2019) to 0.76 (Thompson et al., 2018). However, comparison studies demonstrated substantial diagnostic differences between the two scores (Cesari et al., 2014). Importantly, the two frailty measures propose different concepts regarding the pathophysiological mechanisms underlying frailty. While the FP considers frailty as a biological and physical syndrome, the FI defines frailty as an accumulation of deficits (Searle et al., 2008). A considerable number of these deficits is potentially not modifiable by the present intervention, such as somatic comorbidities. The results suggest that the sensorimotor approach may primarily target the physical characteristics of the frailty syndrome, thus, the FI might be less sensitive in capturing the treatment-specific effects.

There were no significant training effects in secondary outcome measures of sensory function. One potential explanation is that the sensory acuity measures that were used in Study 2 were not sensitive enough and too prone to methodological problems such as response bias or increased within-subjects measurement variability to capture potential changes in sensory function and processing (Humes, Busey, Craig, & Kewley-Port, 2013). Also, sensory decline as determined by simple acuity measures was demonstrated to be only weakly related to age-related functional outcomes, compared to complex temporal sensory processing (Humes et al., 2013). It is conceivable that the sensorimotor training may not have affected sensory acuity per se but rather complex multisensory processing, which were however not directly captured with the present outcome measures.

Primary and secondary outcomes after 90 days of training did not reveal additional training effects, however, improvements achieved during the first 60 days of training were maintained. A larger sample may have been required to find potential effects induced by the sensorimotor integration tasks.

3.2.2.2 Absence of training-induced neuroplasticity effects

There were no robust evidence for training-induced increases in neural efficiency as reflected by changes in sensorimotor brain activity. First, it has to be noted that the subject sample that was used in the present fMRI analyses was reduced (13 in the EG, 8 in the CG), due to a considerable number of participants having contraindications for an MRI assessment. Given that older adults show increased within- and between-subject variability in measures of brain activity (D'Esposito, Deouell, & Gazzaley, 2003; Handwerker, Ollinger, & D'Esposito, 2004), low statistical power in the present analyses might have attenuated the likelihood to observe significant effects. Second, since frailty is a heterogeneous syndrome (Xue, 2011), it can be hypothesized that in different frailty components, structural and functional brain correlates may respond differently to neuroplasticity-oriented sensorimotor stimulation. In fact, previous evidence suggested that not frailty per se, but presence or absence of different frailty components was associated with grey matter volumes in the brain (Nishita et al., 2019). Considering the whole group of frail individuals, these differential relationships may have been missed in the present analyses. Third, it might be that the fMRI motor sequence task used in Study 2 was not sensitive enough to capture training-induced changes in neural processes. Since the motor sequence task did not require subjects to maintain

a certain level of performance (e.g. maintain balance during walking), potentially modifiable compensatory processes probably did not play a role in task performance (Reuter-Lorenz & Cappell, 2008). Finally, the fact that no training effects were observed even in the ROI analyses might be related to the selection and construction of the ROIs based on findings from patients with Parkinson's disease (T. Wu & Hallett, 2005). Due to more pronounced structural and neurodegenerative brain changes in Parkinson's disease (Bohnen & Albin, 2011; Shulman, De Jager, & Feany, 2011), these findings may not be directly transferrable to frailty, reducing the validity of the present analyses.

There were no significant treatment effects in RMTs and MEP amplitudes as a measure of motor corticospinal excitability using TMS. While reduced motor cortical excitability has been shown to be associated with motor deficits in older age (Bhandari et al., 2016; Clark et al., 2015; Fujiyama et al., 2011), studies investigating physical exercise training-induced neuroplasticity using TMS have yielded mixed results with respect to the intensity and duration of the training (El-Sayes et al., 2020; Moscatelli et al., 2020; Turco & Nelson, 2021). Given that the present sensory discrimination and integration training did not explicitly target physical exercise, it might be that it was not potent enough to influence the lowest threshold neurons within the primary motor cortex to induce long-lasting neuroplastic changes (Turco & Nelson, 2021). However, it is possible that potential transient training-induced short-term plasticity effects may have been missed (Turco & Nelson, 2021). Finally, there may be a dissociation between effects on upper and lower limb motor cortex excitability, given that motor control of upper and lower limb muscles differs with respect to the nature of motor tasks performed, the location of representations in primary motor cortex and the corticospinal circuitries innervating the muscles (Kesar, Stinear, & Wolf, 2018). In this context, it can only be speculated about whether it would have been possible to find different neuroplasticity effects on corticospinal excitability of lower limb muscles that potentially underlie the improvement in gait speed and/or frailty observed in the EG.

The BDNF genotype frequency in the total sample of 66.7 % Val/Val homozygotes and 33.3% Met carriers was comparable with the genotype frequencies reported in healthy Caucasian populations (Egan et al., 2003). Moreover, the results indicated an influence of BDNF genotype on pre-to-post changes in frailty as determined by the FP, though the results should be interpreted with caution due to the uneven distribution of BDNF genotypes in the treatment groups and the very low number of Met carriers in the EG.

The results suggest that in the EG, BDNF genotype did not modulate the effect of the sensorimotor training, while in CG, the Met carriers did not benefit from the intervention in the same way as the Val/Val homozygotes. However, possible explanations for these observations remain speculative at this point. While BDNF genotype is known to be a mediator of training-induced neuroplasticity (El-Sayes, Harasym, Turco, Locke, & Nelson, 2019), analysis was limited in the present study due to the small sample size and the uneven distribution of BDNF genotype. Here, larger studies are needed to explore the potential role of BDNF genotype as a predictive biomarker for treatment outcomes in frailty.

3.2.2.3 Strengths and limitations

Study 2 has several strengths. First, Study 2 included an extensive characterization of frailty, as well as physical, sensory, cognitive and neurophysiological functions in a sample of (pre-)frail individuals in order to assess the effects of the present interventions. Second, Study 2 provides promising initial evidence that a sensorimotor training intervention performed at home could possibly help to mitigate frailty extent, declines in physical functioning and, possibly, pain. Thus, the innovative neuroplasticity-oriented approach may stimulate the development and evaluation of new treatment methods targeted at reversing age-related physical and sensorimotor decline. Third, the interventional approach implemented in Study 2 overcomes known problems encountered in frailty intervention studies affecting motivation, adherence and training success (Yardley et al., 2008). The advantages of the present training approach are that the intensive repetition of complex tasks promotes dynamic patient-task interaction and that the adaptive adjustment of task difficulty together with immediate feedback on performance can potentially facilitate sensorimotor learning (G. C. V. Gomes et al., 2018). Thus, this interventional approach provided a feasible way for older people to counteract inactivity and exert a potentially favorable influence on progression of frailty status, which may have the potential for long-term adherence (Callisaya et al., 2021; Valenzuela, Okubo, Woodbury, Lord, & Delbaere, 2018).

Study 2 is also subject to limitations. First, the mechanistic pathways or potential neuroplastic mediators underlying the observed intervention effects on frailty measures could not be determined. The reason is most likely the small sizes of the whole sample as well as of subsamples of fMRI, TMS and the 90-day training, by which statistical power was reduced. Second, due to the lack of a follow-up assessment, there is no

information available about the persistence of the intervention effect and whether it may potentially change the clinical risk profile for long-term adverse health outcomes (Cesari et al., 2015). Third, the present subject sample might represent a selective choice of pre-frail and frail individuals. More specifically, the present exclusion criteria potentially excluded subjects with certain multimorbidities and clinical conditions known to be closely related to frailty and may have favored the inclusion of less frail individuals (Gordon et al., 2017). Thus, it may be that the recruiting and inclusion procedure mainly included subjects with pre-frailty and frailty which was related to (accelerated) aging and less related to comorbidity and disease, limiting generalizability of the present findings to other frailty populations. Finally, blinding of test administrators and participants was not feasible due to logistic and practical issues. Thus, it may be possible that assessor bias and/or participant expectations influenced the observed training effects.

3.2.2.4 Conclusion

This randomized controlled study implemented a neuroplasticity-oriented sensorimotor intervention in (pre-)frail older adults, assuming a major role of the brain in the pathogenesis and potential reversal of frailty. The results provided initial evidence that such an approach based on extensive sensory and sensorimotor stimulation may be beneficial in reducing frailty and physical impairment. However, the underlying mechanisms and clinical value of the interventional approach remain to be determined. Thus, future studies including more subjects representing the whole spectrum of the frailty continuum will be needed to gain insights into potentially underlying neuroplastic mechanisms and the influence of modulatory biomarkers such as BDNF. Also, further studies should examine which contribution and benefits a neuroplasticity-oriented approach might have in the course of a multidomain intervention, i.e. when used in combination with intervention methods proven to effective in frailty (e.g. physical exercise, dietary intervention, cognitive training etc.). Therefore, despite the exploratory character of the study, the present findings may hopefully stimulate future efforts to develop alternative intervention methods to combat frailty-associated degradation mechanisms.

4 GENERAL DISCUSSION

4.1 Summary of findings

The aim of this dissertation was to shed light on an important, yet understudied topic: the relationship between deterioration in sensory and motor systems, and frailty as a manifestation of pathological aging. Two empirical studies were conducted in which the relationship was examined from a methodological and a treatment-oriented perspective. In Study 1, the importance of sensory and motor impairments in the diagnostic characterization of frailty was investigated. In Study 2, the effectiveness of an innovative treatment approach targeting neuroplasticity in sensorimotor systems to counteract sensory and motor impairment and by this, frailty, was evaluated.

Study 1 demonstrated that sensory and motor abilities were independently associated with frailty and thereby provided evidence that decline in sensory and motor systems is likely to be a critical determinant of frailty. Thus, the results of Study 1 provide support for hypothesis 1.1. stating that sensory and motor performance significantly predicts frailty. Study 1 also revealed that while upper extremity motor performance was significantly associated with the FP, lower extremity motor performance, hearing ability and the covariate of depression were significantly related to the FI. This provides support for hypothesis 1.2. stating that relationships of sensory and motor abilities with frailty show differential patterns for the two frailty measures.

The results of Study 2 showed that frailty as determined by the FP was reduced in both the sensorimotor (EG) and relaxation (CG) training group after 60 days of training. While post-hoc tests were significant for both groups, a marginally significant interaction effect indicated that this reduction tended to be stronger in the EG compared to the CG. Therefore, the results only partly confirmed hypothesis 2.1 stating that the sensorimotor training, compared to the relaxation control training, has superior effects in improving frailty. Moreover, activity in sensorimotor brain systems as well as measures of cortical excitability did not significantly differ between pre- and post-training assessments with respect to the intervention condition. Thus, Study 2 did not provide support for hypothesis 2.2. stating that effects of training-induced neuroplastic changes accompany the reduction in the extent of frailty.

4.2 Interpretation of findings

4.2.1 Sensory and motor decline in frailty

In Study 1, motor function in terms of upper extremity dexterity and lower extremity performance was significantly related to frailty compared to pre-frailty as determined by the FP and FI, respectively. These findings are consistent with the large amount of previous evidence demonstrating that physical and motor abilities are important determinants and predictors of frailty (Abellan van Kan et al., 2008; Brown et al., 2000; Davis et al., 2011; Ho et al., 2002; Tay et al., 2019; Theou, Jones, et al., 2011; Toosizadeh et al., 2015). While a mild decrease in motor abilities, including a reduction of muscle strength, a decrease in hand function and a slowing of movements, is also found in non-pathological aging (Beenakker et al., 2010; Bennett et al., 1996; Carmeli, Patish, & Coleman, 2003), motor decline is thought to be exacerbated and accelerated in frailty (Xue, 2011). Previous research suggested that motor decline in frailty is strongly related to a loss of muscle mass, affecting both fine motor (J. A. Martin, Ramsay, Hughes, Peters, & Edwards, 2015; Shinohara, Latash, & Zatsiorsky, 2003) and gross motor skills (Cesari et al., 2006; Wilkinson, Piasecki, & Atherton, 2018). While dysregulations in inflammatory systems have been implicated in the accelerated loss of muscle mass (Roubenoff & Harris, 1997; Visser et al., 2002), the causality of the relationship is still poorly understood (Lowry et al., 2012).

Additionally, in Study 1, reduced sensory function with respect to increased hearing thresholds was identified as a sensory determinant of frailty as classified by the FI. These findings are supported by previous research demonstrating a relationship between hearing impairment and frailty (Doba et al., 2012; Kamil et al., 2014). Apart from auditory perception, sensory impairment in the visual (Klein et al., 2003; Swenor et al., 2020) and somatosensory domain (Vieira et al., 2016) was also associated with the extent of frailty. However, research focusing on the sensory ability – frailty relationship is surprisingly rare. In fact, the decline in sensory abilities appears to play an important role in the development and progression of frailty, though there are still several hypotheses about the underlying linking mechanisms and their directionality. Sensory dysfunction may directly contribute to the development of frailty by affecting walking speed and balance (Swenor et al., 2020, 2015), or it may mediate effects of social withdrawal and physical inactivity on frailty (L. Li et al., 2013; Swenor et al., 2020). Finally, sensory decline and frailty may be affected by similar underlying pathophysiological pathways,

such as hypertension, diabetes mellitus, microvascular disease and inflammatory dysregulation (Gates et al., 1993; Kamil et al., 2014; Liew et al., 2007; Sand et al., 2013; Vieira-Potter et al., 2016). In longitudinal studies, age-related sensory decline was found to be a strong risk factor of pathological conditions of aging including Alzheimer's disease and frailty, preceding the onset of symptoms by several years (Albers et al., 2015; Panza et al., 2018; Tan et al., 2020). The strong implications that sensory loss has with respect to the development of age-related functional decline has even inspired the proposal of a novel sub-phenotype called "sensorial frailty" (Panza et al., 2018). However, further longitudinal studies are needed to characterize the impact of sensory loss on frailty and to disentangle potentially shared pathological pathways and to evaluate causal mechanisms (Tan et al., 2020).

4.2.2 Differentiation between frailty and chronological age

It is important to note that in Study 1, upper and lower extremity motor performance and hearing ability were independently associated with frailty while controlling for age. This suggests that it is not chronological age per se which drives the relationship between sensory and motor functional decline and frailty. While frailty is clearly age-associated, it is widely recognized that it is not the same as chronological age (Fried et al., 2001; Mitnitski, Graham, Mogilner, & Rockwood, 2002; Theou, Jones, et al., 2011). For instance, previous evidence demonstrated that both frailty and chronological age were correlated with physical function but frailty exhibited stronger relationships and remained correlated with physical function when controlling for age, suggesting that the association of frailty with physical function cannot be explained solely by the influence of age (Theou, Jones, et al., 2011). Conversely, it follows that chronological age per se does not necessarily determine the extent of health burden or the risk for developing frailty and thus does not adequately identify the need for support (Elliott et al., 2021). Rather, the focus for the development of effective prevention and treatment strategies should be on the identification of functional determinants such as sensory and motor abilities that are predictive for age-related decline. Correspondingly, inter-individual variation in such determinants may partly provide an explanation for differences between pathological and non-pathological aging (Elliott et al., 2021). Despite the fact that the cross-sectional nature of Study 1 does not allow conclusions about causal mechanisms, the results are consistent with the notion that, although

commonalities exist (Fedarko, 2011), the mechanisms involved in the development of the frailty syndrome differ from the normal, non-pathological aging process (Abellan van Kan et al., 2008; Fulop et al., 2010; Xue, 2011). In this context, Study 1 revealed that there are functional sensory and motor determinants of frailty independent of chronological age, which might represent useful targets for interventional approaches to counteract frailty.

4.2.3 The problem of having different frailty instruments for operationalizing and treating frailty

Among the numerous concepts, models and measures of frailty that have been developed within the last 20 years, the FP and FI have crystallized as the most widely used in scientific research and clinical practice, yet there is no clear gold standard for defining and operationalizing frailty (Bergman et al., 2007; Gobbens et al., 2010). Both approaches have in common that they identify individuals who are at an increased risk of adverse health outcomes and mortality by considering multiple factors and biomarkers that go beyond the explanatory value of chronological age (Kulminski et al., 2008). Rather, frailty is seen as an age-related, multiply determined loss of ability to respond to common stressors, which arises from the reduction of physiological reserve capacity. In this vein, both classifications take into account that people may age at different rates and individuals of the same age may have different risk profiles of mortality (Howlett, Rutenberg, & Rockwood, 2021). Apart from the commonalities, previous comparative studies reported considerable discordances in diagnostic, predictive and conceptual characteristics of the two frailty models (Blodgett et al., 2015; Mitnitski et al., 2011; Theou et al., 2014; Woo et al., 2012). In this sense, the results of Study 1 are consistent with the notion that these two frailty tools are distinct and measure overlapping but differing constructs. In particular, the moderate agreement and diagnostic agreement of 75 % between the two scores found in Study 1 parallels earlier findings showing that different frailty tools may capture distinct but overlapping populations (Aguayo et al., 2017) and should therefore be used in a complementary rather than interchangeable manner (Cesari et al., 2014).

Part of this disparity is likely related to the differential underlying frailty mechanisms and concepts of the two models. The FP views frailty as consisting of a phenotype or biological syndrome that underscores physical decline. The FP hypothesizes frailty to

stem from a biological process reflecting a progressive multi-system dysregulation in distributed but interrelated key physiological and biological systems, thereby lowering the systems' functional capacity to respond to stressors and increasing vulnerability of the individual (Rodríguez-Mañas & Walston, 2017). In this sense, the physical FP describes a specific pathophysiological syndrome, which often presents in the absence of disease or disability, thereby aiming at disentangling frailty from disability and multimorbidity (Fried et al., 2021). However, one limitation of the FP is that it does not consider the role of cognition and psychosocial factors, which were demonstrated to improve the predictive ability (Pilotto et al., 2012). The FI in turn considers frailty as a general age-related health condition that is proportional to the number of age-related health deficits, clinical conditions, symptoms, diseases and disabilities an individual has accumulated over time and by which the risk of poor outcomes is heightened (Howlett et al., 2021). The FI therefore emphasizes the multidimensional deterioration and loss in many areas of functioning including not only physical, but also nutritional, psychological, cognitive and social domains (Panza et al., 2011; Searle et al., 2008). It has been argued that a multidimensional operationalization of frailty may be particularly sensitive in capturing subclinical and age-related comorbidities and various stressors (e.g. sensorial deficits, psychosocial stress, diseases, injuries) that contribute to an accelerated functional decline of several systems and hence a physiological disbalance leading to frailty (Lim et al., 2020; Panza et al., 2018; Xue et al., 2020).

Considering the heterogeneity of the aging process, the differences between instruments may constitute a potential risk for misclassification of older adults. When older persons with different underlying pathophysiologies that determine their frailty status are assessed by the one or the other instrument, the result may be different, which could directly influence the decision about curative measures to be taken. Various definitions of frailty have contributed to the controversy over which components should be included in the frailty syndrome (Aubertin-Leheudre, Woods, Anton, Cohen, & Pahor, 2015). This emphasizes the practical difficulty in choosing a frailty screening instrument and interpreting the discordances (Xue et al., 2020). Moreover, the fact that different instruments may identify different subtypes of older adults as frail limits comparability and cross-validation of findings obtained with different instruments and may hamper the identification of etiological factors, which is essential for developing targeted frailty prevention and treatment measures. Yet, little is known about the factors that may determine the diagnostic and predictive differences between the two

instruments or among the older adults that either instrument classifies as frail (Xue et al., 2020). Study 1 provided evidence that frailty as defined by the physical FP is predominantly characterized by physical and motor determinants. In turn, frailty as determined by the FI may be characterized by shared and/or mediated mechanisms with a broader range of deficits, including sensory, motor and psychological determinants, possibly due to the multidimensional nature of the FI. This raises the hypothesis to be further tested in future studies, whether sensory and motor abilities constitute a discriminatory factor to explain differences between older adults for whom frailty classification by the two frailty instruments agrees or disagrees.

While evidence for the relationship of sensory and motor decline with frailty as well as for diagnostic discordances between the FP and FI is not new, the scientific value of Study 1 consists in the integration of these findings. Most previous studies focused on one or few selected sensory and motor domains, used bias-prone self-report measures or used different outcome measures reflecting frailty, thereby limiting comparability of the findings (e.g. Brown et al., 2000; Castell et al., 2013; Davis et al., 2011; Kamil et al., 2016, 2014; Ng, Feng, Nyunt, Larbi, & Yap, 2014; Swenor et al., 2020; Vieira et al., 2016). However, in Study 1, objective measures of several key sensorimotor systems were simultaneously used to map independent physiological relationship with frailty and these relationships were compared between two established and widely used frailty instruments. The key messages of Study 1 are that decline in different sensorimotor systems is independently associated with frailty and that these relationships may depend on the frailty concept employed. Thus, sensory and motor systems may represent meaningful targets for frailty intervention. In this sense, Study 1 provides the methodological basis for Study 2 in which the efficacy of a neuroplasticity-based sensorimotor training was evaluated.

4.2.4 Integration of the training results into existing treatment approaches in frailty

The results of Study 2 provide support for the increasing view that frailty is potentially modifiable and reversible (Howlett et al., 2021). The neuroplasticity-oriented sensorimotor training described in Study 2 substantially differs from previous interventional approaches in frailty, therefore comparability is limited. The major type of intervention used to ameliorate frailty so far is physical exercise. This kind of intervention was

systematically shown to be effective in improving muscle strength and mass, balance, mobility and activity level (Byrne, Faure, Keene, & Lamb, 2016; Lazarus et al., 2018) as well as reducing the risk of falls (Theou, Stathokostas, et al., 2011). Moreover, multi-component physical exercise interventions including for instance physical exercise, cognitive training and nutritional support were found to have the potential to reverse frailty and improve cognition as well as psychological and social functioning (Cesari et al., 2015; Ng et al., 2015; Tarazona-Santabalbina et al., 2016).

Interventional approaches specifically targeting neuroplasticity in frailty have not explicitly been reported so far. One study showed an improvement in executive function as well as a decrease in activation of the prefrontal cortex during a global cognition test after physical exercise training in frailty, presumably reflecting a training-induced increase in neural efficiency (Liao et al., 2021). Empirical support for training-induced neuroplastic changes was demonstrated in pathological conditions other than frailty. For instance, training-induced changes in sensorimotor and cognitive function were found to be accompanied by plastic changes after cognitive and sensorimotor training in patients with mild cognitive impairment, Parkinson's disease and multiple sclerosis (Fling, Martini, Zeeboer, Hildebrand, & Cameron, 2019; Giehl et al., 2020; Iordan et al., 2020; Liao et al., 2020; Maidan et al., 2017; Nguyen et al., 2019; Vermeij et al., 2017). In this sense, Study 2 was conceived to fill a gap in previous research by using frailty extent as an outcome of a neuroplasticity-based intervention.

While the neuroplasticity-based concept investigated in Study 2 considerably differs from conventional physical interventions, it is conceivable that they both share common modes of actions that determine their respective efficacy. For instance, the effectiveness of physical exercise is probably due to the fact that it acts on multiple different subsystems simultaneously, including the musculoskeletal, metabolic, immune and stress-response system (Fried et al., 2021). A corresponding mode of action may also be transferable to neuroplasticity-based approaches, albeit restricted to the neuronal level. Given that initial evidence also suggested a multi-system decline in several structural (Nishita et al., 2019) and functional (Lammers et al., 2020; Suárez-Méndez et al., 2020) brain networks associated with frailty, the sensorimotor training used in Study 2 has been designed to stimulate several sensory and motor cortical networks simultaneously in order to increase cortico-cortical connectional strength and thereby promote Hebbian plasticity and learning (Mahncke, Bronstone, et al., 2006).

Despite the demonstrated efficacy of previous approaches, the type, intensity, frequency and duration of interventional measures such as physical exercise that may be most effective for a frail individual is less clear (Silva, Aldoradin-Cabeza, Eslick, Phu, & Duque, 2017). Given the heterogeneity and inter-individual variability associated with frailty, the individual dose-response relationship is critical for defining optimal levels of activity (Merchant, Morley, & Izquierdo, 2021; Silva et al., 2017). Correspondingly, individualized exercise interventions were found to be more effective in improving physical outcomes than usual care (Sáez de Asteasu et al., 2019). Similar principles have been identified for neuroplasticity-based interventions by studies showing that neuroplasticity is hampered when the difficulty of a given task is too high or too low (Merzenich et al., 2014; Nahum et al., 2013). Therefore, an adaptive, individualized approach to manipulate task difficulty was also used in the present training program. However, future studies are needed to evaluate the optimal dose of sensorimotor stimulation to most effectively induce neuroplasticity. This will help to determine the specific characteristics of such an intervention which could be critical to whether a particular intervention is successful or not. Yet, evidence for this mechanism is lacking in the present study.

It has to be noted that findings from previous interventional studies are mixed and are difficult to compare, possibly because these studies did not always use frailty as outcome, used varying definitions of frailty, or did not define frailty using validated criteria (Daniels, Metzelthin, van Rossum, de Witte, & van den Heuvel, 2010; Giné-Garriga, Roqué-Fíguls, Coll-Planas, Sitjà-Rabert, & Salvà, 2014; Puts et al., 2017). In Study 2, the direct effect on frailty itself was examined by using two widely used and well validated frailty measures as primary outcomes. Importantly, the training effect was only reflected in the FP, but not in the FI. The strength of the relationship between baseline frailty scores determined by the FP and FI was moderate and was comparable to the relationship observed in Study 1[16]. Also, the relationship of frailty change scores was moderate, but significant. These findings parallel the results obtained in Study 1, suggesting that these two frailty tools are distinct and measure overlapping but differing

[16] It has to be noted that the data in Study 1 and Study 2 stem from the same overall subject sample, yet the samples in the two studies are not identical. For instance, in Study 1, baseline data from the treatment sample was used, hence including subjects who may have dropped out after baseline assessments or during the course of the treatment. These subjects however were not considered for the analyses in Study 2.

constructs. Moreover, Study 2 provided evidence that the use of different frailty measures not only plays a role in determining the actual frailty condition, but also in evaluating change through an intervention. Study 2 implied that comparability between interventional studies using different frailty instruments as outcomes may be limited. Therefore, the methodological considerations derived from Study 1 are also of practical significance.

Possible explanations for this discrepancy are related to the conceptual and operational differences between the two scores, as described above. The FP was argued to capture phenotypic physical decline while excluding disability measures to identify individuals at risk rather than those who are already disabled (Fried et al., 2021; Rodríguez-Mañas & Walston, 2017). Therefore, the FP may be particularly sensitive to detect subtle changes in physical performance measures such as gait speed, balance or muscle strength in non-disabled people (Fried et al., 2021; Rodríguez-Mañas & Walston, 2017). Given that a major part of the sample in Study 2 consisted of pre-frail and non-disabled frail subjects, the reduction of the FP suggests that the training program may have a positive effect on precursory risk factors before a state of overt frailty and subsequent disability establishes. In turn, the FI, due to its multidimensional and continuous character, was assumed to be more sensitive in capturing relationships between frailty and decline in various interrelated systems, as also shown in Study 1. However, because of the multitude of potential items assessed, some of which represent nonmodifiable preexisting comorbidities and disabilities, it may be less sensitive to intervention-induced changes in a single one of these subsystems because the effect may be masked within the overall index (Fried et al., 2021; Rodríguez-Mañas & Walston, 2017). The at least marginal main effect for the FI found in Study 2 suggests that larger effect sizes and/or greater statistical power may be required for such an effect to be observable in the FI. Together, these results again illustrate that frailty instruments should be carefully selected according to the purpose and different instrument should not be used interchangeably. A major challenge for future research is to explore how these tools, which were created to identify frailty pathology, can be reliably used to monitor intervention-induced changes in intrinsic domains of sensory, motor, physical, cognitive, psychosocial and everyday functioning (Merchant et al., 2021).

4.2.5 Frailty-related neuroplastic changes

Neuroplastic changes in pathological and non-pathological aging have been described to represent pathogenic or compensatory mechanisms associated with functional consequences (Cramer et al., 2011). For instance, reduced gray matter volume in frontal regions has been associated with reduced gait performance (Callisaya et al., 2014; Rosano et al., 2012). Moreover, brain activity associated with cognitive and sensory (Cabeza, 2002; Reuter-Lorenz & Lustig, 2005; Zanto & Gazzaley, 2017) as well as motor processing (Bernard & Seidler, 2012; Heuninckx et al., 2008; Ward, 2006) was found to be more widespread and less specific in older compared to younger adults. These reductions of neural specificity were related to functional impairments in sensorimotor performance (Bernard & Seidler, 2012; Cassady et al., 2019; Fettrow et al., 2021; Seidler et al., 2010; Sleimen-Malkoun et al., 2014). While these mechanisms have been reported in healthy older adults and pathological aging conditions such as Parkinson's disease (Poston et al., 2016; T. Wu & Hallett, 2005) and mild cognitive impairment and dementia (Celone et al., 2006; Dickerson et al., 2005; Hämäläinen et al., 2007), preliminary evidence suggested that such mechanisms may also contribute to frailty (Lammers et al., 2020; Pelicioni et al., 2021). However, studies demonstrating direct associations between the frailty syndrome and structural and functional brain changes are rare (W. T. Chen et al., 2015) or failed to find such associations (Nishita et al., 2019). Given that frailty is a heterogeneous syndrome associated with multisystem decline, frailty per se may not be universally associated with a certain brain parameter. Also, it may be that such associations are masked by salient pathologies such as neurodegeneration or inflammatory and metabolic dysregulation. Correspondingly, it may be that potential neuroplasticity effects induced by the sensorimotor training greatly vary between the subjects due to differences in underlying frailty pathologies, which would require a large number of subjects to find such effects on the neuronal level. Moreover, a larger number of subjects would enable to examine different subtypes of frailty stratified by means of the presence/absence of certain deficits and of performance measures. Thus, one explanation for the absence of neuroplasticity effects in Study 2 may be a lack of statistical power.

4.2.6 Mechanisms of sensorimotor plasticity

One hypothesis is that age-related neuronal alterations partly result from reduced engagement in cognitively demanding and stimulating tasks, degraded sensory input and/or weakened neuromodulatory control (Cramer et al., 2011; Hertzog et al., 2008; Mahncke, Bronstone, et al., 2006), which opens possibilities for preventive interventions targeting to promote beneficial brain plasticity. Previous neuroplasticity-based interventions were found to be effective in enhancing cognitive control in healthy older adults (Anguera et al., 2013), improving cognitive impairments in schizophrenia and increasing resilience against neurodegenerative disease onset (Merzenich et al., 2014; Nahum et al., 2013). The training program evaluated in Study 2 has been developed according to principles of sensory and motor plasticity that have previously been identified in interventional and experimental studies. As discussed in Study 2, these mechanisms may have reduced impairments in complex motor behavior, such as gait and hand grip.

The sensorimotor training has been designed to strongly engage the brain through extensive sensory and motor stimulation (Mahncke, Bronstone, et al., 2006). In this context, task difficulty was continuously adapted according to the user's performance (Engineer et al., 2012) in order to increase the signal-to-noise ratio of information processing in the brain (Dosher & Lu, 2017; Lu & Dosher, 2008). The signal-to-noise ratio in central processing has an impact on accuracy and reaction time of a certain behavior and is determined by the ability to extract the signal or by reducing noise, or both. In this context, noise can arise intrinsically from noisy patterns of neuronal firing across populations during stimulus encoding, or extrinsically by variability in the stimulus itself (Faisal, Selen, & Wolpert, 2008). Previous evidence suggested that age-related noisy central processing play a role in the general cognitive (Mahncke, Bronstone, et al., 2006) and sensorimotor (Seidler et al., 2010) decline.

Unimodal sensory discrimination tasks were designed to counteract the age-related reduced distinctiveness of perceptual representations in the visual, auditory and somatosensory domain (Goh, 2011). Stimuli were trained on multiple feature dimensions and response types to overcome the drawback of high stimulus specificity that was hypothesized to be responsible for the absence of sensory training effects in past studies (Deveau & Seitz, 2014). Moreover, the training program included bimodal sensory integration tasks since behavior is largely determined by integrating coincident information across multiple sensory modalities. In this context, the proposition of a temporal

binding window of multisensory integration has been made (Wallace & Stevenson, 2014) within which paired events in different sensory modalities are likely to produce enhanced neuronal, perceptual, and behavioral responses (Brang, Taich, Hillyard, Grabowecky, & Ramachandran, 2013; Stein & Stanford, 2008). The temporal binding window tends to become larger with increasing age (Diederich, Colonius, & Schomburg, 2008), potentially in order to compensate for the decline in overall sensory acuity (Owsley, 2011). Along with that, perception might also become more susceptible to interference from task-irrelevant information that should not be integrated (Poliakoff, Ashworth, Lowe, & Spence, 2006). It could be that the sensorimotor training improved central multisensory integration and thereby ameliorated the ability to overcome sensory conflicts resulting from contradictory afferent input from different senses. This is in line with previous studies demonstrating that multisensory simultaneity training in older adults can lead to a refinement of multisensory temporal discrimination and generalization to non-trained tasks, suggesting multisensory plasticity even in old age (Setti et al., 2014). Also, previous research found that targeting the improvement of sensory integration through training can result in sensory facilitation, which promotes a more effective use of motor strategies important for complex motor behavior (Cattaneo et al., 2007; Gandolfi et al., 2014).

Finally, the training program included sensorimotor integration tasks aimed to improve central nervous processing and integration of sensory information to support motor action execution. While these tasks did not play a role for the effects found after 60 days of sensory discrimination training (sensorimotor integration tasks were provided during the last 30-day period following interim T1 assessment), the sensory discrimination training may already have stimulated and facilitated neuromuscular control mechanisms involved in upper and lower extremity motor function (Dunsky, 2019; Hassan, Imani, & Duque, 2019). The successful generation of movements requires a continuous adjustment of motor commands and the development and constant verification of a sensory plan (Darainy, Vahdat, & Ostry, 2013). Correspondingly, deficits in perceptual discrimination and detection have been linked to deficient motor control in healthy aging (Seidler et al., 2010) and disease (Konczak et al., 2012). In these cases, motor behavior and control are impaired in that goal-directed movements exhibit less precision and greater variability due to neuronal noise in sensorimotor control (Seidler et al., 2010; Van Beers, Baraduc, & Wolpert, 2002). In this context, the term “motor acuity” has been proposed referring to an increased precision and reduced variability

of motor performance. Also, evidence suggested that motor acuity training may decrease movement variability and promote learning-related changes in primary and premotor cortical areas, presumably due to an increase in signal-to-noise ratio in sensorimotor representations (Shmuelof et al., 2014).
However, it is still unknown whether the neuroplasticity mechanisms hypothesized to drive these effects may also transfer to frailty. In particular, frailty may modify the effectiveness of interventions previously found to be successful in non-frail patients, thus limiting their generalizability. Therefore, principles of previous neuroplasticity-based approaches probably need to be adjusted to be effective in frailty.

4.2.7 BDNF

The results of Study 2 were inconclusive with respect to the potential influence of the BDNF biomarker on training-induced effects and neuroplasticity. The results indicated an influence of BDNF genotype on pre-to-post changes in frailty, with no improvement in frailty seen in Met-carriers in the relaxation training group compared with the other groups. However, these results should be interpreted with caution due to the uneven distribution of BDNF genotypes. Moreover, due to reduced number of subjects for whom brain data were available, the study did not allow the analysis of the BDNF genotype-mediated interaction with brain plasticity and learning capacity. In general, the neuronal growth factor BDNF is known to promote neuroplasticity, neurogenesis, synaptogenesis and learning (Egan et al., 2003; E. J. Huang & Reichardt, 2001; Ziegenhorn et al., 2007). More specifically, physical therapy in pre-frail individuals was found to increase reduced plasma levels of BDNF, suggesting that BDNF is a key neuromodulatory factor in mediating the syndrome of frailty (F. M. Coelho et al., 2012). Hence, information about peripheral BDNF levels in Study 2 could have helped to draw conclusions about potential neuroplasticity effects underlying the treatment effect seen in frailty, which the other neurophysiological measures (brain activation assessed by fMRI and brain excitability assessed by TMS) were not able to capture.
The Val66Met polymorphism has been related to reduced secretion and activity-dependent release of BDNF, reduced grey matter volume and impaired memory and motor learning (Egan et al., 2003; Pearson-Fuhrhop & Cramer, 2010), however, the relationship between the BDNF polymorphism and frailty is less well understood.

Therefore, further studies are needed to explore the potential role of the BDNF genotype as a predictive biomarker or mediator of treatment outcomes in frailty.

4.2.8 Frailty and pain

Study 2 revealed that bodily pain was significantly reduced in the EG, but not the CG, after 60 days of training. Chronic pain is a common symptom among community-dwelling older adults affecting more than half of people aged 65 and above (Liberman, Freud, Peleg, Keren, & Press, 2018). Previous studies have also reported an association between chronic pain and low physical activity levels (Plooij, Scherder, & Eggermont, 2012), decline in physical functioning, limitations in the activities of daily living and poor psychological status (Eggermont, Penninx, Jones, & Leveille, 2012). Correspondingly, persistent pain has been identified to be a strong risk factor for the development of frailty (Saraiva et al., 2018).

A considerable amount of research demonstrated that chronic pain is associated with neuroplastic reorganization in somatosensory and motor systems (Flor, 2003; Kuner & Flor, 2016). More specifically, the amount of reorganizational structural and functional changes in the brain, including expansion and shifts in the cortical representation of somatosensory and motor maps, altered functional connectivity as well as alterations in grey matter volume and white matter integrity, has been found to increase with chronicity and to be correlated with the amount of pain (Flor, 2003; Kuner & Flor, 2016). Importantly, these neuroplastic changes have been found to be responsive to targeted treatments aiming at normalizing representational changes and decreasing pain (Moseley & Flor, 2012). For instance, somatosensory discrimination training in upper-limb amputees has been found to improve tactile acuity, reduce phantom limb pain, and reverse shifts in cortical somatosensory representations (Flor et al., 2001). Also, motor training such as mirror therapy and motor imagery was shown to have the potential of normalizing altered motor representations and reducing pain (Moseley & Flor, 2012).

One potential explanation for the positive treatment effect on pain observed in the EG is that intense sensory discrimination training may have reduced age-related changes in cortical representations potentially contributing to pain such as an increased overlap and reduced specificity of sensory and motor maps (Bernard & Seidler, 2012; Flor, 2003; Kuner & Flor, 2016; Mahncke, Bronstone, et al., 2006). However,

somatosensory discrimination training in Study 2 was restricted to the index finger tip, thereby primarily targeting sensory processing in cortical representations of the hand and the fingers. In fact, targeting specific sensory representations to modulate pain requires the delivery of stimuli to the particular body part associated with neuropathic or musculoskeletal pain, such as the stump in amputees with phantom limb pain (Flor et al., 2001) and the back in chronic back pain patients (Flor, Braun, Elbert, & Birbaumer, 1997). Since the pain subscale of the SF-36 does not provide information about the particular site and expression of pain, it is unclear whether somatosensory discrimination training at the index fingers may have improved pain in the hand or upper extremities, possibly associated with age-related arthritis and/or osteoarthritis. Alternatively, it may be that the sensorimotor training improved sensorimotor efficiency, thereby positively affecting motor control for complex motor actions such as gait, as described above. In fact, altered motor control and dysfunctional motor behavior have been implicated in the development and persistence of pain (Schmid, Bangerter, Schweinhardt, & Meier, 2021). Thus, one hypothesis is that by reducing age-related maladaptive motor behavior such as movement slowing, the sensorimotor training may have had a beneficial effect on pain. However, future studies will be needed to more precisely characterize pain phenomena associated with frailty and to disentangle potential interacting mechanisms of neuroplasticity, sensorimotor function and pain in frailty.

4.3 Limitations

The conclusions that can be drawn from Study 1 are that a comprehensive frailty screening tool should include performance-based assessment of sensory and motor function, and that the selection of a suitable frailty instrument should be made with careful consideration of the intended purpose. However, one limitation of Study 1 is that the results do not provide direct guidelines for clinical practice, e.g. in the sense of a modified or “improved” frailty score. In fact, given the heterogeneity of the various existing frailty tools and the associated uncertainties in their application, the intention of Study 1 is not to contribute to this uncertainty. Rather, the value of Study 1 can be seen in that it adds to the body of research aiming to identify determinants and pathological mechanisms in order to approach consensus in the definition of a generally accepted, clinically valid, diagnostically feasible and scientifically meaningful concept of frailty.

Another limitation of Study 1 is that the cross-sectional nature and the use of behavioral performance measures of sensory and motor function do not provide insights into the mechanisms underlying their relationship with frailty, particularly with respect to the postulated maladaptive neuroplastic alterations. Various shared as well as uni- and bidirectional mechanisms were hypothesized to drive the relationship of sensory and motor decline with frailty. In turn, maladaptive neuroplasticity has been implicated in multiple domains related to frailty, including sensory, motor and cognitive function. However, neuroscientific studies using frailty as the target variable are still largely lacking. Therefore, the role that maladaptive neuroplasticity in the sensorimotor system may play in the development and maintenance of the frailty syndrome is still poorly understood.

Study 2 provided evidence for a positive effect of the sensorimotor training on reducing frailty, yet the mechanisms underlying this effect remain elusive. The study setting might not have been optimal for the intended research purpose which might have promoted methodological imponderables and reduced the statistical power to detect potential treatment effects in the outcomes. For instance, recruiting (pre-)frail subjects from the community was time-consuming and the requirement to participate in a multi-month program, including several on-site examination appointments, has probably deterred numerous candidates, limiting the potentially available number of subjects. The strict study inclusion and exclusion criteria likely promoted the inclusion of less frail individuals who might have benefitted less from the intervention compared to

individuals with higher degrees of frailty, limiting generalizability of the findings to an unselected population of frail individuals. In addition, medical contraindications excluded a considerable number of subjects from brain imaging assessments. Also, the question remains as to what extent the training effects on frailty components may transfer to improvements in clinical outcomes. An explanation could be that longer training periods are required to obtain benefits on clinical outcomes or that potentially training-induced changes in frailty status and motor functioning have a delayed effect on clinical measures. Thus, longer training periods and follow-up assessments are warranted in future studies. Similarly, the duration of the training may not have been sufficient to induce stable plastic changes in the brain. Therefore, future interventional studies should be designed in a way that lowers the threshold for participation, includes a representative sample including different subpopulations of frail individuals to increase generalizability of the findings, use neuroscientific methods that are less strict with respect to contraindications and include longer training periods and follow-up assessments to examine the time course and stability of potential training effects.

Finally, it has to be discussed whether the neuroplasticity-based training approach in fact did not have a specific effect on frailty and neuroplasticity and that the reduction in frailty may be driven by other factors. The fact that frailty was also reduced irrespective of the treatment condition (main effect) suggests that some portion of the training effect may be due to an unspecific treatment effect potentially related to the novelty of study participation, dealing with electronic devices or increased social activity. However, the almost significant interaction effect indicated that there may be specific characteristics of the neuroplasticity-based sensorimotor training that are crucial for the treatment effect. Given that the study may be subject to some methodological limitations such as a reduced statistical power, it would be premature to dismiss the neuroplasticity approach in the treatment of frailty. In this sense, Study 2 has pioneered and laid the groundwork for subsequent large-scale studies to pursue the neuroplasticity-based approach and identify the mechanisms and modes of action that are most effective in improving frailty in different frail populations.

4.4 Conclusions and outlook

Pathological aging will constitute a major challenge for societies within the upcoming decades. Despite substantial progress in the field of frailty research, further knowledge on pathophysiological mechanisms and treatment approaches is necessary. In this vein, both studies conducted in the course of the present dissertation contributed relevant findings to understanding conceptual and treatment aspects of the frailty syndrome, but also raised further questions.

Study 1 demonstrated that impairment in sensory and motor systems is independently associated with frailty and frailty instruments of the FP and FI differ in capturing these associations, presumably resulting in differences in frailty classification of the same individuals. This emphasizes that a clarification of the conceptual and operational inconsistencies between these instruments claiming to measure the same construct is needed. This clarification could help to understand the etiological factors and therapeutic needs of individuals identified as frail by either measure because they are probably sensitive to populations with different (functional) characteristics. Moreover, measures of sensory and motor performance should be included in frailty screening instruments because sensory and motor impairment is not only related to pathological aging conditions such as frailty and dementia, but may also have an impact on how older adults interact with and seek support from the healthcare system. Longitudinal studies will be needed to evaluate the predictive value of sensorimotor decline before frailty emerges and to determine the influence of mechanisms known to be associated with various forms of pathological and non-pathological aging, in particular alterations in central nervous structure and function and maladaptive neuroplasticity.

Study 2 found that an innovative tablet-based sensorimotor training targeting neuroplasticity had the potential to reduce frailty, possibly due to a beneficial effect on complex motor actions. However, the study failed in empirically identifying the underlying (neuroplastic) mechanisms and specific characteristics of the training approach underlying the intervention effect. Notably, the study differs from previous interventional studies in several aspects, thereby adding to the existing frailty literature several possible starting points that could be further explored in future studies. First, the study used frailty as an outcome, thereby evaluating the training effect on the multidimensional syndrome of frailty, which has clinical significance due to its predictive value for adverse health outcomes and quality of life. Second, the simultaneous use of two widely used frailty instruments, the FP and the FI, which were demonstrated to overlap but

also differ in their conceptual and operational characteristics, suggested that the choice of the frailty instrument may play a role in evaluating treatment success. Third, the training was based on a novel approach consisting of extensive sensory and motor stimulation in order to increase processing in multiple sensorimotor brain systems simultaneously, counteract inactivity and promote reversal of age-related maladaptive neuroplasticity. Fourth, the difficulty and challenge of the training was individualized to the subject's abilities in an adaptive manner to optimize learning while providing a significant amount of positive feedback to enhance training motivation and adherence. Fifth, the training was constructed as a tablet-based home training, which lowered training barriers and increased feasibility for the subjects. Since previous studies demonstrated mixed results with respect to the efficacy of different approaches, the optimal treatment strategy for frailty is still a matter of debate. The neuroplasticity-based sensorimotor training approach described in Study 2 included several novel training features that may have contributed to the positive training effect. Future studies could manipulate these training features in a controlled manner to provide clues as to what features of an intervention and which mechanisms may be critical in improving frailty. Moreover, future studies may investigate whether adding a neuroplasticity training component may exacerbate positive effects of interventional approaches proven to be successful in frailty such as physical exercise or multicomponent treatment. Lastly, future studies could investigate whether the reduction of pain may mediate the effect of a neuroplasticity-based sensorimotor discrimination training on frailty.

Frailty is a complex syndrome leading to a high burden for those affected, for caregivers as well as for the healthcare system. However, a growing body of promising research showed that frailty is not necessarily the inevitable endpoint of lifelong decline and disease. But even more, it is important to identify innovative strategies suitable for slowing progression in an early state. Interventional studies in frailty are challenging, and while some approaches will fail, others may turn out to be successful. The common goal should be to find ways in which successful aging can be promoted and in which function, independence and quality of life can be maintained in old age.

5 SUMMARY

This dissertation presents two studies, in which the relationship of impairment in sensory and motor systems with frailty was investigated from a conceptual point of view (Study 1) and as a potential target for innovative treatment to reduce frailty (Study 2).
The aim of Study 1 was to identify sensory and motor determinants of frailty as assessed by two common frailty instruments, the frailty phenotype (FP) and the frailty index (FI). Performance measures of sensory and motor function were assessed in 44 pre-frail and frail subjects. Separate multiple logistic regression analyses revealed that frailty as defined by the FP was associated with reduced upper extremity function, while frailty as defined by the FI was independently associated with higher hearing thresholds, reduced lower extremity performance and higher depression scores. This suggests that reduced sensory and motor function contributes to the syndrome of frailty, thereby offering a potential target for treatment, and that different frailty instruments may be differentially sensitive to capture functional impairment in frail populations.
In Study 2, the effectiveness of a 90-day tablet-based sensorimotor training (n=24) targeting the reversal of age-related maladaptive neuroplasticity in the sensorimotor system to counteract frailty was evaluated, compared to a tablet-based relaxation control training (n=24). After 60 days of training, a reduction in frailty as determined by the FP was found for both groups, while the effect tended to be stronger for the sensorimotor training condition. A non-significant reduction in the FI was found irrespective of the group. No training effects were found for sensorimotor brain activity assessed by functional magnetic resonance imaging and corticomotor excitability assessed by transcranial magnetic stimulation. The results suggest that a neuroplasticity-based training may alter frailty, yet the significance of the postulated neuroplastic mechanisms and the specific training characteristics underlying the effect remain to be determined.
Together, the two studies provide evidence that impairment in sensory and motor systems may represent a target mechanism to better understand pathophysiology of frailty and to develop novel, innovative treatment approaches. Longitudinal studies are needed to determine the influence of sensory and motor decline in the development of frailty. The present work may also inspire future large-scale interventional studies to validate the present preliminary, yet promising results and to examine the efficacy and mechanistic principles that approaches targeting the reversal of age-related maladaptive neuroplasticity may have in the treatment of frailty.

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7 CURRICULUM VITAE

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SCHOOL CAREER

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ACADEMIC CAREER

WS 2008/2009	Beginning of studies in Psychology (Bachelor of Science) At Universität des Saarlandes, Saarbrücken
2011	Bachelor thesis: „Wie beeinflussen Fieberkrämpfe das Zusammenspiel von semantischer Verarbeitung und episodischer Wiedererkennung?“
09.11.2011	Bachelor of Science, Grade: 2,0
2011 – 2016	Studies in Psychology (Master of Science) At Universität des Saarlandes, Saarbrücken
2013 – 2016	Master thesis: „The Influence of Working Memory Capacity on Long-Term Memory Formation during Working Memory Maintenance – An ERP Study”
23.06.2016	Master of Science, Grade: 1,4
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Beier, F., Löffler, M., Nees, F., Hausner, L., Frölich, L., & Flor, H. (2021). Promoting neuroplasticity and neuropsychological functioning in frailty through an app-based sensorimotor training: study protocol for a randomized trial. *BMC Geriatrics*, *21*(1), 343. https://doi.org/10.1186/s12877-021-02293-9

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