Improving community walking after stroke;

the effect of dual task treadmill training on gait, cognition and brain control mechanisms of dual task walking in chronic stroke survivors

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Abstract

It is well known that improving community walking ability is one of the major goals in stroke rehabilitation. Even if motor recovery of the lower limbs does occur, the ability to walk in the community is often still impaired. This thesis set out to explore dual task ability after stroke in relation to community walking and explored dual task treadmill training in stroke survivors. In addition, functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS) in stroke survivors during single and dual gait movements were performed to examine dual task effects on brain activation before and after dual task training.

In a cross-sectional trial, 27 limited community walkers were compared to 23 moderate-to-full community walkers. A significant larger proportion of limited community walkers were not confident about walking in the community compared to moderate-to-full community walkers ($p = 0.042$). Moreover mean cognitive response during two-minute-walk with dual task was 11.17 ± 3.62 for limited walkers and 13.48 ± 2.43 for moderate-to-full community walkers ($p = 0.014$). In contrast, moderate-to-full community walkers displayed relative larger reductions in walking distance as a result of dual task in comparison to limited community walkers ($p = 0.068$).

Consequently, a randomized controlled trial was performed in 50 chronic stroke survivors to explore to what extent 10 weeks of treadmill training with concurrent cognitive distraction in comparison to 10 weeks of treadmill training with no distraction would change community walking ability. Stroke survivors who received dual task treadmill training showed larger increases in two-minute-walk distance compared to the control group from baseline to follow with an effect size r of 0.24 and a Cohen's d of 0.50. Significant group and time interactions were seen

for physical activity scale assessments favouring the dual task training group ($p = 0.029$). In addition, on a modified version of the University of Alabama study of Aging Life Space Assessment questionnaire, stroke survivors in the dual task training group scored 54.76 ± 26.64 compared to 41.53 ± 20.88 in the control group at follow-up, ($p = 0.086$). Both training groups improved on walking performance and endurance during training. Feasibility of dual task training was good, with only l0% drop out for intention to treat.

The final part of this thesis focussed on results from fMRI and fNIRS measures that were taken to explore brain activation patterns during single and dual task gait before and after dual task training. At baseline, decreases in brain activation were seen in prefrontal cortex areas during dual task treadmill walking compared to single task treadmill walking. Moreover, fMRI during pedal movements with a concurrent cognitive task showed decreased brain activation compared to pedal movement alone. Dual task trained stroke survivors showed a reduction in right occipital cortex activation during pedalling at follow-up compared to baseline whereas control trained stroke survivors showed increases in this area from baseline to follow-up with a significant difference of activation change between groups ($p < 0.001$). In addition, stroke survivors who had received dual task training showed significant reductions in brain activation during pedalling and increase in activation during dual task pedalling from baseline to follow-up.

The results from the comparisons between limited community walkers and moderate-to-full community walkers suggested that different coping strategies might apply after stroke depending on gait speed, but also indicated that both type of community walkers had difficulties with dual task walking. Dual task treadmill training showed good feasibility and positive effects on walking endurance and performance as well as training without distraction. There were trends suggesting

that stroke survivors who were already physically active and had recovered their walking up to a certain standard were more likely to improve their dual task walking distance after dual training.

Brain imaging measures showed decreases in activation from single to dual task locomotor movements which may relate to reduced dual task ability in stroke survivors, but these changes did not correlate with changes in behavioural measures of dual task. The changes in response to training may relate to plasticity and a recovery of the automaticity of control of normal walking as a result of dual task training.

This thesis has provided novel research, insights and practical implications for dual task training after stroke. More research is needed, for instance to explore the extent to which stroke survivors could benefit from dual task training in more real-life situations.

The use of neuroimaging tools in stroke rehabilitation trials helps to understand how motor control mechanisms change in response to training and could add to tailor rehabilitation to the individual's need.

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Table of Contents

Abbreviations

AS	auditory Stroop task
AS-DT	auditory Stroop task whilst walking
BOLD	blood-oxygen-level dependent
CMI	cognitive motor interference
CoM	centre of mass
CPG	central pattern generator
CT	control training
DPF	differential path length factor
dPMC	dorsal premotor cortex
DT	dual task training
DTE	dual task effect
EEG	electroencephalography
EQ-5D	EuroQol 5-dimensions
FCW	full community walker
FEAT	FMRI expert analysis tool
fMRI	functional magnetic resonance imaging
FMRIB	Oxford centre for functional MRI of the brain
fNIRS	functional near-infrared spectroscopy
FSL	FMRIB software library
GLM	general linear model
H^+	hydrogen
HHb	deoxygenated haemoglobin
HRF	hemodynamic response function
ICF	the international classification of functioning, disability and health
IMU	inertial measuring unit
LCW	limited community walker
LI	laterality index
M1	primary motor area
MBLL	modified Beer-Lambert law
MEG	magneto encephalography
MELODIC	multivariate exploratory linear optimized decomposition into independent components
MOCA	Montreal cognitive assessment
NS	number Stroop
NS-DT	number Stroop whilst pedalling

OHb	oxygenated haemoglobin
PASE	physical activity scale for elderly
PET	position emission tomography
PFC	prefrontal cortex
PMC	premotor cortex
PP	picture-planning task
PP-DT	picture-planning task whilst walking or pedalling
rCBF	regional cerebral blood flow
RCT	randomized controlled trial
REC	research ethical committee
RF	radiofrequency
SAM	StepWatch activity monitor™
SF-36	short form-36 items
SMA	supplementary motor area
SMC	primary sensorimotor cortex
SPECT	single-photon emission computed tomography
SSWS	self-selected walking speed
ST	single task
TIA	transient ischemic attach
TMS	transcranial magnetic stimulation
TMW	two-minute-walk test
TMW-DT	two-minute-walk test with dual task
UAB LSA	University of Alabama study of aging life-space questionnaire

List Figures

List of Tables

Publications

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- Meester, D., E. Al-Yahya, H. Dawes, P. Martin-Fagg and C. Pinon (2014). "Associations between prefrontal cortex activation and H-reflex modulation during dual task gait." Front Hum Neurosci 8: 78.

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- Meester DP, Dawes H, Johansen-Berg H, Al-Yahya E, Dennis A, Wade D, Cockburn J. “Can dual task treadmill training improve community walking in chronic stroke?; a randomized controlled trial”

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Chapter 1. What is stroke and how does walking ability recover after stroke?

Stroke is one of the leading causes of disabilities with impairments in walking as one of the determinants of a stroke survivor's quality of life. This chapter gives an introduction into stroke statistics, pathology and recovery. Brain plasticity is discussed in relation to functional recovery of motor function after stroke. Furthermore community walking after stroke is discussed and an introduction is given into what factors and impairments relate to community walking ability.

1.1 Stroke statistics

Worldwide, approximately 15 million people a year suffer from stroke, of which 6.7 have a fatal stroke (Mendis, Armstrong et al. 2014, World Heart Federation 2016). In the UK, stroke mortality has decreased from 71% to 38% from 1990 to 2010 (stroke.org.uk 2015). Currently, there are 1.2 million stroke survivors living in the United Kingdom (UK) (stroke.org.uk 2015). Risk factors are well known for two-thirds of the stroke survivors (Barnes, Dobkin et al. 2005). Age, gender, race and heredity are amongst the non-modifiable risk factors, however most risk factors of stroke are classified as modifiable: hypertension, diabetes mellitus, hypercholesterolemia, smoking, alcohol abuse, diet, oral contraceptives and atrial fibrillation (Sacco 1995). The latter are associated to life-style and if modified in the correct way can reduce risk of stroke up to 80% (Chiuve, Rexrode et al. 2008). To date, stroke incidence in the United Kingdom remains high with around 152,000 people suffer from a stroke every year (stroke.org.uk 2015). Stroke is a leading cause of disability in adults (Adamson, Beswick et al. 2004), and over a third of stroke survivors remain dependent on others (stroke.org.uk 2015).

A large number of stroke survivors require rehabilitation to retrain motor function or learn how to cope with for instance hemiparesis. The following paragraphs describe the two main types of stroke, the recovery process and specifically emphasise on the effects of stroke on community walking ability.

1.2 **Stroke pathology**

A stroke has been defined as an event, during which a burst or a clot in a blood vessel causes an interruption of the brain's blood supply (WHO 2016). As a result, the cut off of oxygen and nutrients to brain areas causes focal or global loss of cerebral function (Warlow, Dennis et al. 1996). This description accounts for cerebral infarcts, primary intracerebral haemorrhages, intraventricular haemorrhages and most types of subarachnoid haemorrhages. The research presented in this thesis included both ischemic and haemorrhagic stroke survivors. About 85% of strokes are due to cerebral infarction and around 15% are haemorrhagic strokes (Luengo-Fernandez, Gray et al. 2013).

1.2.1 **Pathology of ischemic stroke**

Ischemic strokes are caused by an occlusion in the blood supply to the brain which results in acute loss of focal cerebral or monocular function. Occlusions can be caused by arterial thrombosis or embolisms. When the clinical symptoms last less than 24 hours the syndrome is classified as a transient ischemic attack (TIA) (Warlow, Dennis et al. 1996). Depending on the severity of the ischemic stroke the symptoms presented during a TIA can be very similar to those of a minor ischemic stroke with the only differences being the duration. A minor stroke can last from several days up to a few weeks. During an ischemic stroke the occlusion of the artery results in a range of processes including inflammation, an excess of extracellular excitatory amino acids and formation of free-radicals which cause

energy depletion and can result in cell death (van der Worp and van Gijn 2007). The amount of necrosis (cell death) is determined by the regional cerebral blood flow (rCBF) (Seitz 2010). A reduced rCBF is related to a reduction in cerebral perfusion, which if prolonged leads to further development of the infarct lesion. Early after occlusion the centre of the infarct still has low perfusion and is surrounded by an area which does not function properly due to disturbances in metabolic and ionic processes. Although this area is dysfunctional it preserves its structural integrity and is defined as the ischemic penumbra (van der Worp and van Gijn 2007). If eventually reperfusion takes place, the area containing penumbra can recover, but if the duration of ischemia and lack of rCBF takes too long the penumbra will be included in the infarct.

1.2.2 **Pathology of haemorrhagic stroke**

The majority (78-88%) of haemorrhagic strokes are primary strokes caused by hypertension or amyloid angiopathy leading to spontaneous rupture of a blood vessel (Foulkes, Wolf et al. 1988). Secondary strokes can be caused by vascular abnormalities, impaired coagulation or tumours and in rare cases primary haemorrhagic strokes occur in the subarachnoid space of the brain and are referred to as subarachnoid haemorrhage (Qureshi, Tuhrim et al. 2001). Haematomas (collections of blood) that form as a result of the haemorrhage are presented by oedema, apoptosis, necrosis and inflammatory cells (Qureshi, Mendelow et al. 2009). In the acute stage, haematoma areas are characterized by hypoperfusion and in combination with hypometabolic processes and mitochondrial dysfunction can lead to ischaemia (Siddique, Fernandes et al. 2002). However, reperfusion can recover to normal values over the course of 2-14 days and leave parts of neuronal tissue inside and surrounding the haematoma in touch and salvageable (Mutlu, Berry et al. 1963, Qureshi, Tuhrim et al. 2001).

1.3 Brain plasticity after stroke

The pathology of ischemic and haemorrhagic strokes is different, but the neurological recovery, functional symptoms and - rehabilitation is similar. Loss of function by undamaged brain tissue connected to the lesion area is defined as diaschisis (Andrews 1991) and can recover over time. Several studies have shown that plasticity potential in the lesioned brain is greater than in the healthy brain (Losseff 2004). Plasticity leads to changes in organization and size of cortical networks. The mechanism behind plasticity could partly be explained by levels of developmental proteins responsible for neuronal growth, apoptosis and cell differentiation that rise early after stroke. Studies using transcranial magnetic stimulation (TMS) have shown increases in size of motor maps in early recovery stages after stroke which related to improvement of function (Traversa, Cicinelli et al. 1997). Next to the spontaneous restitution of brain areas by biochemical and gene-induced processes, brain plasticity is also characterized by substitution. Substitution refers to the process in which brain areas (partially) take over functions from the areas that were affected by the stroke and is mainly promoted by external stimuli such as cognitive and motor rehabilitation (Losseff 2004). Both restitution and substitution processes have been suggested to make large contributions to functional improvement (Kwakkel, Kollen et al. 2004).

1.3.1 Measuring brain plasticity after stroke

Neuroimaging techniques have been used to explore brain plasticity. Functional magnetic resonance imaging (fMRI) is the current gold standard in neuroimaging (see paragraph 2.1). In an activation likelihood estimation meta-analysis of position emission tomography (PET) and fMRI studies Rehme et al. (2012) explored the neuronal activity related to motor movements after stroke in ipsilesional (affected hemisphere) and contralesional (unaffected hemisphere) brain areas. It was shown

that stroke survivors in the acute phase after stroke show higher activity in contralesional motor areas and increased bilateral activity in premotor areas compared to healthy controls (Rehme, Eickhoff et al. 2012). The direction and size of changes in neuronal activity patterns depend on the degree of motor impairment and time since stroke (Grefkes and Ward 2014). In an fMRI study of Rehme et al. (2011) less impaired stroke survivors showed similar patterns of movement-related activity when moving their affected hand as healthy controls compared to severely impaired survivors who showed decreased task-related activity within 72 hours after stroke. Over time (2-10days) severely impaired stroke survivors showed increases in movement-related activity in contralesional and bilateral brain areas (primary motor cortex (M1), dorsal premotor cortex (dPMC), supplementary motor area (SMA) and cingulate cortex (Rehme, Fink et al. 2011). Eventually, these activation patterns exceeded patterns as seen in normal healthy subjects. In a follow-up examination at 4 months post stroke, activity patterns in the severely impaired group changed back to activation patterns that were comparable to healthy adults, reflecting the recovery of hand function. Further analyses showed significant positive relationships between the increases in neuronal activity in the early acute stage of stroke and the extent of motor recovery (Rehme, Fink et al. 2011). This study together with others showed that better motor recovery was associated with a change to more normal brain activity patterns, comparable to those of healthy adults (Ward, Brown et al. 2003, Calautti, Jones et al. 2010, Wu, Quinlan et al. 2015).

1.3.2 **Brain plasticity related to lower limb function**

The work described in the previous paragraph investigated brain plasticity related to recovery of upper limb function after stroke. One great challenge is to image the brain during the recovery process of the lower extremities. Only few studies have

assessed movement-related activity of lower limbs after stroke. Kim et al. (2006) explored cortical activity related to locomotor recovery in 10 stroke survivors during fMRI scans performed at ± 5 weeks after stroke and again at 6 months after stroke onset. Study participants flexed and extended their knee at a metronome-controlled rhythm (0.5Hz). In the subacute stage, stroke survivors showed increased contralesional motor-related activation in the primary sensorimotor cortex (SMC) and SMA compared to healthy controls. After 6 months, activations were stronger in the ipsilesional SMC and activations in the contralesional SMA and PMC and cerebellum had reduced compared to baseline. Further analyses showed that stroke survivors improved their locomotor function from poor - to good ambulation over the course of half a year (Kim, You et al. 2006) related to shifts in laterality index (LI) of the SMC of the paretic leg. Increases in LI for SMC of the paretic correlated with increases in motor function score. Measuring movement-related brain activity with fMRI whilst someone is moving their legs is hard as it becomes difficult for the person being measured to keep their head still in order to provide good quality images. Furthermore, active movement of the paretic leg during a brain scan can be difficult for severely impaired stroke survivors and there are fewer options for movement modalities compared to upper limb paradigms. To tackle the challenge of the imaging modality, another technique, called functional near-infrared spectroscopy (fNIRS) has been used to explore longitudinal changes in brain activity with functional recovery of locomotor function. Miyai et al. (2003) explored brain activity during treadmill walking in 8 stroke survivors before and after two months of inpatient rehabilitation. On average these stroke survivors were three months post stroke when entered in the study. Results showed a shift from increased SMC activity in the unaffected hemisphere compared to the affected hemisphere at baseline to more activity in the affected hemisphere after two months of rehabilitation. This improvement in LI of SMC significantly correlated with improvements of the LI for swing phase of the

unaffected leg. Furthermore increased activity in the PMC in the affected hemisphere was measured post rehabilitation (Miyai, Yagura et al. 2003). The increased neuronal activity in these areas could reflect improvements in motor function and reorganization of motor networks and is similar to findings in plasticity research of upper limb function (Weiller, Ramsay et al. 1993).

1.4 **Functional recovery after stroke**

Of all disabilities caused by stroke, upper limb (77%) and lower limb weakness (72%) are amongst the most common impairments (stroke.org.uk 2015). Upper and lower limb weaknesses are caused by hemiparesis, reduced muscle strength and impaired proprioception. These motor impairments cause stroke survivors to have difficulties performing their daily activities. Depending on the severity of the stroke, people will receive a certain amount of inpatient rehabilitation which often is complemented with outpatient rehabilitation and ongoing support. Together with spontaneous recovery, physical therapy can improve the functional ability after stroke. Wade et al. (1985, 1987) showed that depending on the functions studied, more than 50% of stroke survivors after an acute stroke is functionally independent at three months. It is therefore not surprising that rehabilitation after stroke is often performed in the first three months, but rehabilitation programs in the later stages after stroke have been showing promising results, for instance to increase walking speed and endurance (Ferrarello, Baccini et al. 2011, Teasell, Mehta et al. 2012, Dobkin and Dorsch 2013).

The International Classification of Functioning, Disability and Health (ICF) developed the ICF Core Sets for stroke and specified walking, speaking, toileting and eating amongst the core ICF categories of the ICF component *activities and participation* (Geyh, Cieza et al. 2004). This thesis focusses for a large part on the functional recovery of walking after stroke. Two out of three people who suffer an

acute stroke have a walking impairment directly after stroke with half of these not being able to walk without personal assistance (Jorgensen, Nakayama et al. 1995). After rehabilitation, 64% of stroke survivors walk independently, 14% walks with assistance and 22% do not regain walking function (Jorgensen, Nakayama et al. 1995). This suggests a relative good recovery of walking in a large number of stroke survivors after an acute stroke. However a successfully retrieved walking ability does not necessarily mean that one can also walk independent in the community, which refers back to the ICF model of activities and participation. When the activity of walking has recovered at a personal level it does not always mean that a person is automatically able to participate as a member of the society.

1.5 **Recovery of community walking after stroke**

Improvement of walking ability is the number one goal of stroke survivors during rehabilitation (Bohannon, Andrews et al. 1988). In a study of Lord et al (2004) 130 stroke survivors were asked to indicate the importance of being able to get out and about in the community. Only 9 stroke survivors (6.9%) found this mildly important or not important whereas the other 93.1% indicated the ability to walk in the community essential (40.8%), very important (33.8%) or important (18.5%) (Lord, McPherson et al. 2004). Being able to walk in the community has received increased attention in the last two decades (Shumway-Cook, Patla et al. 2002, Lord, McPherson et al. 2004, Lord and Rochester 2005, Robinson, Shumway-Cook et al. 2011, Oh and Park 2013). When categorized within the framework of ICF, recovery of community walking would be depending on recovery of health condition (in this case stroke), placed within physical – and contextual factors (World Health Organization 2001).

Research studies have shown that amongst the important factors that influence recovery of community walking after stroke are: walking speed, balance, muscle

strength, cardiovascular endurance, depression, cognition and self-efficacy (Robinson, Shumway-Cook et al. 2011, Bowden, Embry et al. 2012). Next to these internal factors community ambulation requires being able to cope with distractions of the environment whilst walking. In such dual task situations, mental load has to be shared amongst the mobility task and the cognitive dual task (Patla and Shumway-Cook 1999). Both motor - and cognitive performance decline in dual task situations compared to single task performances of the same tasks. This cognitive motor interference is larger in stroke survivors compared to healthy age-matched controls (Brown, Sleik et al. 2002, Hyndman, Ashburn et al. 2006). Moreover, studies have shown that stroke survivors had difficulty performing cognitive tasks during walking or whilst performing balance tests (Haggard, Cockburn et al. 2000, Bowen, Wenman et al. 2001, Brown, Sleik et al. 2002, Cockburn, Haggard et al. 2003, Hyndman, Ashburn et al. 2006, Plummer-D'Amato, Altmann et al. 2008).

Chapter 2 of this thesis will discuss relationships between dual task ability and community walking after stroke in more detail. Moreover, importance of gait speed as indicator for types of community walker will be discussed and related to dual task walking measures.

Chapter 2. Relationships between types of community walker and dual task performance in chronic stroke survivors

The aim of this thesis is to explore what factors influence community walking ability after stroke and how dual task training could possibly improve community walking ability. Gait speed has shown to be one of the most important predictors of community walking ability. Therefore this chapter presents the results of a study that explored dual task walking ability in stroke survivors and compared two groups of stroke survivors based on community walking speeds.

2.1 Introduction and rationale

A stroke often affects very basic abilities as speaking and walking which in turn limits people in activities and participation as specified by the ICF (Geyh, Cieza et al. 2004) (see paragraph 1.4). Stroke survivors who regain ability to walk in the community are able to participate in a number of meaningful activities and therefore have better quality of life (Alguren, Fridlund et al. 2012). Navigating through complex environments requires confidence about walking ability and ability to perform executive tasks at the same time (Lord, McPherson et al. 2008, Barnsley, McCluskey et al. 2012).

Gait speed is one the most important determinants of community walking and can be used to clinically classify a stroke survivor's level of community ambulation. In a large observational trial of 147 stroke survivors Perry et al. (1995) quantified that gait speeds higher than $0.8ms^{-1}$ were needed for full community ambulation. Limited community walking was related to a walking speeds between $0.4ms^{-1}$ and

0.8ms^{-1} and stroke survivors who were only able to walk inside their household areas walked at speeds lower than 0.4ms^{-1} (Schmid, Duncan et al. 2007).

However, community walking ability cannot be predicted by gait speed alone (Perry, Garrett et al. 1995). An individual's age, stroke onset and psychological factors also contribute to dual task limitations (Keenan, Perry et al. 1984, Lord, McPherson et al. 2004). Furthermore social-environmental factors, such as presence of husband or wife, social life, area of residence and climate, may also affect the amount of community walking in stroke survivors (Barnsley, McCluskey et al. 2012).

Many different dual task circumstances may occur during community walking. How well someone is able to deal with these circumstances depends for a large part on a person's dual task ability. Behavioural changes in either the cognitive task or gait task during dual task situations are referred to as the process of cognitive motor interference (CMI) (see paragraph 1.5). CMI occurs when activity in brain networks involved in both motor control and cognitive task execution exceed structural or strategic capacity (Fischer and Plessow 2015). Theoretical models explaining the mechanisms behind dual task interference argue that there are two ways capacity limits are reached. The bottleneck principle (Pashler 1984) explains that the processes of two tasks cannot happen at the same time and therefore have to occur in succession, causing interference with the performance of the tasks. The second model, which is described amongst others, by McLeod (1977) and Tombu and Jolicœur (2003), suggests that capacity used for task processes can be shared and that task interference will occur when the shared capacity exceeds the brain capacity. Whether CMI is best dealt with by the brain using serial processing (model Pashler) or parallel processing (model Mcleod and model Tombu and Jolicœur) is under debate, however it is suggested that both models could occur depending on which exact multitasks are executed (Fischer and Plessow 2015).

Effects of CMI on gait have been summarized by Al-Yahya et al. (2011) in a systematic review and meta-analysis of 66 studies which showed that the extra task in dual task walking reduced walking speed of both healthy participants and subjects with neurological conditions. Moreover subgroup analyses showed that dual task conditions caused reductions in cadence and stride length and increases in stride time and stride time variability in both healthy participants and people with neurological conditions. The large variation between methodology and neurological populations of studies included in this review makes it challenging to interpret results for specific populations like stroke survivors.

The magnitude of CMI may differ per task and population studied, and in addition, may be specific to tasks acting on certain aspects of cognition (Al-Yahya, Dawes et al. 2011). For instance a simple verbal fluency task like naming animals or reciting the alphabet shows little CMI compared to a more complex serial subtraction task which requires attention and working memory and is therefore more likely to affect gait (Montero-Odasso, Muir et al. 2012, Beurskens, Helmich et al. 2014). It has been shown that stroke survivor's changes in gait speed due to dual task are larger compared to healthy older adults (Al-Yahya, Dawes et al. 2011), however this work is limited and the cognitive tasks used as distractor (serial subtraction) do not always relate to daily life situations such as community walking.

The next part of this chapter describes a study which was set out to explore differences in dual task ability and community walking between stroke survivors walking at limited community walking speeds and stroke survivors walking at moderate-to-full community walking speeds. In this comparison we looked at dual task effect (DTE) on gait and cognitive performance in stroke survivors walking overground and on a treadmill in relation to community walking measures. Moreover, a novel planning task was used to explore a cognitive test that related to

daily live as a measure of dual task ability and to compare this test with a well-established cognitive test, the auditory Stroop.

It was hypothesized that stroke survivors who walked at lower walking speeds would show larger decrements in cognitive - and walking measures during dual task walking tests compared to stroke survivors walking at faster speeds. We expected to see relationships between size of DTE and community walking measures.

2.2 Methods

2.2.1 Study Population

Stroke survivors were recruited from hospitals, GP practices, stroke clubs and via advertisements in local newsletters and magazines. Table 2.1 shows the inclusion and exclusion criteria. The study was approved by the local NHS Research Ethics Committee (REC reference: 12/SC/0403) and all participants gave their informed consent to participate in the study according with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Table 2.1. Inclusion and exclusion criteria

Inclusion	Exclusion
• At least 6 months post stroke • Ischemic or Haemorrhagic stroke • A clear walking deficiency as shown in a reduced two-minute-walk distance or abnormal gait • Able to walk on a treadmill • Able to give informed consent	• Concurrent other neurological condition • A Mental state that precluded safe participation as stated by GP • Psychological disorder • Aphasia severely limiting communication/not being able to response to dual tasks

2.2.2 **Experimental procedure**

Upon arrival participants were seated in a comfortable chair and were given an explanation about the testing protocol. After having given informed consent participants completed a series of questionnaires. Where needed, stroke survivors were guided through the questionnaires with help of a trained researcher.

Any available or obtainable descriptives around the stroke (type, location, date of stroke) and medication and medical history were recorded. Handedness was measured with the Edinburgh handedness questionnaire (Oldfield 1971) and cognitive ability was measured with the Montreal Cognitive Assessment (MOCA) (Nasreddine, Phillips et al. 2005). Aphasia was not assessed with a tool, but in case of participants with limited communication, a short test was done in which cognitive tasks that were executed during the treadmill test (see below) were practiced to assess whether the person was able enough to participate in the cognitive aspect of testing. The impact of stroke on physical independence during daily activities was measured with the Barthel Index (Wade and Collin 1988).

Physical activity levels were measured with the Physical Activity Scale for Elderly (PASE) (Washburn, Smith et al. 1993). Health and wellbeing were assessed through the Short-Form-36 (Ware and Sherbourne 1992) and the EuroQol-5D (Hurst, Kind et al. 1997). In addition two questions were asked regarding community walking: “Do you get out of the house as much as you like?” and “Do you feel confident when walking in the community?”. For both questions participants were asked to answer with “yes” or “no”.

The next part of the assessment consisted of a treadmill walking test with and without distraction. A Physical Activity Readiness Questionnaire (Shephard 1988) was conducted to check for any contra-indications to safe participation in (treadmill) exercise. First the participants were helped on the treadmill (Woodway, model elg 70/200, Cranlea Human Performance Limited, Birmingham, United

Kingdom), either by using a step or a hoist. The participants then chose a treadmill speed which they found comfortable and (if possible) comparable to their normal overground walking speed. During the selection of walking speed the researcher made the stroke survivor experience a range of speeds without giving feedback about the speed. The latter was done to prevent the person selecting a speed based on what they think they should walk rather than their actual comfortable speed. The stroke survivor then walked at this self-selected-walking-speed (SSWS) for some time to get comfortable with the treadmill. If needed the person was allowed to hold one or both side-bars of the treadmill whilst standing and walking. In some cases participants received some extra familiarisation sessions outside the assessment to get comfortable with treadmill walking.

After having set the SSWS, participants were sat down on a chair on the treadmill and received an explanation about the treadmill test. The treadmill test was executed following a block design in which participants performed one of five tasks for +/-30 seconds (s) alternated with 20s rest periods. Each task was repeated five times resulting in a total test-time of 21 minutes (min). The five tasks were: Auditory Stroop task whilst standing (AS), Walking at SSWS, Picture-planning task (PP), Auditory Stroop task whilst walking (AS-DT) and the Picture-planning task whilst walking (PP-DT).

The AS is a well-established auditory version of the Stroop task (Shor 1975). During the AS the participant listened to the words “High” and “Low” spoken out at either a high pitch or a low pitch. The stroke survivor was asked to verbally indicate, by saying “high” or “low”, whether the word was spoken out at a high or low pitch. The inter-stimulus-interval was set at 3.5s which was higher than the 2s interval that previous studies (Smulders, van Swigchem et al. 2012, van Ooijen, Heeren et al. 2015). However, stroke survivors in those studies were less disabled and therefore able to walk at considerably higher speeds and deal with greater task difficulty.

The PP task was a customized task, designed to test the executive function of planning in a single task and dual task condition. The stroke survivor faced a screen whilst standing or walking on the treadmill. Two pictures of the same daily activity were presented on the screen, but each picture represented a different action within the activity (see Figure 2.1). The objective of the task was to verbally indicate which picture came first (i.e. by saying “top” or “bottom”).

Both the AS - and the PP task were presented through Presentation® software (Presentation version 16.5). This software took audio recordings of the verbal responses to the AS and PP and provided text files with reaction times.

A **B**

Figure 2.1 Two examples of stimuli represented during the picture planning task. The objective of the task was to verbally indicate the first picture in the sequence. A. Two pictures of a person who is making a sandwich, the bottom picture is the first picture in the sequence. B. Two pictures of a woman who brushes her teeth, the top picture is the first picture in the sequence.

Next to cognitive responses, temporal gait parameters were assessed during the treadmill test. Centre of mass movements were taken through an inertial measuring unit (IMU) (Philips, Eindhoven, The Netherlands). The IMU (Philips, Eindhoven, The Netherlands) comprising of a tri-axial accelerometer, gyroscope and

magnetometer was placed over the L3-L4 inter-vertebral space (Auvinet, Berrut et al. 2002) corresponding to the projected centre of mass (Esser, Dawes et al. 2012). Furthermore, heart rate was monitored and recorded throughout the treadmill assessment through a heart rate monitor worn around the waist (Polar Electro Ltd, United Kingdom).

The final part of the assessment consisted of two two-minute-walk tests (TMW) (Butland, Pang et al. 1982) performed on a 16 meter track set out with two cones on a corridor. Instructions were to walk at SSWS, make turns around the cones and to continue walking until the researcher would call to stop. One normal TMW was performed in which the participants walked on their own. In a second TMW participants were asked questions whilst performing the test (TMW-DT). Questions focussed on the person's planning of daily activities (e.g. "Can you tell me how your day started today?"). The order of the normal TMW and the TMW-DT was randomized between participants to rule out differences in walking distance between the two tests as a result of exhaustion during the second walk test.

At the end of the test day participants received a StepWatch Activity Monitor™ (SAM) (OrthoCare Innovations, Seattle, WA). The participants were asked to wear the SAM during day time (except when swimming or showering) for 7 full days onward from the day after the assessment day.

2.2.3 **Data processing**

Means, standard deviations and confidence intervals were calculated for all data. The data set was divided in two groups based on overground walking speeds above or below $0.8ms^{-1}$ (Perry, Garrett et al. 1995, Schmid, Duncan et al. 2007). Stroke survivors walking slower and faster than $0.8ms^{-1}$ were categorized as limited community walkers (LCW) and moderate-to-full community walkers (FCW)

respectively. Demographic descriptives, MOCA score, Barthel Index, handedness questionnaire and TMW(-DT) distances were inputted in excel sheets and double checked for faulty entries. Normality of data was checked using the Shapiro-Wilk test. Data for stroke onset was not distributed normally and skewed to more stroke survivors within a year since stroke. Therefore, for further analyses, data for stroke onset was log transformed using a base-10 log. PASE scores were calculated combining type of activity and amount of repetitions per week and also included activity during household activities. EQ-5D scores were transformed into an index between 0 and 1 (van Hout, Janssen et al. 2012) and a separate rank score (0-100). SF-36, scores were averaged and divided into a total score, mental health score and physical health score, each on a scale between 0-100. Finally the answers to the two questions regarding community walking were scored 1 and 0 for "yes" and "no" respectively.

Gait characteristics were measured during TMW tests and during the treadmill assessment and were retrieved from IMU data. IMU readings were post-processed in a customized LabVIEW program (Version 11.0.1f2, National Instruments, Austin, TX, USA). To reduce drift, raw acceleration signals were integrated and filtered using a second order Butterworth band pass filter with low and high cut-off frequencies of 0.5Hz and 25Hz respectively (Steins, Sheret et al. 2014). Peak and troughs from double integrated amplitudes were taken to measure CoM displacements. For the TMW tests, 10-20 seconds of data from the middle part of the 2 minutes was taken for further processing. A similar approach was used for the IMU data gathered during the treadmill test, where 10-15 seconds of the middle part of each task block was taken for further processing.

Overground walking speed was calculated from the two-minute-walk distance with an addition of 10% for turns taken:

$$Overground\ walking\ speed\ (ms^{-1}) = \frac{TMW\ distance * 1{,}10}{120\ seconds}$$

Temporal gait characteristics were taken from peak to peak timings and step frequency was taken as the peak frequency present in the Fourier analysis. Cadence, stride time of both legs, stride time ratio of left/right (longest stride time/shortest stride time), step time and step time variability were calculated. Step time variability was taken from the average standard deviation of step time.

Data gathered with the SAMs was extracted and processed with StepWatch™ Analysis Software 3.1. (OrthoCare Innovations, Seattle, WA). SAMs were worn for 7 full days and data from those 7 days was analysed. During the study, some participants indicated that they had worn SAMs the wrong way around or forgot to put on in the morning, therefore it was decided that days showing a total amount of step counts less than 10% of the daily average across a week were disregarded and considered as SAM not (correctly) worn. For all other days, up to a maximum of 7 days, average steps per day, maximum daily step count per week and sum of all steps taken in a week were calculated by the device software.

For scoring on the AS and PP tasks, percentage of correct responses, reaction times and a composite score were calculated. The composite score took into account speed-accuracy trade-off and was calculated using the following formula:

$$Composite\ score = \frac{Correct\ responses\ \%}{Reaction\ time\ (s)} * 100$$ (Springer, Giladi et al. 2006)

2.2.4 **Statistical analysis**

Statistics were performed in SPSS version 21. Independent t-tests were performed to test for significant differences between LCW and FCW. In case of non-normal distributed data Chi-square or Fisher's exact test were used.

2.3 **Results**

2.3.1 **Descriptives**

50 stroke survivors (31 ischemic, 17 haemorrhagic and 2 combined ischemic and haemorrhagic) were recruited and entered into the study. Stroke participant information is given in Table 2.2. Barthel Index was significantly lower in LCW with a mean of 18.3 ± 2.2 compared to FCW who had a mean score of 19.9 ± 0.3. Categorization according to community walking speeds resulted in significant lower walking speeds for LCW compared to the FCW group. Mean overground walking speed and treadmill walking speed for LCW were $0.52ms^{-1} \pm 0.15ms^{-1}$ and $0.28ms^{-1} \pm 0.11ms^{-1}$, compared to $1.13ms^{-1} \pm 0.20ms^{-1}$ and $0.58ms^{-1} \pm 0.24ms^{-1}$ for FCW respectively. In addition a significantly larger amount of stroke survivors from the LCW group made use of a walking aid or personal support. No significant differences were found between LCW and FCW for demographic values, stroke characteristics, cognitive function and level of aphasia.

Table 2.2 Descriptive data per type of community walker

Measure	**LCW (< 0.8ms^{-1})**	**FCW (> 0.8ms^{-1})**	**Independent sample T-test (α = 0.05)**
Demography	**(n = 27)**	**(n = 23)**	
Male / female	12/15	14/9	*0.272*[a]
Age (years)	63.33 ± 13.84	59.39 ± 16.39	*0.361*
Handedness: right / left	24 / 3	18 / 5	*0.864*[b]
Stroke details	**(n = 27)**	**(n = 23)**	
Ischemic / Haemorrhagic / both	14 / 11 / 2	17 / 6	*0.181*[b]
Right / Left / mid – brain	14 / 9 / 4	12 / 8 / 3	*1.000*[b]
Stroke onset (Log^{-10})	1.30 ± 0.44	1.47 ± 0.51	*0.239*
Clinical characteristics	**(n = 27)**	**(n = 23)**	
Barthel Index	18.3 ± 2.2	19.9 ± 0.3	***< 0.001***
MOCA	24.3 ± 5.1	25.6 ± 2.9	*0.310*
(mild) aphasia: yes / no	5 / 22	1 / 22	*0.361*[b]
Walking characteristics	**(n = 27)**	**(n = 23)**	
Walking aid: none / stick / personal support	3 / 20 / 4	17 / 6	***< 0.001***[b]
Overground walking speed (ms^{-1})	**(n = 27)** 0.52 ± 0.15	**(n = 23)** 1.13 ± 0.20	***< 0.001***
Treadmill walking speed (ms^{-1})	**(n = 27)** 0.28 ± 0.11	**(n = 23)** 0.58 ± 0.24	***< 0.001***

LCW; limited community walkers, FCW; moderate-to-full community walker, MOCA; Montreal Cognitive Assessment Scale. P-value represents result of independent sample t-test to test difference between values for LCW and FCW, α = 0.05. a; Chi-square test, b; Fischer's exact test.

2.3.2 **Primary measures**

Walking measures showed that FCW walked significantly further during the TMW without and with dual task compared to LCW (see Table 2.3). The distances walked by FCW during the TMW and TMW-DT were 123.47 ± 21.78 and 105.10 ± 20.41 compared to 56.87 ± 16.63 and 51.22 ± 15.73 for the LCW ($t = -11.966$; $p < 0.001$ and $t = -10.292$; $p < 0.001$). The ability to plan during the TMW-DT was similar for LCW and FCW ($p > 0.05$), however there was a significant difference between the number of responses between the two groups of walkers, 11.17 ± 3.62 and 13.48 ± 2.43 respectively ($t = -2.560$; $p = 0.014$). When asked about their walking in the community, stroke survivors in the FCW group were more likely to say yes to the questions: "Do you get out of the house as much as you like?" and "Do you feel confident when walking in the community?", compared to stroke survivors in the LCW. This difference was significant for the question regarding the person's confidence ($X^2 = 4.978$; $p = 0.042$) and there was a trend towards a significant difference for the first question ($X^2 = 4.194$; $p = 0.074$).

During the TMW tests, various temporal gait measures were measured and calculated (Paragraph 8.1.1, Appendix 2.A, Table 2.A1). Mean TMW distance was 85.23m ± 41.73m and 73.95m ± 35.36m for the TMW-DT. The TMW-DT distance was significantly shorter by 12.17% ± 9.57 % ($p <0.001$; $t = 7.129$). Cadence reduced significantly with 4.80% ± 7.86% from 95.49 ± 23.46 steps/min during normal walking to 90.85 steps/min ± 23.03 steps/min during dual task walking ($p = <0.001$; $t = 4.240$). As a result, step time increased significantly with 5.11% ± 9.28%, from 0.70 sec ± 0.20 sec to 0.73 sec ± 0.22 sec ($p = 0.002$; $t = -3.263$). Step time variability was on average 22.67 ± 43.60% higher during dual task walking compared to normal walking, with values of 0.09 sec ± 0.08 sec and 0.11 sec ± 0.11 sec ($p < 0.001$; $t = -2.535$). Stride time ratios and step frequencies were not

significantly different between single and dual task walks showing values of respectively 1.02 ± 0.03 and 1.02 ± 0.02 and 1.49Hz ± 0.41Hz and 1.39Hz ± 0.44Hz.

When exploring the DTE on TMW and gait parameters no significant differences were found between LCW and FCW (Paragraph 8.1.1, Appendix 2.A, Table 2.A2).

Table 2.3 Comparison between types of community walker for community walking measures

Primary Measure	**LCW ($< 0.8ms^{-1}$)**	**FCW ($> 0.8ms^{-1}$)**	**P-value**
Two-minute-walk tests	**25**	**23**	
TMW	56.87 ± 16.63	123.47 ± 21.78	***<0.001***
TMW-DT	51.22 ± 15.73	105.10 ± 20.41	***<0.001***
Cognitive response during TMW-DT	**24**	**23**	
Planning ability (1-3)	2.63 ± 0.71	2.82 ± 0.49	*0.656*[b]
Number of responses	11.17 ± 3.62	13.48 ± 2.43	***0.014***
Community walking question	**26**	**23**	
"Do you get out of the house as much as you like?": yes/no (1/0)	13/13	18 / 5	*0.074*[a]
"Do you feel confident when walking in the community?": yes/no (1/0)	11/15	17 / 6	***0.042***[a]

LCW; limited community walkers, FCW; moderate-to-full community walker, TMW; two-minute-walk test, TMW-DT; two-minute-walk test with distraction. P-value represents result of independent sample t-test to test difference between values for LCW and FCW, α = 0.05. a; Chi-square test, b; Fischer's exact test.

2.3.3 **Secondary measures**

Differences in secondary measures between LCW and FCW are presented in Table 2.4. LCW scored significantly lower ($t = -2.019$; $p = 0.049$) on the SF-36 physical domain compare to FCW, 47.3 ± 17.0 and 57.0 ±15.0 respectively. Moreover LCW scored an EQ-5D index of 0.64 ± 0.22 compared to 0.80 ± 0.12 for FCW ($t = -3.133$; $p = 0.003$). No differences were found for the mental domain score and total SF-36 score. Physical activity measures showed more significant differences between LCW and FCW. PASE scores were on average 68.7 ± 29.8 for LCW and 101.0 ± 59.0 for FCW ($t = -2.370$; $p = 0.024$). Step activity as measured with SAMs was significantly higher in FCW compared to LCW (see Table 2.4).

2.3.4 **Gait measures during treadmill walking**

The same gait parameters as measured and calculated during the TMW tests were explored during the treadmill walking test with distractor tasks. During the AS-DT the average step time was 0.85 sec ± 0.18 sec, 2.93% ± 6.91% shorter compared to 0.88 sec ± 0.21 sec during treadmill walking ($p = 0.005$; $t = 2.919$). Cadence, stride time ratio, step frequency, and step time variability were not significantly differently during the AS-DT compared to just treadmill walking (Paragraph 8.1.2, Appendix 2.B, Table 2.B1).

Table 2.4 Comparison between types of community walker for secondary measures

Secondary Measures	LCW (< 0.8ms^{-1})	FCW (> 0.8ms^{-1})	P-value
Health and Wellbeing	**27**	**23**	
SF-36 total score	54.4 ± 17.7	61.5 ± 17.0	*0.160*
SF-36 Mental score	61.9 ± 19.5	64.3 ± 20.8	*0.684*
SF-36 Physical score	47.3 ± 17.0	56.5 ±15.0	***0.049***
EQ-5D index	0.64 ± 0.2	0.8 ± 0.1	***0.003***
EQ-5D score	63.8 ± 19.9	73.5 ± 14.69	*0.063*
Physical activity	**26**	**23**	
PASE	68.7 ± 29.8	101.0 ± 59.0	***0.024***
PASE excl. household activities	23.5 ± 13.5	36.3 ± 30.3	*0.071*
	25	**19**	
SAM_daysworn (days)	6.5 ± 1.1	6.6 ± 0.7	*0.833*
SAM_perday (steps)	2171 ± 1230	4147 ± 1477.4	***< 0.001***
SAM_sum (steps)	13985 ± 8322	27353 ± 9945	***< 0.001***
SAM_max (steps)	3208 ± 1550	5938 ± 1857	***< 0.001***

LCW; limited community walkers, FCW; moderate-to-full community walker, SF-36; Short-Form-36, EQ-5D; EuroQol-5D, PASE; Physical activity scale for elderly, SAM; StepWatch Activity Monitor™. P-value represents result of independent sample t-test to test difference between values for LCW and FCW, $\alpha = 0.05$.

Comparing the characteristics of gait during the PP-DT with treadmill walking alone, both cadence and step time significantly changed. Cadence increased on average with 3.18% ± 9.31% from 75.65 steps/min ± 17.00 steps/min during treadmill walking to 77.64 steps/min ± 17.19 steps/min during the PP-DT ($p = 0.020$; $t = -2.399$), whereas step time decreased with 3.11% ± 6.48% from 0.88 sec ± 0.21 sec to 0.85 sec ± 0.18 sec ($t = 3.309$; $p = 0.002$). No differences between the PP-DT and normal treadmill walking were found for stride time ratio, step time variability and step frequency.

Similar to the TMW tests, no differences were found between the DTE seen in LCW and FCW (Paragraph 8.1.2, Appendix 2.B, Table 2.B2).

2.3.5 **Cognitive performance during treadmill walking**

Overall results of cognitive performance during the treadmill walking test showed that only during the PP-DT stroke survivors scored significantly lower during the DT condition compared to the performing the PP whilst standing (Paragraph 8.1.3, Appendix 2.C, Table 2.C1). Composite scores decreased with -9.80% ± 19.52% from 0.48 ± 0.12 during PP to 0.43 ± 0.12 during PP-DT ($p < 0.001$. $t = 4.346$).

It was found that LCW scored significantly ($p = 0.002$, $t = -3.304$) lower in the PP task compared to FCW with composite scores of 0.43 ± 0.12 and 0.53 ± 0.09 respectively (Paragraph 8.1.3, Appendix 2.C, Table 2.C2). No differences were found between LCW and FCW for DTE on cognitive performance for (Paragraph 8.1.3, Appendix 2.C, Table 2.C3)

2.4 Discussion

2.4.1 Walking performance and confidence about community walking per type of community walker

To our knowledge this is the first study to explore DTE effect in stroke survivors in relation to community walking ability. In addition, it is also the first study to have compared stroke survivors walking at limited community walking speeds to moderate-to-full community walking speeds for dual task - and community walking ability. The difference in walking speed between LCW and FCW resulted in clear significant differences between LCW and FCW on the TMW tests. As a result of higher walking speeds, FCW walked on average twice as far on both the TMW and TMW-DT compared to LCW. This large difference in walking performance resulted in a lack of confidence in most LCW when walking in the community. This is in accordance with findings from Perry et al. (1995) and Schmid et al. (2007) who categorized stroke survivors in different community walking categories according to their overground walking speed and community walking ability as determined by clinical expertise and a 19-item questionnaire. The two questions used in this study are a less robust method of assessing community walking ability, but can provide some valuable information.

2.4.2 Differences in dual task effects between types of community walker

The next step in this study was to assess DTE on walking performance and cognitive performance during overground - and treadmill walking. Looking at the whole population, we found a significant DTE of distraction during the TMW on the two-minute-walk distance. This was expected as other work has shown before that walking speed is one of the main aspects of gait which gets affected by CMI (Al-Yahya, Dawes et al. 2011). Interestingly when comparing LCW to FCW a

trend towards a larger DTE on walking distance was seen in FCW, whereas we hypothesized to see larger effects in LCW. Although DTE was giving in relative percentages, with an average speed of $0.52ms^{-1} \pm 0.15ms^{-1}$, LCW already walked at very slow speeds. Therefore, even though they decreased speed during TMW-DT, there were fewer margins to change walking speed compared to FCW, who walked at an average speed of $1.13ms^{-1} \pm 0.20ms^{-1}$ without distraction.

Being able to reduce the walking speed further during dual task walking might actually be an advantage to FCW in comparison to LCW when it helps to retain cognitive responsiveness. Results from cognitive responses showed that LCW were not able to give as many responses as FCW during the TMW-DT although their ability to talk about planning during walking was not different. No single cognitive task measure was performed for the overground dual task test so the cognitive response during the TMW-DT could not be compared with a single cognitive measure. However, cognition as measured with the MOCA was not different between types of community walker. Stroke survivors walking at lower speeds were more likely to have an impaired walking pattern and therefore had to focus more on their walking which resulted in a reduced cognitive response during walking with distraction. These outcomes suggest that there are different strategies to cope with CMI after stroke. Which strategy is used may depend on walking speed.

Next to walking distance, cadence, step time and step time variability were significantly different during the TMW-DT compared to the normal TMW test. This is in line with earlier studies which found changes in gait parameters in response to dual task (Plummer-D'Amato, Altmann et al. 2008, Dennis, Dawes et al. 2009).

Changes in gait parameters were not different between LCW and FCW, which could be related to the variability in the data, but also indicates that walking pattern

adaptations in response to distraction are similar for stroke survivors with different walking speeds.

On the treadmill we found changes in cadence and step time during distracted treadmill walking across all stroke survivors. Changes caused by the PP-DT were slightly stronger than changes caused by the AS-DT. The changes in cadence and step time were in the opposite direction compared to overground walking. On the treadmill stroke survivors walked at their self-selected walking speed, but were not able to change this speed during the dual task conditions and therefore increased their cadence in response to the cognitive distraction. Furthermore no increase in step time variability was seen on the treadmill which suggests that the treadmill enabled a more stable walk during dual task walking compared to overground walking. Again no differences were found between LCW and FCW when DTE on gait was compared between the two groups.

In general stroke survivors only scored less on the PP when it was performed whilst walking compared to the AS in which scores for single and dual task were similar. This suggests that the AS was easier to execute whilst walking whereas the PP was more complex and caused more interference resulting in lower scores during dual task. The PP-DT was a visual task, relating more to community walking settings, where visual stimuli are common and executive planning is needed to navigate environments.

When LCW and FCW were compared for DTE on cognitive performance during the AS-DT no significant differences were found. However when the single task performances on both tasks were compared between both types of community walker, results showed that LCW scored significantly lower on the PP compared to FCW.

Consequently, although scoring lower on the PP in dual task, LCW had a trend towards a smaller DTE on cognitive performance compared to FCW. The LCW had more difficulty during the single task PP that was performed standing on the

treadmill. It has been showed before that stroke survivors have increased cognitive demands during postural control compared to healthy adults (Brown, Sleik et al. 2002, Roerdink, De Haart et al. 2006). It is possible that the LCW required more cognitive demands for postural control whilst standing on the treadmill and therefore were not able to provide full attention to the cognitive task. However, since we haven't measured balance this is only a hypothesis.

Finally no relationships were found between DTE on cognition and gait and community walking measures.

2.5 **Conclusions**

Ability to walk in the community can be a major contributor to the quality of life after stroke. In this study we found that on average a group of stroke survivors categorized LCW, were less independent (defined by the BI), scored lower on the physical subdomain of the SF-36 score and had a lower EQ-5D index in comparison to a group of FCW. During a dual task overground walk, DTE seemed to affect walking performance and cognitive performance differently between type of community walkers with greater reduction of cognitive performance in LCW and greater reduction of walking performance in FCW. On a treadmill these differences did not show. Moreover additional work is necessary to establish whether there are differences in DTE between types of walkers in other dual task tests and to investigate possible effect of dual task training in both types of community walkers.

Chapter 3. Dual task training after stroke: a randomized controlled trial

The next step in exploring dual task walking ability in relation to community walking ability after stroke is to explore dual task training after stroke. This chapter presents a study which describes the research that has been done so far and the limited evidence available so far due to lack of good solid methodology in previous dual task studies in stroke. Consequently a randomized controlled trial is described which explored the effects of 10 weeks of dual task treadmill training in comparison to treadmill training without distraction in 50 chronic stroke survivors. Effects on walking ability, community walking ability and training feasibility are discussed.

3.1 Introduction and rationale

Gait training after stroke has been studied in a large number of studies and its effectiveness has been analysed through different reviews, systematic reviews and meta-analyses (Dickstein 2008, States, Salem et al. 2009, Bowden, Embry et al. 2012, Charalambous, Bonilha et al. 2013, Mehrholz, Pohl et al. 2014). Walking training included physiotherapy or high-intensity therapy, strength training, cardiorespiratory training, or a mixture of these different approaches. Dose and duration of training period, intensity of training, equipment used and specific targeted stroke populations all have been linked to gait training effectiveness. In an extensive systematic review, Langhorne et al. (2009) showed that while most of the conventional gait rehabilitation approaches in stroke did improve walking speed, only cardiorespiratory training interventions showed significant evidence for improvements in walking ability as measured with speed and endurance.

Current walking rehabilitation is mostly done overground and through using treadmills. Treadmill training can be more easily intensified and combined with for instance body weight support systems compared to overground training. A disadvantage of treadmill training in comparison with overground training is that a treadmill walking cannot always replicate the challenges that different surfaces, obstacles and environments cause when people walk in the community.

Following technology development, studies have shown ways to replicate overground challenges during treadmill training by introducing virtual reality (Corbetta, Imeri et al. 2015). These novel techniques have shown promising results in small stroke trials, but need further exploration and larger clinical trials to determine effects on walking performance, community walking and quality of life after stroke.

Next to replicating physical challenges of community walking, more focus has been given to the dual task aspect of community walking. The lack of confidence to walk in the community that stroke survivors often present is probably related to the fact that people after stroke represent more difficulty when performing a cognitive task whilst walking (Plummer-D'Amato, Altmann et al. 2008, Hall, Echt et al. 2011).

Dual task training after stroke has been studied and published in about 20 trials over the past decade. Recently Wang et al. (2015) published a systematic review and meta-analysis about the current evidence for dual training on balance and gait were discussed. Here we discuss six studies that explored the effect of dual task on gait speed. Three used virtual reality training (Jaffe, Brown et al. 2004, Yang, Tsai et al. 2008, Cho and Lee 2013), one robotic virtual reality training (Mirelman, Bonato et al. 2009), one virtual reality training with body weight support (Xiao, Mao et al. 2012) and one study used ball manipulation (Yang, Wang et al. 2007) as distraction during walking.

Overall these studies suggested good feasibility and positive effects of dual task walking training after stroke on gait speed compared to control training. However, there are some methodological limitations to consider. Studies used relatively short training periods varying between two, three, four and six weeks. In addition only three studies (Jaffe, Brown et al. 2004, Yang, Tsai et al. 2008, Mirelman, Bonato et al. 2009) had a follow-up. Hence, limited evidence is available for the long term effects of dual task walking training. The largest population studied was 25 (Yang, Wang et al. 2007), but in this study the control group performed no exercise at all which makes it difficult to interpret the specific effect that the dual task aspect of training may had on improvements in gait speed. Control groups in other studies received training with content that deviated more from the dual task training than just the dual task aspect. For instance, two studies used lower training intensities in control groups compared to dual task groups (Xiao, Mao et al. 2012, Cho and Lee 2013).

Increasing walking speed and with that community walking ability has shown to increase health and wellbeing and quality of life after stroke (Schmid, Duncan et al. 2007). However, as presented in Chapter 2 and other work (Smulders, van Swigchem et al. 2012), even stroke survivors walking at speeds related to community walking ($>0.8ms^{-1}$) can still present dual task walking limitations.

To date, no reasonably sized randomized controlled trial has been performed (largest had 25 (Yang, Wang et al. 2007)) with a good control condition to explore dual task walking training after stroke. The lack of good control groups in previous dual task training studies has prevented examination of the feasibility and effectiveness of the dual aspect of these types of training. Moreover no tasks related to daily activities such as the picture planning tasks used in Chapter 2 have previously been used in dual task training studies.

Therefore, this study set out to explore, in chronic stroke survivors, to what extent 10 weeks of treadmill training with concurrent cognitive distraction in comparison

to 10 weeks of treadmill training with no distraction would change community walking ability. The walking content of the dual task training group and control training group was kept exactly the same and a large part of the cognitive content of dual task training related to daily life situations.

Community walking ability was assessed through overground walking performance, physical activity and community walking related questionnaires measured directly after 10 weeks of training and at 10 weeks follow-up. In addition, change in health and wellbeing after training and at follow-up was measured. We hypothesized that walking training would increase walking speed, –endurance and perception of health and that in addition training of dual tasking would improve community walking by increasing dual task ability and confidence about community walking. Finally, feasibility of the chosen study methods was analysed and discussed.

3.2 **Methods**

3.2.1 **Population and study design**

Building further on work described chapter 2 a phase 1 single-blinded randomized controlled trial was designed to explore the effects of a dual task walking training in stroke survivors. Stroke survivors were recruited from the study described in Chapter 2. The eligibility criteria were the same as described in Table 2.1, with the addition that stroke survivors who showed a contraindication to safe participation in an exercise intervention as reported by their GP were excluded. Data gathered in the study described in Chapter 2 were used as baseline scores. After these baseline assessments stroke survivors were randomized into a Dual Task treadmill training group (DT) or a Control treadmill training group (CT). The randomization was performed in blocks of 6 participants and was stratified for self-selected treadmill walking speed and type of stroke. To stratify for treadmill walking speed, stroke

survivors were categorized as slow walkers (self-selected treadmill speed < 0.4ms^{-1}) or moderate to normal speed walkers (self-selected treadmill speed > 0.4ms^{-1}). Treadmill speed was chosen over overground speed as walking training occurred on the treadmill. Study participants in both the DT group and CT group received an active intervention consisting of 20 walking training sessions divided over 10 weeks.

3.2.2 **Walking training**

The walking component of training consisted of 30 minutes of treadmill walking at an intensity which required the body to work in the aerobic training zone, between 55% and 85% of the age predicted maximum heart rate (220 – age) (Fletcher, Balady et al. 2001). Blood pressure and heart rate were measured in advance and directly after each training session to make sure it was within safe limits (systolic ≤ 170, diastolic ≤ 100). Furthermore heart rate was assessed throughout training sessions to keep the stroke survivors training in the aerobic training zone. Training started with a 10 minute warm-up on the treadmill and ended with 5 minutes cool down resulting in a total training time of 45 minutes. The aim of training was to increase walking speed and training intensity over the course of 10 weeks. If stroke survivors were not able to walk safely for the full 45 minute, the trainer decided in agreement with the person on shorter duration of training. For these study participants, increase of time on treadmill was prioritized before increases of speed were introduced into the training. Walking speeds were self-selected, but care was taken to keep the person in the aerobic training zone. Treadmill inclination was introduced in those stroke survivors who got to the point that their walking speed had increased so far that further increase would result in transition to running.

The stroke survivors were trained by professional staff experienced in working with neurological populations. To minimize differences between training delivery

practice sessions were arranged to align training methods and care was taken to have good communication between staff. The aim was to have the participants training for 10 weeks in succession with two sessions per week, however due to sickness, holiday or family circumstances, not all stroke survivors were able to complete the training within 10 weeks. Together with the training staff, the principal investigators decided to endeavour to have as many study participants completing the 20 sessions as possible, even if they could not complete the training within 10 weeks. Therefore, in some occasions the training period was extended with 2 or 3 weeks maximum. Consequently if for logistical reasons, the full amount of 20 sessions could not be completed effort was made to get up to as many sessions as possible.

3.2.3 **Dual Task training**

Stroke survivors who were randomized into the DT training group received walking training in which they were also given additional tasks whilst walking on the treadmill. The walking component was exactly as described in the previous paragraph. Each training session contained three types of distraction: various cognitive tasks, an audio fragment, talking about planning daily activities. Ten minutes of training time were devoted for each type of distraction. An overview of the tasks is given in Table 3.1. To be able to quantify progress on cognitive task performance over the training period each task was scored. More detail about the scoring of the tasks is given in the paper in paragraph 8.2.3, Appendix 3.C.

Table 3.1. Overview of tasks used in dual task training

(Adapted from paragraph 8.2.3, Appendix 3.C**)**

Task	Description	Duration
	Cognitive Task Block	2 * 5min
Auditory Stroop	*A randomized series of the word "High" and "Low" are played through speakers at a high or low pitch. The subject must state the pitch of the word that was just said.*	2min30sec
Serial Subtraction	*The person is asked to count backwards from a number between 290 and 300 in steps of 3, 4 or 7.*	2min30sec
Clock Face Task	*A time is given verbally and the person must state whether the corresponding clock face has hands on the left, right or both sides of the clock.*	2min30sec
Letter Fluency	*A letter of the alphabet is given and the person is asked to name as many words as they can think of that start with that letter.*	2min30sec
Alternative uses	*The person is given an object and has to come up with alternative uses for that object.*	2min30sec
Creativity	*The purpose of the task is to name as many objects that have a certain attribute (e.g. objects that are tall).*	2min30sec
	Radio	10min
Radio or other audio fragment	*An audio fragment is played which is then used as topic of conversation between the trainer and trained person.*	10min
	Planning	2 * 5min
Planning of activities of daily living	*The person is asked to describe how they plan their daily activities; from short actions as: making a cup of tea, to planning an upcoming day out or holiday.*	5min

3.2.4 **Control training**

Participants of the control training followed the walking protocol described in paragraph 3.2.2. They were trained one-on-one in a quiet room to limit distraction. The only form of distraction during the sessions occurred when the trainer interacted with the participant to check heart rate, comfort and to stimulate the participant to concentrate on the walking movement.

3.2.5 **Primary and Secondary outcome measures**

Stroke survivors were assessed at three time points in a separate gym unit, part of the Universities' sports centre. At each time point the effect of training group on community walking measures and health and wellbeing was assessed (see Table 3.2). All measures and data processing steps have been described in detail in paragraph 2.2.2 and 2.2.3. In addition a follow-up interview containing a modified version of the University of Alabama (UAB) study of Aging Life-Space Assessment (LSA) was conducted (Peel, Sawyer Baker et al. 2005). The original UAB LSA consists of a questionnaire which assesses how much a person has been spending in different life spaces for the past four weeks. The life spaces are divided up into 5 levels:

Life-Space Level 1: **Other rooms of your house besides the room where you sleep.**

Life-Space Level 2: **An area outside your porch deck or patio, hallway (of an apartment building) or garage, in your own yard or driveway.**

Life-Space Level 3: **Places in your neighbourhood, other than your own yard or apartment building.**

Life-Space Level 4: **Places outside your neighbourhood, but within your town.**

Life-Space Level 5: **Places outside your town.**

For each Life-Space Level the interviewer asked the subject to indicate whether they had spent time in the Life-Space Level and if so, how much time they had spent and whether they had required any personal assistance or equipment for walking support (e.g. walking stick or walker). For this trial the UAB LSA was reduced to Life-Space Levels 2 till 5 and the stroke survivor was specifically asked how much time they spend "walking" in each Life-Space Level. The scoring was kept the same as being specified in the original UAB LSA (Peel, Sawyer Baker et al. 2005). For each Life-Space Level a multiplication of three values was made resulting in one score per level. The first value was given when the stroke survivor spend time in a Life-Space Level. This value was equivalent to the number of the Life-Space Level. This value was then multiplied with a value between 1 and 4 for the amount of times a week a person had spent in the Life-Space Level. Finally the first two values were multiplied with a value of 1, 1.5 or 2 for the level of independence when walking in a Life-Space Level. The community walking score was given by the sum of the score for Life-Space Level 2-5. An example of the modified UAB LSA questionnaire can be found in Paragraph 8.2.1, Appendix 3.A.

Stroke survivors were recruited through hospitals, GP practices, stroke clubs and via advertisements in local newsletters and magazines. The progression of stroke survivors in both training groups was not only described using the data collected at assessments, but participants were also followed during training to monitor training progression and determine feasibility and effectiveness of the gait and cognitive part of both the control and dual task treadmill training. The data of in-training progression and feasibility of training methods were analysed and described by one of the professional trainers (Paragraph 8.2.3, Appendix 3.C). In this chapter, those in-training results and the feasibility of training will briefly be described and discussed.

Table 3.2. Primary and secondary outcome measures

Primary outcome measures
Community walking • TMW distance with and without dual task • DTE on two-minute-walk with dual task and planning ability during two-minute-walk • Community walking questions • Step activity for a week (step count/day) • Physical Activity Scale for Elderly
Secondary outcome measures
Health and wellbeing • SF-36 scores • EQ-5D scores
Follow-up measure • Modified Life Space Assessment

TMW; two-minute walk test, DTE; Dual task effect

3.2.6 **Sample size and randomization**

This study was powered as a phase 1 feasibility study. Training group sizes of 20 were determined sufficient to allow for effect sizes to be calculated on measures as walking performance and trial participation. To allow for 20% drop-out group sizes were set at 25. Randomization was performed through a computer generated randomization list that randomized stroke survivors 1:1 into either the Dual task training group or the control training. To balance training groups for walking performance the randomization list was stratified through minimisation for baseline treadmill speed and participation in fMRI study. Trainers and stroke survivors were aware of training groups, and stroke survivors in the DT group and CT group were trained by the same trainers. Training was delivered one-on-one and contact between stroke survivors was limited to prevent the participants from both groups chatting about the content of training. The researcher conducting the assessments was blinded to group allocation and was also being kept away from the training site when training took place.

3.2.7 **Statistical analyses**

Statistics were performed in SPSS version 21. Independent t-tests were performed to test for significant differences between the CT and DT group at baseline. In case of non-normal distributed data Chi-square or Fishers exact test were used**.** A Linear Mixed Models approach was used (Littell, Pendergast et al. 2000) with an Unstructured, Autoregressive or Toeplitz covariance matrix to model fixed factors for time and training group which was selected based on goodness-of-fit variables such as Akaike's information criterion (AIC) (Akaike 1974) and Schwarz's Bayesian criterion (SBC) (Schwarz 1978). An interaction term for Time*Group was added to the model only if this interaction was significant. Bonferroni corrections were used to explore changes between visits, and groups for different time points. Generalized linear models were used to explore effects of group and

time on binary data. Pearson correlations were performed between modified UAB LSA score and baseline score on TMW-DT independently for both training groups.

3.3 **Results**

Figure 3.1 shows a flow diagram of the trial. Out of the 50 stroke survivors who were included in the study 26 were randomized into the dual task training group and 24 into the control training group. Table 3.3 presents the clinical characteristics and mean baseline scores for stroke survivors in per training group. No differences between the DT – and CT group were found for age, sex, handedness, type of stroke and location of stroke. A significant difference ($t = -2.447$; $p = 0.018$) was found for stroke onset. Log-10 values for stroke onset were 1.22 ± 0.39 for stroke survivors in the CT group and 1.53 ± 0.51 for stroke survivors in the DT group. Furthermore both training groups did not differ for MOCA scores, Barthel Index, aphasia and walking characteristics (see Table 3.3 for detailed information).

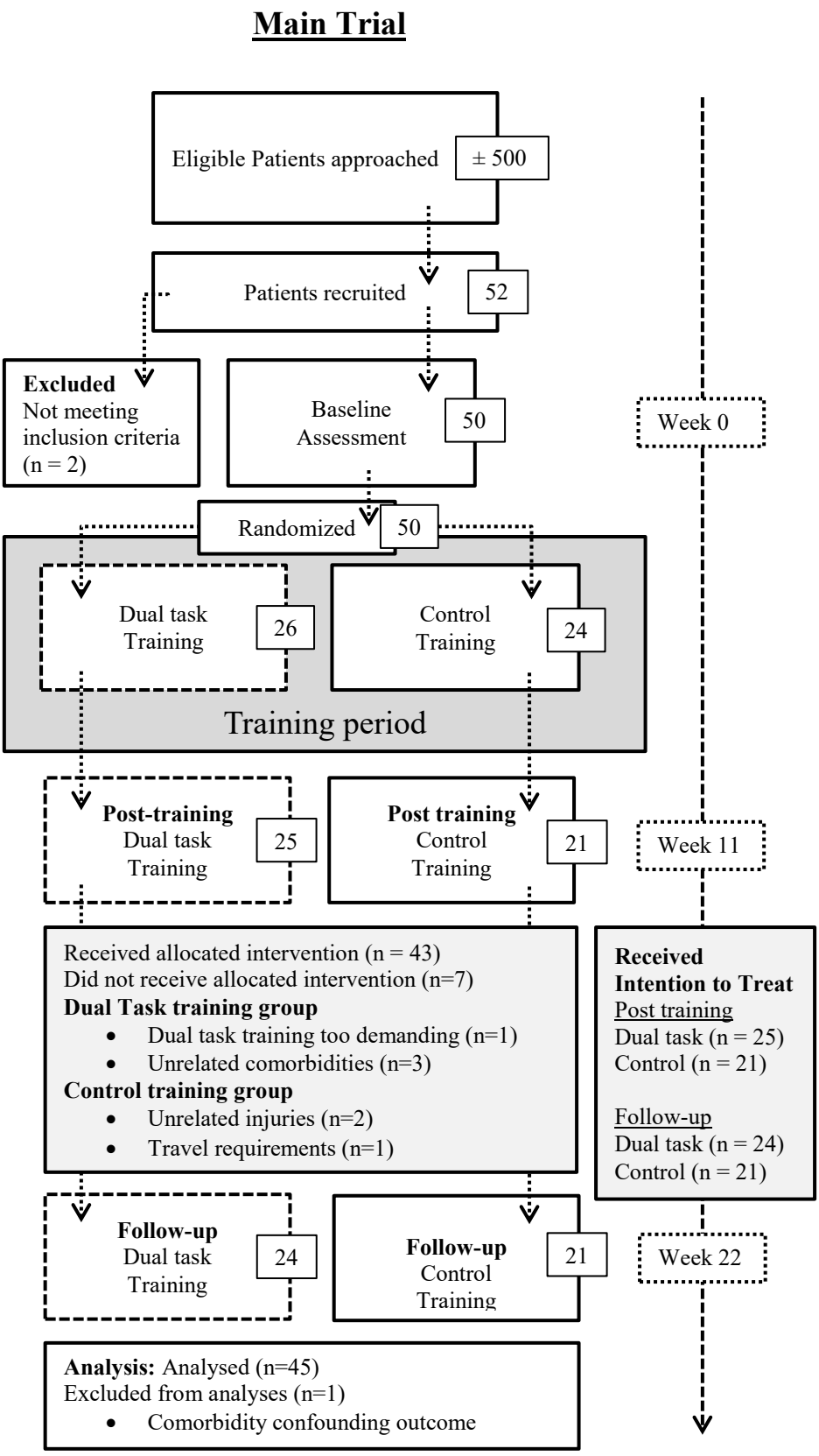


Figure 1. Flow diagram

Table 3.3 Descriptive data containing population mean and standard deviation values

Measure	Control Group (n = 24)	DT Training Group (n = 26)	Independent sample T-test
Demography			
Male / female	11 / 13	15 / 11	*0.402*[a]
Age (years)	62.25 ± 15.53	60.85 ± 14.86	*0.745*
Handedness: right / left / no preference	21 / 3	20 / 3 / 3	*0.382*[b]
Stroke details			
Ischemic / Haemorrhagic / both	13 / 10 / 1	18 / 7 / 1	*0.678*[a]
Right / Left / mid – brain	13 / 6 / 5	13 / 11 / 2	*0.261*[b]
Stroke onset (Log^{-10})	1.22 ± 0.39	1.53 ± 0.51	***0.018***
Clinical characteristics			
Barthel Index	19.2 ± 1.2	18.9 ± 2.3	*0.489*
MOCA	25.3 ± 3.5	24.5 ± 4.8	*0.535*
(mild) aphasia: yes / no	2 / 22	4 / 22	*0.270*[b]
Walking characteristics			
Walking aid: none / stick / personal support	7 / 15 / 2	13 / 11 / 2	*0.291*[b]
TMW	86.73 ± 41.96	90.66 ± 36.11	*0.729*
TMW_DT	75.44 ± 33.21	78.50 ± 32.60	*0.749*
Treadmill walking speed (ms^{-1})	0.40 ± 0.23	0.43 ± 0.24	*0.721*

MOCA; Montreal Cognitive Assessment Scale. P-value represents result of independent sample t-test to test difference between values for LCW and FCW, a; Chi-square test, b; Fischer's exact test. Significance level for statistical tests, α = 0.05

3.3.1 **Primary outcome: Two-minute-walk tests**

Both training groups showed significant increases in walking distances for both TMW ($F = 11.132$; $p<0.001$) and TMW-DT ($F = 9.196$; $p<0.001$). Means and standard deviations of TMW and TMW-DT data at different visits together with results of linear mixed models are given in Table 3.4, which shows an increase in TMW and TMW-DT at the follow up time point in both groups. Figure 3.2 shows the slope of increase in TMW in both groups and in the DT group continuing to increase over time. There was heterogeneity in responses in both groups. No significant differences between groups were found for improvement on TMW and TMW-DT. However when the increases from baseline to follow-up for both groups were explored for effect size, the increase of 12.82m ± 13.72m in the DT group vs 5.97m ± 13.95m in the CT group corresponded with an effect size Cohen's d of 0.50 (see Table 3.5). A Cohen's d of 0.20 was found on the TMW-DT for a larger increase in the DT training group compared to the CT group. DTE on walking distance during TMW-DT did not change significantly over time and without differences between groups ($p > 0.05$), but there was a trend towards significant decrease in DTE over time ($F = 2.809$; $p = 0.071$). Although no significant differences between groups were seen, largest mean decrease in DTE was seen in the control training group from -0.14% ± 0.08% post training to -0.9% ± 0.10% at the follow-up visit (see Table 3.4).

3.3.2 **Primary outcome: Community walking and physical activity**

Responses to two community walking questions showed a significant (Wald Chi Square = 9.643; $p = 0.008$) increase for number of stroke survivors from both groups who indicated 'yes' to the question: "Do you feel confident when walking in the community?" Data and generalized linear model results of 'yes-' and 'no-responders' are presented in Table 3.6. In the DT group the percentage of 'yes-

responders' increased from 61.54% at baseline to 70.83% post-training and 79.17% at follow-up. For the participants in the CT group 'yes-responders' increased from 52.17% to 80.95% to 90.00% respectively. The strength of increase was different between the two training groups indicated by a significant Time*Group interaction with the CT group improving more (Wald Chi Square = 12.673; p = 0.027). No significant differences between groups and over time were seen in percentage of 'yes-responders' for the question: "Do you get out of the house as much as you like?"

Physical activity as measured with step activity monitors and with the PASE questionnaire showed no significant differences between groups or changes over time ($p > 0.05$). However a significant interaction ($F = 3.701$; $p = 0.029$) for Time*Group was found for the PASE questionnaire (See Table 3.7). Stroke survivors receiving dual task training increased on average from 73.4 ± 46.6 at baseline to 87.8 ± 46.8 post training and 88.3 ± 41.9 at follow-up compared to stroke survivors in the CT group who decreased on average from 94.7 ± 48.3 to 71.4 ± 43.7 to 75.4 ± 43.2 respectively.

Table 3.4 Linear mixed model results for two-minute-walk without and with dual task

Outcome measure	Group	Baseline	Post-training	Follow-up	Linear Mixed Model results			
		Model means (SEM)	Model means (SEM)	Model means (SEM)	Effect	df	F	*p-value*
Two-minute-walk distance (m)	Control	**86.74** (8.54)	**93.17** (8.58)	**92.75** (8.62)	Group	*45.793*	*0.362*	*0.550*
	Dual Task	**90.66** (8.20)	**99.68** (8.21)	**103.47** (8.24)	Time	***85.983***	***11.132***	***<0.001***
Two-minute-walk with dual task distance (m)	Control	**75.44** (7.33)	**79.72** (7.35)	**82.97** (7.40)	Group	*45.976*	*0.191*	*0.665*
	Dual Task	**78.50** (7.03)	**84.26** (7.04)	**88.82** (7.06)	Time	***86.172***	***9.196***	***<0.001***
Two-minute-walk Dual task effect (DT-ST) / ST *100	Control	**-10.80%** (1.90)	**-13.70%** (1.90)	**-9.10%** (2.00)	Group	*44.382*	*1.809*	*0.186*
	Dual Task	**-13.40%** (1.90)	**-15.80%** (1.90)	**-14.00%** (1.90)	Time	*44.028*	*2.809*	*0.071*
Two-minute-walk Cognitive response (Number of responses)	Control	**11.92** (0.83)	**12.37** (0.86)	**13.88** (0.90)	Group	*33.529*	*2.084*	*0.158*
	Dual Task	**11.23** (0.80)	**12.61** (0.82)	**12.20** (0.85)	Time	***38.068***	***5.664***	***0.007***

DT: Dual task walk, ST: Single task walk, df: degrees of freedom. Significance level for mixed model, α = 0.05

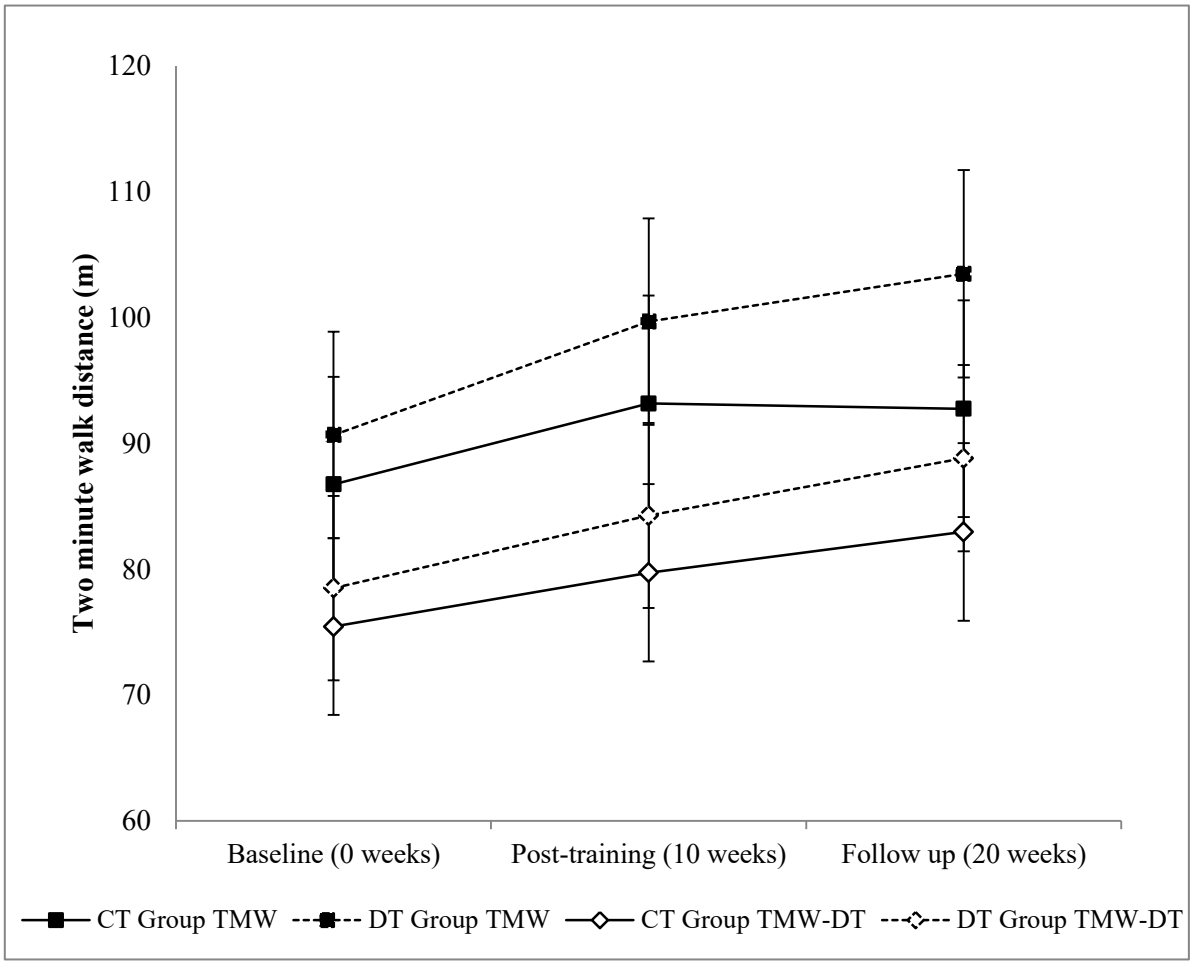


Figure 3.2 CT: Control, DT: Dual Task , TMW: two-minute-walk , TMW-DT two-minute-walk with dual task. Average two-minute-walk data of stroke survivors in dual-task group (dotted line) and control group (solid line). Data from both the two-minute-walk without (square solid marker) and with dual task (diamant open marker). Error bars indicate standard error of the mean.

Table 3.5 Cohen's d effect sizes for comparison between groups for change from baseline to follow-up in two-minute-walk distance without and with distraction

Two-minute-walk		**Two-minute-walk with dual task**	
Control	Dual Task	Control	Dual Task
Change (m) ± stdev	*Change (m) ± stdev*	*Change (m) ± stdev*	*Change (m) ± stdev*
5.97 ± 13.95	**12.82 ± 13.72**	**7.81 ± 13.87**	**10.34 ± 11.75**
Cohen's d	*effect-size r*	*Cohen's d*	*effect-size r*
0.50	**0.24**	**0.20**	**0.10**

Table 3.6 Generalized linear model results for community walking questions.

					Generalized linear model		
Outcome measure	Group	Baseline	Post-training	Follow-up	Group effect	Time effect	
Community Walking Q1 *Do you get out of the house as much as you like?*	Control	No = 9 Yes = 14	No = 7 Yes = 14	No = 4 Yes = 16	*Wald Chi Square (p-value)*	*Wald Chi Square (p-value)*	
	Dual Task	No = 9 Yes = 17	No = 6 Yes = 18	No = 7 Yes = 17	0.015[a] (0.902)	1.545[a] (0.462)	***Interaction effect***
Community Walking Q2 *Do you feel confident when walking in the community?*	Control	No = 11 Yes = 12	No = 4 Yes = 17	No = 2 Yes = 18	*Wald Chi Square (p-value)*	*Wald Chi Square (p-value)*	*Wald Chi Square (p-value)*
	Dual Task	No = 10 Yes = 16	No = 7 Yes = 17	No = 5 Yes = 19	0.589[a] (0.443)	**9.643[a] * (0.008)**	**12.673[a,b] + (0.027)**

a. Generalized linear model: Wald Chi Square, * Significant effect of Time on outcome measure

b. Results from model with just the interaction term Group*Time, [+] significant Group * Time interaction for outcome measure

Significance level for generalized linear model, α = 0.05.

Table 3.7. Linear mixed model results for Physical Activity Scale and Step Activity Monitors

Outcome measure	Group	Baseline	Post-training	Follow-up	Linear Mixed Model results			
		Model means (SEM)	Model means (SEM)	Model means (SEM)	Effect	df	F	*p-value*
Physical Scale for Elderly	Control	**94.72** (9.36)	**74.65** (9.79)	**77.31** (9.93)	Group	*47.316*	*0.019*	*0.892*
	Dual Task	**74.26** (9.11)	**86.89** (9.11)	**89.95** (9.41)	Visit	*83.684*	*0.237*	*0.789*
					Group * Visit	***83.684***	***3.701***	***0.029****
Step Activity Monitor (Steps/day)	Control	**2747** (402)	**2949** (411)	**2619** (424)	Group	*45.910*	*1.391*	*0.244*
	Dual Task	**3469** (390)	**3411** (390)	**3131** (389)	Visit	*75.235*	*1.570*	*0.215*

SEM; Standard error of the mean, df; degrees of freedom. Significance level for mixed model, α = 0.05

3.3.3 **Secondary outcome: Health and Wellbeing**

Perception of health changed significantly over time as a result of 10 weeks of treadmill training for stroke survivors in both groups (see Table 3.8 for details). In addition, when asked about their health on the day through the EQ-5D questionnaire, on average stroke survivors from both groups increased their EQ-5D index scores over time. For both the SF-36 scores and the EQ-5D score no significant differences were seen between groups ($p > 0.05$).

3.3.4 **Follow-up assessment: Modified Life Space Assessment**

At follow-up a trend towards a significant difference on the modified UAB LSA (Figure 3.3) between the CT and DT group was found favouring the DT group. Mean score on the modified UAB LSA for the DT group was 54.76 ± 26.64, range 11.00 – 92.00 and 41.53 ± 20.88 for the CT group, range 10.00 – 112.00. Multiple regression analysis showed TMW-DT distance at baseline ($\beta = 0.261$, $t = 2.024$, $p = 0.050$) and type of training group ($\beta = 0.528$, $t = 4.097$, $p < 0.001$) as significant predictors for the modified UAB LSA score at follow-up (Model: adjusted $R^2 = 0.318$, $p < 0.001$) (for scatterplot see Paragraph 8.2.2, Appendix 3.B, Figure 3.B1).

Table 3.8 Linear mixed model results for perception of Health and Wellbeing

Outcome measure	Group	Baseline	Post-training	Follow-up	Linear Mixed Model results			
		Model means (SEM)	Model means (SEM)	Model means (SEM)	Effect	df	F	Sig.
SF-36 Total Score	Control	**60.9** (3.6)	**66.7** (3.7)	**67.2** (3.7)	Group	*48.682*	*1.900*	*0.174*
	Dual Task	**54.7** (3.4)	**61.3** (3.5)	**60.3** (3.5)	Time	***64.918***	***6.629***	***0.002***
SF36-Mental score	Control	**65.2** (3.8)	**69.5** (3.9)	**72.0** (3.9)	Group	*48.435*	*1.317*	*0.257*
	Dual Task	**61.0** (3.7)	**66.3** (3.7)	**62.8** (3.7)	Time	***65.960***	***3.821***	***0.027***
SF-36 Physical score	Control	**56.0** (3.5)	**60.8** (3.7)	**59.7** (3.7)	Group	*48.385*	*2.160*	*0.148*
	Dual Task	**47.4** (3.4)	**55.6** (3.5)	**55.3** (3.5)	Time	***71.968***	***5.524***	***0.006***
EQ-5D index	Control	**0.71** (0.04)	**0.78** (0.04)	**0.73** (0.04)	Group	*47.031*	*0.027*	*0.870*
	Dual Task	**0.72** (0.04)	**0.76** (0.04)	**0.71** (0.04)	Time	***86.669***	***3.795***	***0.026***

SEM; Standard error of the mean, df; degrees of freedom. SF-36; Short-Form-36, EQ-5D; EuroQol-5D

Significance level for mixed model, α = 0.05

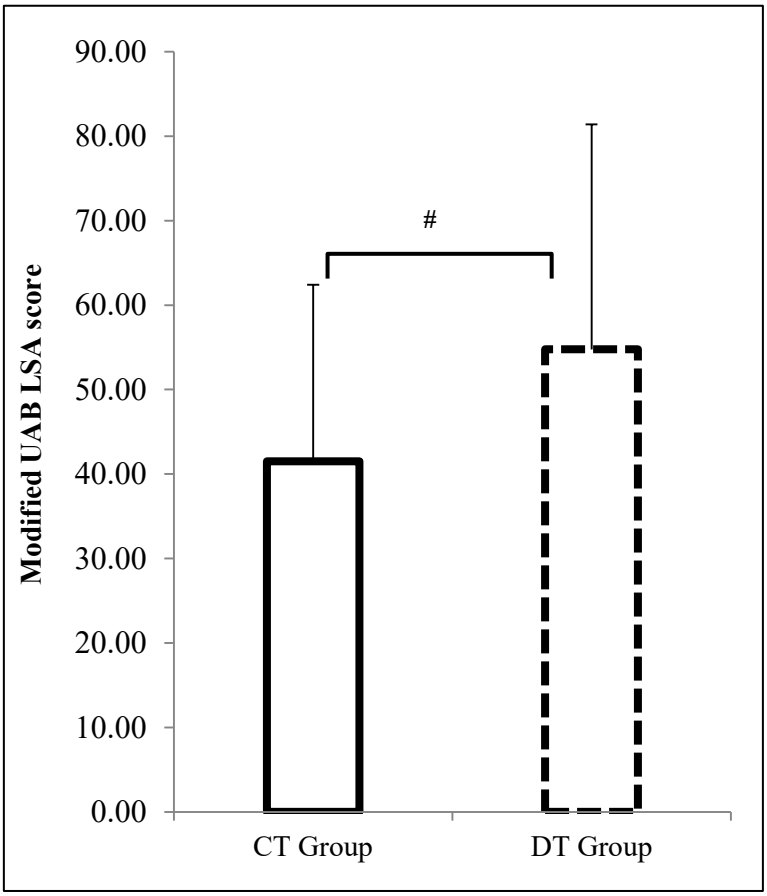


Figure 3.3 Mean scores of the Control (CT) and Dual Task (DT) training group for the modified UAB Life Space Assessment at follow-up. # Independent t-test: trend towards significant difference between training groups through (t = -1.763; p = 0.086).

3.3.5 **Training feasibility and in training progression**

There were no adverse health outcomes as a result of the training and adherence could considered to be high. Out of the 50 stroke survivors who entered training, 43 completed the full training period (Paragraph 8.2.3, Appendix 3.C). Five participants withdrew due to comorbidities, one due to travel requirements and one found the dual task training too demanding. Two stroke survivors who dropped out did complete intention to treat for the assessments. Furthermore it was found that 42 out of 43 stroke survivors increased their walking speed and time on the treadmill during the 10 weeks of training. There were no significant differences of training improvements of treadmill walking speed, duration, and average heart rate between the CT group and DT group ($p > 0.005$). Mean changes from the start to the end of training were +0.8 ± 0.6km/h and +1.0 ± 0.7km/h for treadmill speed and +13 ± 11min and +12 ± 8min for training session duration in the CT group and DT group respectively. Moreover mean relative heart rate during sessions were 61 ± 1 % for the CT group and 62 ± 1% for the DT group. For the cognitive part of the dual task training we found that certain tasks proved to be easier to score than others. Of the cognitive tasks, the clock face and serial subtraction task were scored over time and analysed together with the response to the radio/audio fragment and the planning task (For details on scoring and processing see paragraph 8.2.3, Appendix 3.C). Stroke survivors improved their scores on the clock face task from 82 ± 23% at training session one to 94 ± 17% at session 18 ($p = 0.03$) and on the radio task from 88 ± 21% to 98 ± 8% . No changes between the start of training and the end of the training period were found for the serial subtraction task and the planning task in which all stroke survivors score the maximum of 100% at the end compared to 93 ± 14% the start of training ($p > 0.05$).

3.4 Discussion and Conclusions

For the first time in a well-controlled phase 1 study we have shown that when compared to a comparable physical training only group a combined physical and cognitive training group improved on a number of mobility measures in chronic stroke survivors. Both groups improved but the DT training improved community walking more as measured by significant group and time interaction for the PASE and a trend towards a higher life spaces questionnaire score for the DT group at follow-up. Moreover, small and moderate effect-sizes were seen for larger increases on the TMW-DT and the TMW in the DT group compared to the CT group from baseline to follow-up.

3.4.1 Overground walking

Both single and dual task training approaches seemed to be well tolerated. Moreover both groups showed progression on two-minute-walk tests, community walking and health and wellbeing after 10 weeks of training and at follow-up. Stroke survivors allocated to the DT group increased their TMW on average with 12.82 meter at follow-up compared 5.97 meter for stroke survivors receiving the control training. These increases would roughly correspond to increases of 17.91 and 38.46 meter on a six minute walk (Bohannon, Bubela et al. 2014). This is in accordance with others studies in stroke survivors that found increases in walking speed and endurance following treadmill interventions. Mehrholz et al. (2014) calculated a pooled mean increase of 20.08 meter on the six minute walk at the end of their study.

Following 10 weeks of treadmill training stroke survivors from both groups increased their TMW-DT distance to a similar extent as they increased on the TMW. The difference in extent of increase on the TMW between the two training

groups was not significant different. On the TMW-DT, differences between the two groups were smaller and again significant over time for both groups. As both the TMW and TMW-DT increased to similar extents, no significant change in DTE on the walking distance was seen over time in either group. In other words, the improvement in walking performance overground, did not affect the extent to which it was affected by dual task. However, when exploring the cognitive performance scores during the TMW-DT, it showed that both groups improved significantly on the number of responses given during the walk. This suggests that the improvement in walking performance led to further increases in walking distances and enhancement of cognitive function during walking. These results are in accordance with the data that have been discussed in chapter 2, where it was shown that stroke survivors walking at moderate-to-full community walking speeds had a higher cognitive response during the TMW-DT compared to stroke survivors walking at limited community walking speeds. Care needs to be taken with the interpretation of cognitive responses during dual task measurements in stroke. Recently, Yang et al. (2016) have published the results of a reliability and validity study of dual task assessments in community-dwelling stroke survivors. They found that the reliability of DTE measurement on gait was moderate to good, but only poor to fair for the cognitive aspect of a dual task. Furthermore, within a dual task, reliability of performance on the cognitive tasks was lower than reliability of the gait task. Effectively measuring dual task ability and the DTE on gait and cognition in stroke is challenging and requires further studying to explore optimal assessment methods.

3.4.2 **Health and wellbeing**

Next to improvements in walking distance, EQ-5D index, SF-36 total - and domain scores improved significantly over time in both training indicating the positive

effect of cardiovascular training on health and wellbeing. This is a stronger effect than found in a study published by Gordon et al. (2013) who found a trend towards improvement in the physical domain of the SF-36 in stroke survivors receiving aerobic training compared to stroke survivors receiving massage on the hemiplegic leg.

3.4.3 **Community walking**

The possible effect of dual task training on community walking ability was also assessed in this study through questions about community walking. Over time and between groups there was no effect of training on the response to the question: "*Do you get out of the house as much as you like?"* When asked more specifically about community walking, over time more stroke survivors in both groups responded "yes" to the question: "*Do you feel confident when walking in the community*?". Remarkably, the amount of people responding with "yes" compared to "no" improved relatively more in the CT group compared to the DT group leading to a significant interaction between time*group in favour of the CT group. This was unexpected, but is possibly explained by the relatively larger amount of "no" responders at baseline in the CT group compared to the DT group, creating more room for improvement in the CT group. Nonetheless this shows that the improvement in walking speed and endurance, regardless of any improvement in cognitive ability has a significant effect on the perceived confidence of a stroke survivor. In contrast, the results of the PASE and SAM data suggested little to no improvement in amount of walking and physical activity over time. The PASE did show a significant interaction favouring the DT group, suggesting that the training had a more positive effect on those stroke survivors in increasing their weekly physical activity. Care should be taken when drawing conclusions from the PASE results as the scores were, although non-significant ($t = 1.569$; $p = 0.123$), slightly

different between groups at baseline, it is possible that the DT group had more room to improve starting from a lower baseline score. On the other hand this would not explain why the CT group showed a reduction on the PASE score over time. This suggests that stroke survivors from the CT group got less active towards the end of study compared to the start. The data from the step activity monitors does not support this finding as there were no significant changes in step activity over time in either group.

This is similar to results in a small sample of stroke survivors in a study by Michael et al. (2009) who found increases in six minute walk distance and improvements on the berg balance scale, but no change in step activity following 6 months of physical activity training. The step activity monitors can only provide information about the amount of step activity, but it does not allow as a measure of community walking as the data cannot tell where people walked.

Results from the modified UAB LSA can provide some insight in where stroke survivors walked over a period of 4 weeks in advance of the follow-up measurement. Some consideration should be taken into account as recently the scoring system of the UAB LSA was debated and discussed (Baker, Bodner et al. 2016, Portegijs, Viljanen et al. 2016, Siordia 2016, Siordia 2016). Moreover, for this study, the UAB LSA was slightly modified and focussed on just walking so therefore results from this questionnaire are discussed to highlight interesting trends rather than drawing strong conclusions with clinical implications. There was a trend towards a higher modified UAB LSA score for stroke survivors in the DT group at follow-up, indicating that they more frequently walked in life space areas described as “places outside their neighbourhood” and “places outside their town”. It has been shown before that walking speed and distance relate to community walking ability (Bijleveld-Uitman, van de Port et al. 2013). The results of the correlation analysis suggest that stroke survivors who got allocated to the DT

intervention and who had a better walking ability, as measured with the TMW-DT distance, and higher physical activity levels, had higher community levels at follow-up. Although the modified UAB LSA was only assessed at follow-up, other community measures did not differ at baseline assuming that it is likely that community walking ability was similar between the groups at baseline. Dual task treadmill training may be more effective to increase community walking ability compared to just treadmill walking, but only in stroke survivors who already have recovered their walking up to a certain standard and are already physically active. The current dataset is too small to provide exact numbers for walking ability and physical activity levels above which stroke survivors are more likely to benefit from community walking training.

3.4.4 **Study and training feasibility**

The feasibility of training was explored and written up in a separate paper which is attached in paragraph 8.2.3 (Appendix 3.C). There was a dropout of 14% in training and 10% for the assessments. These percentages were around what we expected in this neurological population. Next to feasibility, in-training results showed on average significant improved cognitive performance during the clock face task and an improved response during the audio fragment and the planning task blocks. The intervention was easy to deliver in community settings and could be delivered within stroke care pathways. Our findings support that a combined approach is feasible and may deliver better outcome than physical training alone and as such should be considered as an effective approach to improve walking performance and community walking ability.

It is difficult to compare the feasibility of this study with other dual task trials as most had much shorter training periods and lower numbers of participants. In

comparison to other treadmill training studies at aerobic training intensities, in a trial by Globas et al. (2012) who explored the effectiveness of a 3 months treadmill training in a randomized controlled trial with 36 stroke survivors, 17% of stroke survivors participating had dropped out for walking assessments at follow-up. A trial by Kuys et al. (2011) with 30 stroke survivors of whom 15 underwent high-intensity treadmill exercise for 6 weeks on top of regular physiotherapy versus 15 who underwent regular physiotherapy only, 3 stroke survivors had dropped out of each group the follow-up assessments at 18 weeks.

Other dual task trials have often made use of virtual reality to deliver the dual task aspect of training (Jaffe, Brown et al. 2004, Yang, Tsai et al. 2008, Mirelman, Bonato et al. 2009, Xiao, Mao et al. 2012, Cho and Lee 2013). Virtual reality training is a promising and developing technique which allows for creating forms of distractions which are similar to the real distractions that stroke survivors meet when walking in the community. However, practically, virtual reality systems can be very expensive and may need large spaces for set-up, creating challenges when one for instance wants to train study participants in community leisure centres. The delivery of cognitive task through audio devices or through interaction with the training professional worked well. On average stroke survivors seem to cope well with the dual task training and intensity of training was similar for both training groups. The costs for this type of cognitive training are much lower than virtual reality systems requiring specialized treadmills and multiple computer systems or cameras (Jaffe, Brown et al. 2004, Yang, Tsai et al. 2008). Moreover it would be very feasible to run a community-based multi-site trial with the currently used types of distractions, whereas virtual reality techniques limit the training locations to where that particular equipment is available. Some of the cognitive tasks used in the dual task training were difficult to quantify and future work should therefore

aim on improving analyses of cognitive progression during dual task training interventions (Paragraph 8.2.3, Appendix 3.C).

3.4.5 **Limitations and future perspective**

There were some limitations in this study which may have had an influence on the extent to which training had an effect on (dual task) walking ability of stroke survivors. Our population was heterogeneous with a high variation in the clinical characteristics and walking ability of stroke survivors. This means that our results are widely interpretable and possibly applicable to a large stroke population, but it also means that some of our inconclusive findings may have been a result of the high variation in scores on our primary and secondary outcomes. A simple solution would be to include a larger number of stroke survivors, but that would also mean higher costs and more resources needed affecting the practicability of such a trial. Ideally another objective measure of community walking would be included to add to the current available measures. Current community walking measures are mostly questionnaire-based and rely on retrospective memory of stroke survivors which may not always be reliable. Other measures, such as step activity monitors, tell us something about walking activity, but not specifically community walking. One possible new measure that could be promising is the use body cameras, which would not only provide information about physical activity, but also about where this activity takes place (Hodges, Berry et al. 2011, O'Loughlin, Cullen et al. 2013). However, ethical issues around this type of instrumentation need to be carefully considered before it could be implemented in neurological population such as stroke (Kelly, Marshall et al. 2013).

Chapter 4. Neuroimaging of gait with fMRI and fNIRS

The current chapter gives an introduction into neuroimaging and describes the use of neuroimaging techniques for measurement of brain activation during gait. Using these techniques can help understand the underlying mechanisms of brain plasticity and motor recovery after stroke.

4.1 Introduction into neuroimaging

Brain activation influences the functional state of the brain. Activation is characterized by an increased neuronal activity which leads to increased consumption of glucose and oxygen (Belanger, Allaman et al. 2011). As a result, neuronal activity is followed by changes in blood oxygenation and blood flow which are also known as the blood-oxygen-level dependent (BOLD) response (Obrig and Villringer 2003). The BOLD response occurs approximately 1-5 seconds after neuronal activity and stimulates an increase in blood flow to the active brain area. The increase in blood flow typically exceeds the demand resulting in a relative concentration increase in oxygenated haemoglobin and a relative decrease in deoxygenated haemoglobin (Gore 2003). Changes in blood flow, volume and oxygenation are known as the hemodynamic responses and are in relation to neural activity referred to as being part of neurovascular coupling (Buxton, Uludag et al. 2004, Fabiani, Gordon et al. 2014). Both neuronal activity and hemodynamic responses can be measured using different brain imaging techniques. Neuronal activity can be measured by electroencephalography (EEG) or magneto encephalography (MEG), whereas hemodynamic responses can be measured using functional magnetic resonance imaging (fMRI) and functional

near-infrared spectroscopy (NIRS). Other techniques as PET and single-photon emission computed tomography (SPECT) measure the hemodynamic responses in the brain after a radioactive tracer is injected in the subject's bloodstream. Decisions on which brain imaging technique to use in research are made upon costs, subject safety, desired imaging resolution (both spatial and temporal) and behavioural methodology (i.e. imaging during movement, cognitive task or other). Figure 4.1 provides a plot of the spatial and temporal characteristics of the above mentioned imaging techniques. FMRI provides high spatial resolution (down to 1mm) but has low temporal resolution (several seconds) compared to EEG and MEG (down to 10 milliseconds) (Jezzard, Matthews et al. 2001). Although they can provide reasonable spatial resolution, both PET and SPECT have poor temporal resolution, are very high in costs and have considerable safety arrangements, because they use radio-active tracers. Therefore, both are most often used as a diagnostic tool rather than a research measurement tool. FNIRS is one of the cheaper techniques and is much more applicable when exploring brain activation during large movements (i.e. walking, cycling or rowing) and has a spatial resolution down to $1cm^2$ (Ferrari and Quaresima 2012).

The studies described in this thesis have used both fMRI and fNIRS to explore brain activation during locomotor movements. The next section of this chapter explains the physical and physiological concepts of these techniques and comments on the use of them in research on neuroimaging of gait.

4.2 **Physiology of fMRI; the gold standard in neuroimaging**

FMRI, the gold standard in neuroimaging, is a non-invasive tool which uses the magnetic properties of Hydrogen (H^+) molecules of deoxygenated haemoglobin (HHb) to measure changes in oxygenation of blood in the brain. Brain activity causes a rise in concentration of oxygenated haemoglobin (OHb), but more

importantly, HHb levels decrease relatively which means that the MRI signal in that area will be slightly stronger (around 1%) compared other non-active areas (Gore 2003). Quantifying neuronal activity with fMRI is done by measuring the blood flow and energy metabolism related to the neuronal activity. By creating maps of glucose - or oxygen consumption and maps of local blood flow, neuronal activity maps can be determined (Jezzard, Matthews et al. 2001).

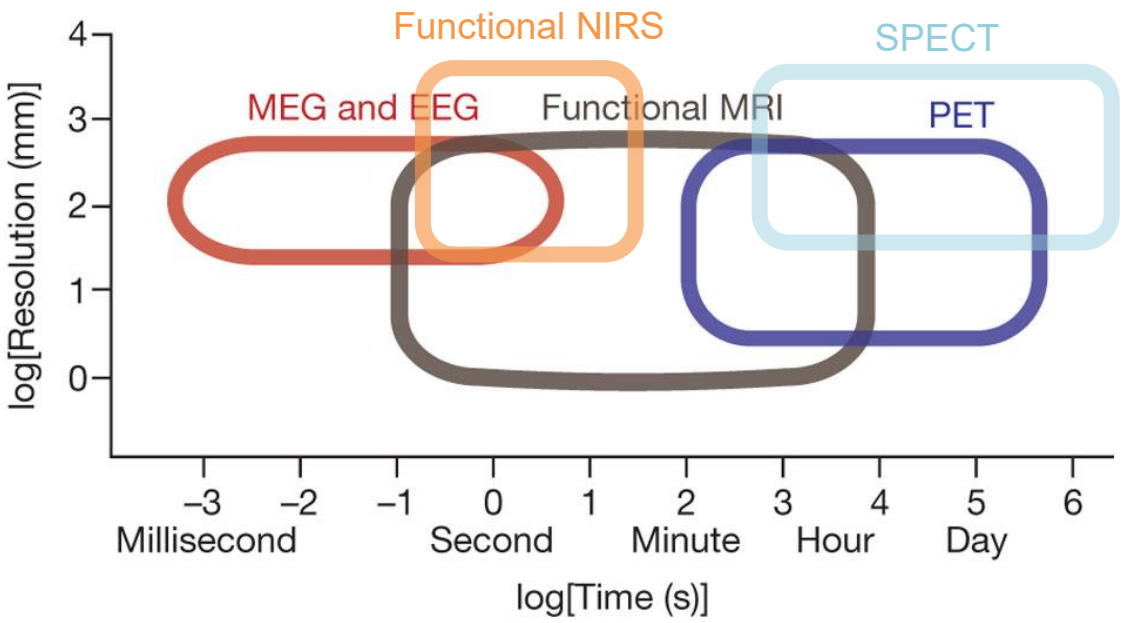
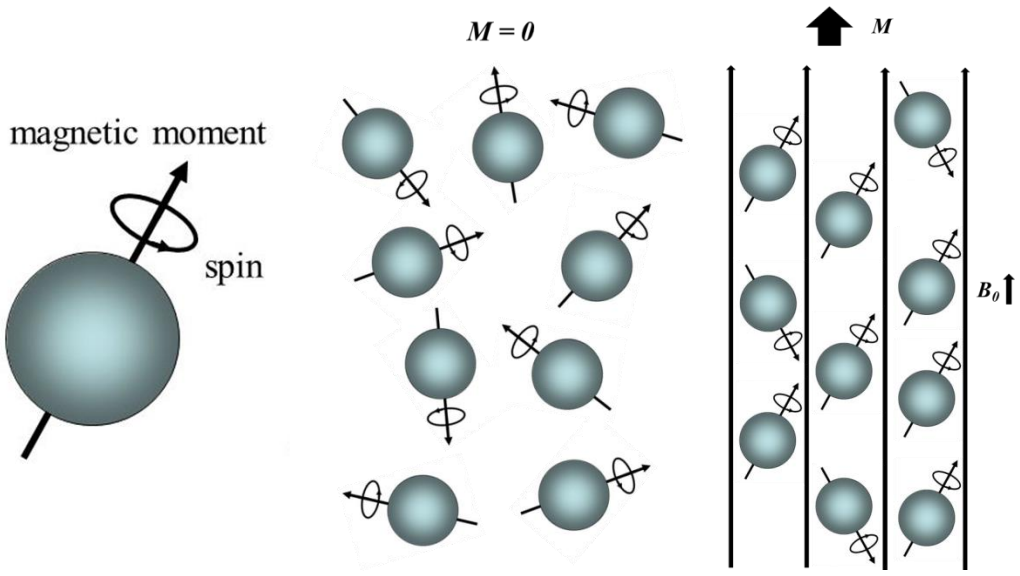


Figure 4.1 Plot of temporal - and spatial resolution of: MEG; Magnetic Electroencephalography, EEG; Electroencephalography, NIRS: Near-infrared spectroscopy, MRI; magnetic resonance imaging, PET; Position emission tomography and SPECT; Single photon emission computed tomography. (Adapted from (Meyer-Lindenberg 2010)).

4.3 **Principles of fMRI**

During an fMRI scan, the brain tissue is placed in a (strong) magnetic field which affects all different molecules within the brain. Here we focus on the H^+ nuclei

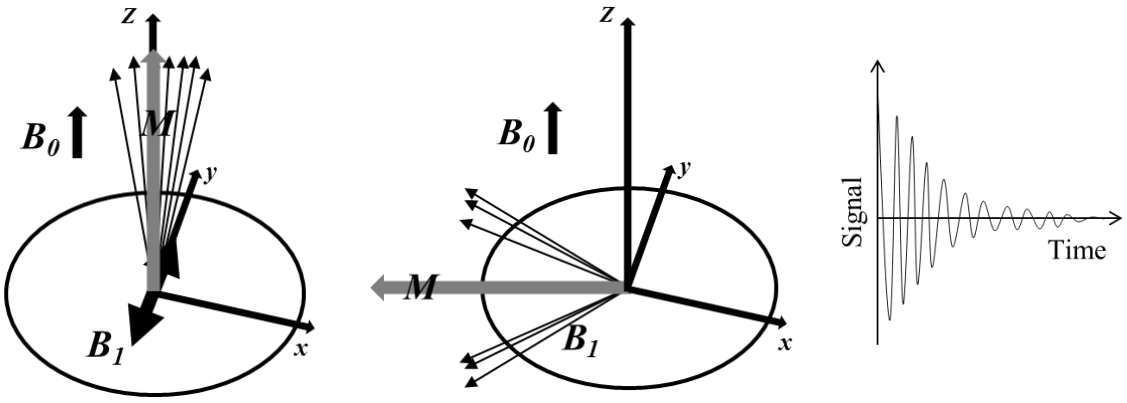
within HHb, which eventually provide the signal for the fMRI image. Each H^+ nucleus has a magnetic moment, which has a random direction (Figure 4.2A). A sample of randomly aligned H^+ nuclei will just before they are introduced to an external magnetic field, B_0, have a net magnetic moment of zero (Figure 4.2B). Whilst in B_0 the sample will have just a few more H^+ nuclei that align parallel to the direction of B_0 compared to nuclei that align anti-parallel (Figure 4.2C). The magnetic moment of the nuclei will cause a spin around the axis that is parallel to B_0 which has a frequency that to referred to as the Larmor frequency. This frequency is proportional to the field strength of B_0.



A. **B.** **C.**

Figure 4.2 Physics of MRI. A. A hydrogen nucleus spinning around its axis and generating a magnetic moment. B. A sample of H^+ nuclei without the presence of an external magnetic field is randomly orientated and has a net magnetic moment of zero. C. With the presence of B_0, more nuclei orient parallel to B_0 compared to anti-parallel generating magnetic moment *M* (based on figures from (Jezzard, Matthews et al. 2001)).

However, B_0 on its own does not cause a 'change' in signal coming from the H^+ nuclei which can be measured. Therefore an oscillating magnetic field, B_1, is applied which is oscillating at a radiofrequency (RF) equal to the Larmor frequency of the nuclei spins. B_1 is applied perpendicular to B_0 and therefore perturbs the direction of magnetic moments of the H^+ nuclei (Figure 4.3A). Following the perturbation, the magnetic moment of the sample of nuclei will align to the direction of B_1 and generate a signal once B_1 is turned off (Figure 4.3B). This signal can be picked up by a receiver coil (Figure 4.3C).



A. **B.** **C.**

Figure 4.3 The MRI signal A. An oscillating B_1 field is introduced through a radiofrequency pulse and can change the orientation of moment *M*. B. A typical radiofrequency pulse tips moment *M* 90° into the *x-y* plane C. As soon as the radiofrequency pulse stops, a signal will be measurable which will reduce in strength over time until the net moment *M* is aligned back to B_0 and the signal is zero (based on figures from (Jezzard, Matthews et al. 2001)).

The time it takes for the net magnetization to recover to the main direction of B_0 is termed T1. T2 is the time that it takes for the magnetization in the transverse plane (Figure 4.3) to decay and is influenced by the random fluctuations in the Larmor frequency at a molecular level. Areas in the human head, especially around the

sinuses, will show different magnetic susceptibility and therefore nuclei in different areas will experience slightly different magnetic field strengths. Next to this, due to field inhomogeneity, fluctuations will appear in the B_0 also affecting the behaviour of nuclei. The decay in transverse magnetization as a result of these field and sample inhomogeneities is called $T2^*$ and may be even more important than T2. The main reason for this argument is that tiny magnetic changes in the blood as a result of HHb levels also attribute to $T2^*$. Therefore $T2^*$ closely relates to the BOLD response and provides crucial information necessary to generate the image contrast that reflects the BOLD response.

In a typical fMRI experiment a 90° pulse will be used to flip moment *M* into the transverse plane (Figure 4.3B) followed by a 180° pulse to refocus the factors that drive $T2^*$ and generate a measurable signal. This type of sequence is called a spin echo and is commonly used in fMRI sequences.

To extract a signal from a specific location in the brain, magnetic field gradients (G) are applied in the direction *x, y* and *z* through gradient coils situated in the magnet bore. Introduction of a gradient along the *z* direction (G_z) will cause Larmor frequencies of nuclei spins to vary as a function of position and enables spatial encoding of the frequency of spins along a particular direction in space. An RF pulse at a certain frequency under the presence of G_z will then only excite nuclei that spin at Larmor frequencies within that range. The size of this range will influence the thickness of the slice that will be excited and is influenced by the pulse length and bandwidth of the RF pulse and the steepness of G_z. Two more gradients are introduced to encode the signal. One gradient is in the read direction (G_x) as a function of position to produce a projection in the direction of that G_x. The third gradient (G_y) is applied to encode the projection of the signal intensity and phase.

Frequencies coming from MRI signals measured along the directions *x* and *y* can be described in an array which is referred to as k-space. Via a Fourier transform, the data stored in k-space can be turned into a 2D MRI image.

4.3.1 **Temporal resolution**

FMRI has a relatively slow temporal resolution as it depends on the BOLD response which normally occurs over the course of 5-7 seconds. An area activating in response to a stimulus initially can show a brief decrease in signal followed by an increase which levels after 5-7 seconds.

Depending on the type of stimulus, once level, the signal may stay stable until the stimulus stops and the BOLD signal decreases into an undershoot after which it recovers slightly to get back to baseline level. The undershoot is hypothesized to be related to the slow recovery of the cerebral blood flow after synaptic activity (Jezzard, Matthews et al. 2001). The possible initial decrease was shown by optical imaging studies in animals and thought to be related to rapid deoxygenation (increases in levels of HHb) of the capillary blood together with synaptic activity related oxygen use (Malonek and Grinvald 1996, Chen, Friedman et al. 2005). However, fMRI studies and optical imaging studies in later years, did not always report the initial dip and instead found increases in total haemoglobin levels (Chen and Zhou 2011, Martin, Zheng et al. 2013). This latter effect could possibly be explained through an active neurovascular coupling, but the exact mechanism is still under debate (Hillman 2014).

4.3.2 **Spatial resolution**

The spatial resolution in fMRI can be up to 1mm precise, but does depend on a few factors. One very important factor is the contribution to the signal of large vessels. Because of their size, they ship larger amounts of blood and the challenge in fMRI

is to limit the contribution of signal coming from these vessels as the important part of the signal is found in the capillaries, which are closest to the site of neural activity. One way to deal with this is through the use of specific pulse sequences (Bandettini 2001). Increasing magnetic field strength of the scanner is the best way to increase the contribution of capillary signal. Some other technical changes can be made by for instance making use of bipolar gradients or quadrature surface coils (Lin, Rajan et al. 1998, Jezzard, Matthews et al. 2001). However, introducing these technical changes can introduce new challenges, such as limitations for motion correction techniques.

4.3.3 **Motion and slice timing correction**

As with most neuroimaging techniques, the signals collected are very sensitive to motion. Especially in fMRI a head movement as small as 1mm can cause a major motion artefact in the data. Therefore it is very important to provide clear instructions to a subject being scanned and to try to prevent movement as much as possible. Small cushions can be used to give stability to the subject's head and furthermore any other cushions or aids that comfort the subject will help to reduce the head motion. However, especially when scans get longer, when subjects are asked to move an upper or lower limb during the scan, and when measuring neurological populations, it is impossible to rule out head motion completely.

The goal in motion correction is to end up with statistically activated areas of which the activation can be attributed to the task or behaviour being tested and not to head motion or motion related to task execution (Johnstone, Ores Walsh et al. 2006).

The acquisition time of slices that are collected in one volume is slightly different for each slice. Slice time correction is used to correct for these different timings and also functions as motion correction by aligning all slices within one volume as

if they all were acquired at one time point which allows for much easier processing during the next steps.

Additional motion correction may be needed and can be achieved by creating an additional parameter for statistical modelling which accounts for time points at which large motion artefacts are visible in the fMRI data. Independent component analysis can be used to split datasets in artefactual and non-artefactual components which can then be detected through manual or automatic selection (Griffanti, Salimi-Khorshidi et al. 2014, Salimi-Khorshidi, Douaud et al. 2014). Regardless of all motion artefact correction techniques that can be applied, there is no absolute solution for removal of artefacts yet, but effective minimization can be achieved.

4.4 **Imaging locomotor movements with fMRI**

Studies that have investigated brain activity and motor control during locomotion using fMRI were often designed around the neuroimaging technique. The study protocols have to account for the size of the equipment and the sensitivity of the equipment to motion artefacts. Moreover due the MRI machinery, the subjects have to lie down and their head and body have to stay in a fixed position to prevent any motion of the head while the scan is performed. Nevertheless, fMRI can still be used to examine leg and or feet motions related to human gait. Studies have used lower limb movement (Hollnagel, Brugger et al. 2011, Toyomura, Shibata et al. 2012), knee flexion (Luft, Smith et al. 2002) and ankle flexion (Francis, Lin et al. 2009, Trinastic, Kautz et al. 2010) to investigate brain activation during imitated walking or during movement of lower limb joints.

Motor imagery of walking is another paradigm which has often been used (Bakker, De Lange et al. 2008, Wagner, Stephan et al. 2008, Wang, Wai et al. 2008, Crémers, Dessoullières et al. 2012, Zwergal, Linn et al. 2012) to study brain areas associated with human gait. Subjects were asked to imagine the walking movement

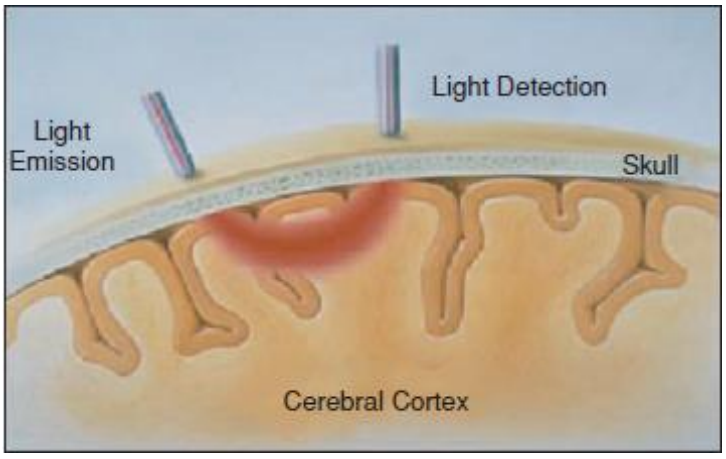
after practice outside the scanner (Jahn, Deutschlander et al. 2008, Wagner, Stephan et al. 2008) or by watching a video in the scanner in which they had to imagine that they were the walking person in the video (Wang, Wai et al. 2008, Wang, Wai et al. 2009).

Although these studies have provided information about what brain areas could be associated with human gait, they have not been able to image brain activity during real gait due to the limitations of a MRI scanner. FNIRS is a very interesting alternative to fMRI for measuring brain activation during movements as the technique enables recording of brain signals during real gait.

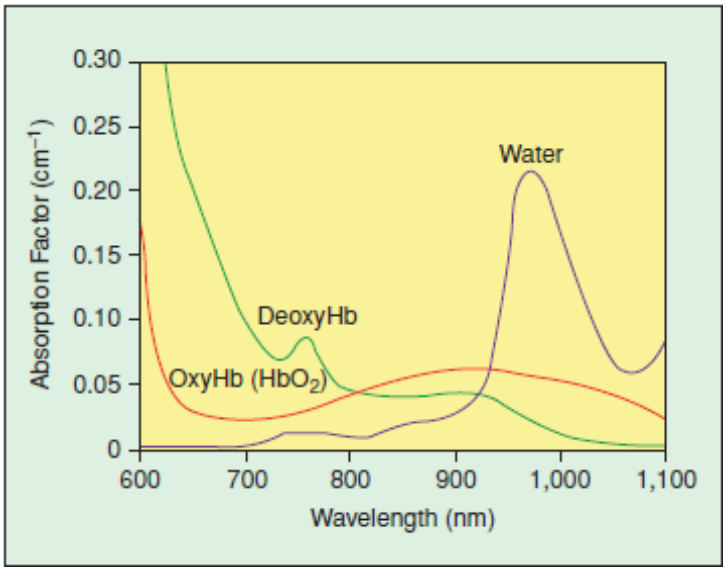
4.5 **The fNIRS signal**

The method of fNIRS uses light in the near-infrared range and relies on the optical properties of brain tissue which change depending on the functional state it is in (Bunce, Izzetoglu et al. 2006). During an fNIRS measurement, near-infrared light is shone into the brain through a light-source-optode placed such that it is in contact with the skin on the subject's head. At a certain distance from this optode, commonly between 30mm and 40mm, another detector-optode is placed to measure the intensity of light that is detectable from the initial light that was shone into the head. The light interacts in the brain with biological tissue through absorption and scattering (Obrig and Villringer 2003). Scattering of near-infrared light causes the light to travel between source- and detector optodes following a banana-shaped profile (Gratton, Maier et al. 1994) (see Figure 4.4A). Scattering and absorption rates of the light depend on the functional state and it will cause the light to cover a larger path than the set inter-optode distance (distance between light source and detector). Moreover the length of the path varies between individuals and changes with age (not consistently) due to differences in bone, myelin and muscle content within the field that light travels through (Duncan,

Meek et al. 1996). Near-infrared light at wavelengths between 600-900nm is used in fNIRS. This specific band is used as water, the most present substance of the brain, does not absorb much light at these wavelengths. Moreover, the chromophores OHb and HHb have high absorption rates in this part of the near-infrared spectrum (Figure 4.4B).



A



B

Figure 4.4 The fNIRS signal A. Banana-shaped profile of near-infrared light when shone through a human brain. B. Absorption rates of water, oxygenated - and deoxygenataed haemoglobin in near-infrared light between 600-1100nm (Figures from Bunce et al. (2006)).

Using the modified Beer-Lambert Law (MBLL), light absorption of chromophores in haemoglobin can be estimated and relative concentration changes and oxygenation of haemoglobin can be measured (Reynolds, Wyatt et al. 1988, Cope, Delpy et al. 1989). The MBLL can be described by the following equation:

$$OD_{\lambda} = \varepsilon_{\lambda} \cdot c \cdot L \cdot B + OD_{R,\lambda}$$

OD_{λ}: optical density of the medium that the light is travelling through

λ: wavelength used (nm)

ε_{λ}: chromophore's extinction coefficient ($mM^{-1} \cdot cm^{-1}$)

c: concentration of the chromophore (mM)

L: inter-optode distance (cm)

B: differential path length factor (DPF)

OD_{λ}: oxygen independent light loss due to scattering

Assumptions have to be made when using the MBLL in fNIRS, because it is a non-invasive technique and it cannot distinguish between light scattering and absorption. The most important assumption is that the DPF is constant during the entire measurement allowing for a calculation of concentration change from the change in optical density. Although the DPF is taken as stable within a measurement, it has been calculated for different modalities (e.g. head, arm, leg) at different ages in healthy young adults (Duncan, Meek et al. 1995). These standard DPF values can be used to optimize MBLL calculations (Duncan, Meek et al. 1996). Another assumption that has to be made is that the area the light is travelling through is homogenous, which is not true, but as the light only travels through the upper layer of the cerebral cortex the area is relatively "homogenous" (Obrig and Villringer 2003). Together with the assumption that the change in volume of the

"sampled" area is homogeneous within the sampled volume and the limited depth to which the light can penetrate the head, fNIRS can 'only' provide a spatial resolution up to 1cm^2 (Fukui, Ajichi et al. 2003, Bunce, Izzetoglu et al. 2006).

Temporal resolution of fNIRS is better with some systems being able to provide resolutions up to 100Hz (Ferrari and Quaresima 2012). In addition, fNIRS is able to provide information about concentration changes of both OHb and HHb, giving it an advantage over fMRI which is limited to paramagnetic properties of HHb and has a much lower temporal resolution due to acquisition of the signal by magnetic resonance (Huppert, Hoge et al. 2006).

4.5.1 **Measurement paradigm and motion correction**

Another two great advantages of fNIRS over fMRI are low costs and mobility, allowing for use in static and dynamic positions. FNIRS does not have the postural constraints that for instance fMRI and PET do (Mihara and Miyai 2016), is very safe and can be used in infants, elderly and clinical populations. When measuring in dynamic positions and challenging populations, motion artefacts are more likely to be present. Therefore the importance of motion artefact corrections has grown with development of fNIRS especially when being used during research paradigms involving large human movements.

To account for the signal to noise ratio and the prospect of motion artefacts most experiments in fNIRS make use of either a block design or an event-related design to generate multiple repeats of a certain condition and increase the signal to noise ratio (Bunce, Izzetoglu et al. 2006). In such designs, task blocks normally have durations around 30 seconds alternated by rest period of similar duration. This time is enough to elicit and allow the typical BOLD response to occur and be measured over 10-20 seconds, followed by a rest period in which the haemoglobin

concentration can restore to the baseline level and a sufficient contrast between task and rest can be generated.

Light sources and detectors of NIRS systems can be fixed to the head through optode holders, caps or other ways, however none of those will provide full stability of the optodes when the head is moving. Therefore, every now and then sources and detectors may lose contact with the skin causing a disturbance in the collected signal. This disturbance can occur as a spike in the signal or a shift of the signal from the baseline level (Brigadoi, Ceccherini et al. 2014).

Motion and physiological artefacts can be dealt with through different methods. Some of these use additional measures alongside the NIRS channels used for measuring brain activation, by for instance adding in one or more short distance channels to monitor superficial blood flow (Umeyama and Yamada 2009, Robertson, Douglas et al. 2010, Gagnon, Yucel et al. 2014) or to monitor the actual motion of the head through accelerometers and detect deviations from baseline hemodynamic levels (Virtanen, Noponen et al. 2011).

Other ways of motion correction techniques explore the frequencies and amplitudes of signals and act to filter out those parts of the signal that relate to noise or cardiorespiratory signals like heart rate and breathing. Amongst these techniques is Kalman filtering (Izzetoglu, Chitrapu et al. 2010), wavelet filtering (Molavi and Dumont 2012), principal component analysis (Zhang, Brooks et al. 2005), correlation-based signal improvement (Cui, Bray et al. 2010) and spline interpolation (Scholkmann, Spichtig et al. 2010).

Brigadoi et al. (2014) explored the latter in a cognitive experiment, where a motion artefact was elicited through jaw movement. Wavelet filtering was found to be most effective in removing artefacts and recovering most of the signal. Next, other techniques can be effective, but their effectiveness may depend on the type of data, certain assumptions about relationships between OHb and HHb and stableness of the correction technique (Brigadoi, Ceccherini et al. 2014).

4.5.2 **Imaging with fNIRS during gait**

Over recent years fNIRS has been used more often to measure brain activity during human walking (Holtzer, Mahoney et al. 2011, Huppert, Schmidt et al. 2012, Kurz, Wilson et al. 2012, Karim, Schmidt et al. 2013, Koenraadt, Roelofsen et al. 2013). The fNIRS technique has the advantages of being mobile, less susceptible to movement artefacts than other neuroimaging modalities; and being relatively comfortable to wear, it does not interfere with natural walking patterns (Bunce, Izzetoglu et al. 2006).

Miyai et al. (2001) measured brain activity with fNIRS during 4 conditions: while subjects were walking on a treadmill, while standing and swinging the arms, during dorsi- and plantar flexion and during imagery of walking. In addition Suzuki et al. (2004) investigated activities in the prefrontal and premotor areas while subjects were walking at slow and faster speeds and while subjects were running. Following up on this study Suzuki et al. (2008) explored the differences in brain activities between prepared and unprepared walking. More recent studies have also introduced brain imaging with fNIRS during backwards treadmill walking (Kurz, Wilson et al. 2012) and while performing balance exercise as part of a video game (Seraglia, Gamberini et al. 2011).

Given the safe nature of fNIRS, it is a very comfortable tool to use in clinical populations. Therefore it is not surprising to see the growing use of this technique in stroke. In this population, it can help understand the changes that underlie recovery after stroke. When specifically looking at rehabilitation of gait, Miyai et al. (2002, 2003) made use of fNIRS to investigate which areas contribute to restoration of gait after stroke and found changes in the sensorimotor cortex and premotor cortex in response to 2 months of inpatient rehabilitation. Moreover these changes correlated partly with change in gait parameters and in further studies relationships between changes in gait and change in brain activation in

sensorimotor cortices in response to body weight support training were found (Miyai, Suzuki et al. 2006). In more recent years studies found relationships between balance scores and brain activation (Mihara, Miyai et al. 2012, Fujimoto, Mihara et al. 2014). Dual task gait has started to be investigated in stroke and with fNIRS as neuroimaging measure (Beurskens, Helmich et al. 2014, Al-Yahya, Johansen-Berg et al. 2015).

4.6 Other neuroimaging techniques used to measure brain activation during locomotor movements

4.6.1 EEG

Hemodynamic responses are coupled to neuronal activity of the brain. EEG measures the electrical currents that are generated when neurons fire signals. The current produced by a single neuron is too small to get picked up by the electrodes. Studies in small populations have been performed using EEG to measure brain activity during human gait (Wieser, Haefeli et al. 2010, Lau, Gwin et al. 2012, Presacco, Forrester et al. 2012). EEG is relatively light to wear; the systems can be portable which enables for use during actual walking. EEG measures have been performed during precision stepping on a treadmill by Presacco et al. (2011, 2012), slow treadmill walking (Petersen, Willerslev-Olsen et al. 2012) and backwards walking (do Nascimento, Nielsen et al. 2005). Furthermore lower limb movements like ankle flexion (Do, Wang et al. 2011) and feet movement while seated (Raethjen, Govindan et al. 2008).

4.6.2 SPECT and MEG

One of the earlier studies exploring brain activity during gait was performed using SPECT (Fukuyama, Ouchi et al. 1997). This study evaluated 14 normal subjects after voluntary walking. The technique is not used very often since it requires the

injection of a radioactive tracer is someone bloodstream. MEG is able to pick up small changes in magnetic fields caused by changes in neuronal activity using superconductive magnets. The system requires the subject to sit down and is very sensitive for any head movement. Furthermore it is very expensive equipment. So far no studies have been performed using MEG to investigate brain activity during foot movements linked to human gait.

4.7 **Brain areas involved in locomotor control**

The work presented in this thesis has focussed on the cortical contribution to gait, but no locomotor movement can take place without spinal control. In animals spinal control of locomotion has been really well described with an emphasize on the main role for central pattern generators (CPGs) (Grillner 1985). These CPGs are described as spinal circuits that in absence of cortical input can control locomotion by timing the flexion and extension of muscles involved in different parts of the step cycle. The existence of CPGs has only been proven in animals, however research in spinal cord injured subjects has suggested the existence of CPG in human locomotion (Minassian, Jilge et al. 2004, Gerasimenko, Roy et al. 2008). Electromyography patterns similar to that in animals were present during human locomotion in paraplegic subjects following epidural stimulation (Dimitrijevic, Gerasimenko et al. 1998). The researchers of this study suggested that activation of the neurons through stimulation led to the start of movement and that continuation was stimulated through peripheral input. The amplitudes of electromyography activity did however lose strength over time which relates to the absence of descending input from supraspinal locomotor pathways. Those pathways have been found in the cerebellum. In people with damages to the cerebellum disturbed gait patterns have been seen with an emphasis on disturbances in balance and coordination of gait (Horak and Diener 1994, Morton

and Bastian 2004). Moreover Jahn et al. (2008) used fMRI and identified regions in the cerebellum and brainstem during mental imagery of standing, walking and running in healthy subjects that were linked to fine motor control. Finally, connections between regions in the cerebral cortex and the cerebellum and spinal cord are thought to drive the automaticity of walking (Yang and Gorassini 2006).

Through imaging techniques that are mentioned in the previous paragraph different brain regions are known to be activated and involved during control of human locomotion. Walking control is mostly automatic, but supported by neural connections through the cortex, brainstem and spinal cord and modulated through central and peripheral outputs (Nielsen 2003, Yang and Gorassini 2006). From the central control mechanism in the cortex, the prefrontal cortex, premotor cortex, supplementary motor area and sensorimotor area are active during walking control (Fukuyama, Ouchi et al. 1997, Hanakawa, Fukuyama et al. 1999, Miyai, Tanabe et al. 2001, Suzuki, Miyai et al. 2008).

Chapter 5. Neuroimaging during dual task walking

FMRI and fNIRS have not only been used to explore brain activation during gait, but also to explore brain mechanisms during dual task walking movements. This chapter discusses the research that has been done and describes a study which used fNIRS to explore prefrontal cortex activation during dual task treadmill walking in young healthy adults

5.1 **Overview of literature**

Neuroimaging of gait has been used to increase knowledge about central walking control and explore relationships between brain activations and gait performance (Edamura, Yang et al. 1991, Andersen and Sinkjaer 1999, Schneider, Lavoie et al. 2000). Moreover in populations with gait disturbances, such as elderly people or those with neurological deficits, neuroimaging studies have been performed to investigate brain activation patterns and brain structures in relation to gait impairments (Mihara, Miyai et al. 2007, Dawes, Enzinger et al. 2008, Enzinger, Johansen-Berg et al. 2008, Cremers, D'Ostilio et al. 2012, Fujimoto, Mihara et al. 2014).

Walking in a (clinical) research environment often means a subject performing a walking movement on a walkway or treadmill. A challenge emerges when results from walking control studies are translated to daily life where walking can be challenged with uneven paths and internal - and external distraction. In those real life situations a person sometimes has to be able to perform a concurrent task during walking for instance avoiding an object, watching traffic or communicating whilst walking. In this regard, many studies have explored the effects of dual task

on gait and cognition in healthy and clinical populations (Plummer-D'Amato, Altmann et al. 2008, Dennis, Dawes et al. 2009, Hegeman, Weerdesteyn et al. 2012, Nascimbeni, Caruso et al. 2015, Wrightson, Ross et al. 2016). In addition recent studies have started to explore the neural correlates of dual task walking in healthy young adults (Beurskens, Helmich et al. 2014, Mirelman, Maidan et al. 2014, Lu, Liu et al. 2015), and neurological conditions such as Parkinson's disease (Maidan, Nieuwhof et al. 2016, Maidan, Rosenberg-Katz et al. 2016) and stroke (Al-Yahya, Johansen-Berg et al. 2015).

The next part of this chapter summarizes a research study published in 2014 (Meester, Al-Yahya et al. 2014) which measured prefrontal cortex activation, soleus Hoffman's reflex amplitude and step time during dual task treadmill walk in healthy young adults. The aim of this study was to explore the effects of dual task treadmill walking on components of central and peripheral control mechanisms of gait and to describe the relationship between these measures. Moreover this study was used to optimize fNIRS handling and methodology for the later use in stroke survivors (Chapter 6). For the sake of clarity and the other work described in this thesis the methods and results of the peripheral measures (Hoffman's reflex) have been left out of the next paragraphs.

5.2 A pilot study to explore PFC activation and step times during dual task treadmill walking in young healthy adults

5.2.1 Introduction

Walking is a largely automatic process although it is controlled by the cortex, brain stem and spinal cord, and modulated through integration of neural signals from central and peripheral inputs at spinal and supraspinal level (Nielsen 2003, Yang and Gorassini 2006). Activation of cortical motor networks, including the motor, premotor, and prefrontal cortex (PFC) has been observed during walking (Fukuyama, Ouchi et al. 1997, Hanakawa, Katsumi et al. 1999). However, whilst it has been reported that cognitive tasks interfere with walking performance (Suzuki, Miyai et al. 2004, Al-Yahya, Dawes et al. 2011), the underlying mechanism of how cortical interference affects gait and mobility has not yet been described. In this study we explored the impact of an additional cognitive task, which placed demands on the PFC (McCulloch 2007) on walking at self-selected and fast walking speeds (Suzuki, Miyai et al. 2004, Suzuki, Miyai et al. 2008, Al-Yahya, Dawes et al. 2009). We hypothesized that additional cognitive load would increase PFC activity. We further expected that increasing both speed and the cognitive load would provoke a further increased activity in the PFC. As such, this study set out to explore the mechanism behind healthy individuals safely performing dual task walking.

5.2.2 Study population

Seventeen healthy subjects (7 men; 10 women), 15 right handed and 2 left handed, participated in this study. Mean age was 27.8 ± 6.3 with age range 22-44 years; mean height and weight were 1.75 ± 0.11m and 69.1 ± 15.2kg respectively. All

subjects gave written informed consent according to the Declaration of Helsinki before the start of the experiments and this study was approved by the University Research Ethics Committee.

5.2.3 Methods

5.2.3.1 Study design

Subjects walked on a treadmill while concurrently performing a cognitive task at a normal and faster walking speed. Measures of fNIRS were performed on the PFC and step time was calculated from centre of mass (CoM) accelerations. Standard methodology, utilising several practice trials was used to familiarize participants with the treadmill and varying speeds (Woodway ELG 75, Germany) and thus determine preferred walking speed close to normal over ground walking speed (Voloshin 2000). A faster walking speed was determined by increasing the normal walking speed by 20% (Voloshin 2000). The treadmill was programmed for 5 repetitions of walking and dual task walking alternated with rest periods in which the treadmill was stationary. Both walking and walking with distraction were performed in blocks of 30 seconds, and rest periods varied from 20-40 seconds. The rest periods had a varying length to prevent subjects anticipating the start of the next block. Subjects performed 5 repetitions of walking and walking with distraction at each of the two speeds. For the cognitive task, subjects were asked to count backwards in steps of seven from a number presented by the investigator.

5.2.3.2 fNIRS Imaging

A continuous wave (782nm, 859nm) fNIRS instrument (Oxymon, Artinis Medical Systems, The Netherlands) was used to measure PFC activation. Two identical plastic holders consisting of four optodes each (2 sources, 2 detectors) in a 4-channel arrangement with an inter optode separation of 30 mm were placed on

each participant's forehead using a custom-built spring-loaded array optode holder covering the area linking Fp1, F3 and F7 and the area linking Fp2, F4, and F8 according to the international 10-20 EEG electrode system, which corresponds to the left and the right PFC respectively (Leff, Elwell et al. 2008). To monitor haemodynamic responses, blood pressure and heart rate were measured at baseline and at the end of the programme.

5.2.3.3 Step time recording

Step time was measured using an inertial measuring unit (Philips, Eindhoven, The Netherlands) comprising a tri-axial accelerometer, gyroscope and magnetometer placed on the CoM (Esser, Dawes et al. 2012). Post-processing and analysis was performed in a pre-written program in LabVIEW2010 (National Instruments, Austin, USA). Step time was taken as the gait variable of interest with the time interval between trough-to-trough centre of mass excursions during one gait cycle (Esser, Dawes et al. 2009).

5.2.3.4 Data processing

Raw fNIRS signals were collected at a sample rate of 10Hz. HHb and OHb concentrations were calculated (Oxysoft 2.1.6), filtered with a low pass filter set at 0.67Hz (Labview 6.1) and visually inspected for motion artefacts, missing signals and noisy signals. Blocks with missing signals or artefacts were excluded from analysis. A moving average filter with a width of 4 seconds was used to smooth the signal. Block averages of the 5 task + rest repetitions were calculated and the middle 10 seconds of each task and rest periods used for statistical analyses. To offset low spatial resolution of fNIRS, and provide a better indication of general measured activity in the PFC, the 4 channels on both the left PFC and the right PFC were averaged.

Statistics

Descriptive statistics were performed on demographic and gait control parameters. Paired t-tests were used to examine differences in haemoglobin concentrations during task and rest blocks. The effects of task and speed on brain measures and step times were examined using repeated measures ANOVA models. Pearson correlations were performed to investigate relationships between changes in OHb concentrations and step time variability. For all statistical tests, alpha level was set at 0.05 a priori, and SPSS Bonferroni adjusted P-values are quoted.

5.2.4 **Results**

5.2.4.1 Descriptives

Individuals' average self-selected normal walking speed was 1.22 ± 0.24m/s, range 0.7 - 1.5m and faster walking speed was 1.48 ± 0.26m/s, range 1.0 – 1.7m/s. Blood pressure and heart rate were stable with a mean blood pressure of 117 ± 10.6 / 75 ± 6.7mmHg, range 98/63mmHg to 136/89mmHg and a mean heart rate of 75 ± 12.3bpm, range 60 - 109bpm. Blood pressure and heart rate did not significantly ($p>0.05$) change from baseline to normal and faster walking speed. Cognitive task score was not significantly ($p>0.05$) different between speeds. Average answer rate was 10.3 ± 3.8 answers during normal walking and 10.5 ± 3.8 during faster walking with respectively mean error rates of 0.4 ± 0.4 and 0.4 ± 0.3.

5.2.4.2 fNIRS imaging

Average OHb and HHb concentrations are summarized in Figure 5.1. Repeated measures ANOVA results are shown in Table 5.1. For single and dual task blocks at normal and faster walking speed, relative OHb concentrations were significantly ($p < 0.05$) higher during the task compared to the average rest block followed after

each task in both hemispheres. HHb changes were significantly ($p = 0.011$) lower during dual task blocks compared to rest in the right PFC when walking at a faster walking speed.

In the right cortex OHb concentrations increased significantly with dual task ($F = 4.632$; $p = 0.049$) from 0.23 ± 0.1mmol/l to 0.34 ± 0.1mmol/l at normal speed and from 0.21 ± 0.1 to 0.51 ± 0.1 at faster speed. In the left cortex, a trend was shown towards significant increases ($F = 3.535$; $p = 0.080$) of OHb concentrations with dual task, with increases from 0.23 ± 0.1mmol/l to 0.38 ± 0.1mmol/l and 0.22 ± 0.1mmol/l to 0.46 ± 0.1mmol/l for normal and faster walking speed respectively. HHb concentrations were not significantly affected by task or speed. Increases and decreases in OHb and HHb were not significantly different between speeds. No significant interactions were found between task and speed for both OHb and HHb concentrations.

5.2.4.1 Step time

Averages and variability step times are described in Table 5.2. Changes of mean step time and variability step time were not significantly ($p>0.05$) different between tasks and walking speeds. Furthermore repeated measures ANOVAs did not show interactions between task and speed (see Table 5.3).

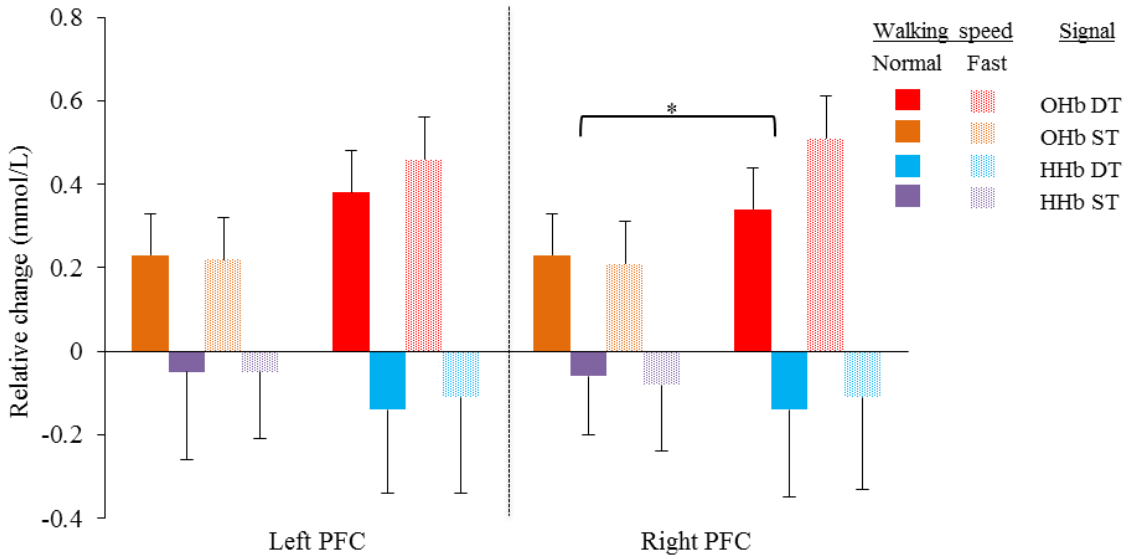


Figure 5.1. Mean relative changes and standard deviations in OHb (red and orange) and HHb (purple and blue) during normal and fast (dotted bars) walking in the left and right cortex. Results of single task (orange and purple) and dual task walking (red and blue) are presented. PFC = prefrontal cortex, OHb = oxy haemoglobin, HHb = deoxy haemoglobin, ST = single task, DT = dual task. * significant higher OHb concentration change during dual task walking compared to single task walking in the right cortex (p=0.049).

Table 5.1. Summary statistics of ANOVA for Oxy and Deoxy haemoglobin concentrations

	Left PFC Hemisphere				**Right PFC Hemisphere**			
	OHb		**HHb**		**OHb**		**HHb**	
Effect	*F*	*Sig.*	*F*	*Sig.*	*F*	*Sig.*	*F*	*Sig.*
Task	3.535	0.080	3.396	0.085	4.632	**0.049***	2.107	0.169
Speed	0.213	0.651	0.188	0.736	1.776	0.204	0.045	0.835
Task*Speed	0.471	0.503	0.076	0.786	2.425	0.142	1.231	0.286

Task = single and dual task walking, speed = normal and faster walking speed, PFC = prefrontal cortex, OHb = oxy haemoglobin, HHb = deoxy haemoglobin. Significant higher OHb concentration change during dual task walking compared to single task walking in the right prefrontal cortex (p=0.049)*.

Table 5.2. Averages ± standard deviations of step times and step time variability.

	Normal walking speed		Fast walking speed	
	Single task	**Dual task**	**Single task**	**Dual task**
Step time (ms)	528.4 ± 41.3	532.4 ± 46.1	524.3 ± 39.8	51.6 ± 38.3
Step time variability (ms)	105.0 ± 134.1	124.6 ± 139.4	63.4 ± 81.3	54.1 ± 48.5

Variability of step time was measured using the standard deviation.

Table 5.3. Repeated measures showing the effect of task and speed on step time and step time variability.

Step time		**Step time variability**	
F	*Sig.*	*F*	*Sig.*
0.966	0.341	1.436	0.251
0.108	0.746	0.205	0.658
3.339	0.088	3.387	0.087

Variability of step time was measured using the standard deviation. For all statistical tests, alpha level was set at 0.05 a priori.

5.2.4.2 Correlations between central activation and step times

No significant relationships were found between PFC activity and step times. Changes in OHb concentrations did not correlate with step time variability. Changes in OHb concentrations in the left cortex due to dual task and changes in step time showed the highest correlation of 0.420 close towards a trend; p=0.11. Error rates of cognitive task performance were not correlated with significantly higher or lower concentrations of OHb or HHb or changes due to single and dual task.

5.2.5 **Discussion and Conclusion**

We found healthy young adults responded to additional cognitive loading during treadmill walking with increased PFC activation, but unlike individuals after stroke or the elderly, this activation was not associated with altered gait parameters (Al-Yahya, Johansen-Berg et al. 2015). The absence of changes in gait parameters between different walking conditions indicates that young healthy individuals are able to cope with additional cognitive loads and changes in speed during walking. Therefore it is proposed that the observed increases in PFC activity allowed individuals to perform additional tasks simultaneously, without affecting cortical output. When exploring correlations between dual task changes in PFC activation and step time, the highest Pearson r^2 found was 0.420 which was not significant ($p=0.11$). This indicates that in a healthy young population central mechanisms are activated in response to cognitive loads but that gait performance can successfully be maintained. Moreover no significant changes in PFC activity were found with increased speed suggesting there might be differences in control mechanisms of faster speeds, or greater capacity for adaptation, in younger populations. This supports the hypothesis that in healthy individuals there is adequate central capacity to cope with subtle changes in walking. The methodologies used in this study do have some limitations. FNIRS is a developing modality with great opportunities (Belda-Lois, Mena-del Horno et al. 2011), but it also has a poor spatial resolution, low depth penetration and is variable with regards to signal quality between individuals (Toronov, Zhang et al. 2007, Seraglia, Gamberini et al. 2011). Furthermore due to practical reasons and subject comfort we only measured the PFC, and were therefore unable to explore other motor networks (Suzuki, Miyai et al. 2004, Karim, Schmidt et al. 2012, Kurz, Wilson et al. 2012) which may provide further insight into gait and balance control.

5.2.6 **Suggestions for future studies**

Although previous studies using treadmill testing have shown changes in gait parameters, the method may lack some ecological validity for understanding gait control for community mobility. Our population selected an average walking speed of $1.2ms^{-1}$ which is lower than the average walking speed for this age group (Bohannon and Williams Andrews 2011) resulting in fast walking speeds, set at 120% of normal walking speed, which were more reflective of a normal walking pace. This study and others have shown the potential of fNIRS for the exploration of neural activation during dual task walking. Gait control mechanisms under speed and dual task conditions now need to be explored in older adults, and people prone to falls or poor balance and mobility. In stroke survivors, fNIRS has proven to be a very suitable neuroimaging tool. Not only to monitor brain damage or plasticity (Obrig and Steinbrink 2011), but also as brain computer interface (Rea, Rana et al. 2014), neurofeedback tool (Mihara and Miyai 2016) and to measure brain activation during movement (lin, Lin et al. 2009). With all these applications, the use of fNIRS in motor rehabilitation studies could help to design novel rehabilitation programs tailored to the individual needs.

Chapter 6. Underlying mechanisms of dual task effect on brain activation, cognition and walking control in stroke.

This penultimate chapter describes two neuroimaging studies that were performed within the randomized controlled trial described in chapter 3. The aims of these studies were to explore dual task effects on brain measures and measures of cognition in during real walking (fNIRS) and a bipedal task (fMRI). Furthermore training induced brain changes were discussed for single and dual task walking and in relation to behavioural changes such as community walking and dual task performance.

6.1 Introduction and rationale

In addition to measuring the effectiveness of dual task walking training on community walking in chronic stroke survivors, this thesis set out to explore underlying mechanisms of dual task training and walking control through neuroimaging of gait. The challenge in dual task training after stroke is to understand why someone finds difficulties with community walking and which type of intervention is needed to tackle these difficulties. To our knowledge, no research has been done in which neuroimaging measures were performed in stroke during dual task walking before and after training. Some work has been done by Luft et al. (2008) and Enzinger et al (2008) who explored changes in activation during gait movements in response to treadmill training. These studies used fMRI to assess brain activations during lower limb movement before and after training in chronic (time since stroke ≥ 6 months) stroke survivors. Brain areas that showed

significant changes during gait movements that correlated with improved gait were the posterior lobe of the cerebellum (Luft, Macko et al. 2008), the primary sensorimotor cortex, cingulate motor area, caudate nucleus and the thalami (Enzinger, Dawes et al. 2009). The changes found by Enzinger et al. (2009) were associated with increases in walking endurance.

To explore changes in brain activation in response to dual task training we needed to understand what happened with the control of walking during CMI (paragraph 2.1). Dual task effects on central - and peripheral output have been investigated and measured as changes in brain activity and peripheral reflexes in healthy adults (Beurskens, Helmich et al. 2014, Meester, Al-Yahya et al. 2014, Mirelman, Maidan et al. 2014). Suzuki et al (2008) showed that when healthy young adults were cued about the start of a treadmill, brain activity increased in the prefrontal (PFC) and premotor cortex (PMC) areas compared to treadmill walking without preparation. Furthermore, others showed relationships between increased stride-time variability and supplementary motor area (SMA) activation (Kurz, Wilson et al. 2012) and a link between volume of the PFC area and walking speed (Rosano, Studenski et al. 2012). These studies indicate the importance of the PFC in motor control, especially in a changing environment where gait becomes less automatic and preparation and adaption of gait occur.

During the assessments that were performed in the clinical trial exploring dual task treadmill training compared to treadmill training without distraction (Chapter 3), fMRI and fNIRS were used to explore changes in brain activation during single and dual task gait before and after the training period. FMRI was used during single and dual bipedal tasks to explore what areas activated during movement and cognitive task performance. Furthermore we explored how these activation patterns changed during dual task and how brain activation related to walking performance and cognitive performance in chronic stroke. FNIRS was used to explore PFC and

PMC activation during single and dual task treadmill walking in relation to behavioural measures.

Furthermore using both neuroimaging modalities brain activation patterns were explored both over time and between two different training groups. It was hypothesized that CMI would increase demands on the PFC and therefore increase prefrontal cortex activation during dual task - compared to single task walking.

We expected to see differences in how dual tasking affected brain activations in stroke survivors who had received dual task training compared to stroke survivors who had received training without distraction and that these changes would relate to behavioural improvements of walking. PFC activation during dual task gait exercises was expected to decrease more after dual task training compared to treadmill training without distraction, due to there being decreased demands on the brain and an increased automaticity of walking control.

6.2 **Methods**

A randomized controlled trial was performed to explore dual task related brain activation before and after 10 weeks of treadmill training without and with distraction in chronic stroke survivors. Fifty chronic stroke survivors, at least 6 months post stroke, participated in fNIRS measurements (see paragraph 6.3 for more details). A subpopulation of 20 stroke survivors were recruited and screened for eligibility into an fMRI sub-study. Two stroke survivors were not included as they did not pass the MRI safety screen.

6.2.1 **Methods: fMRI sub-study**

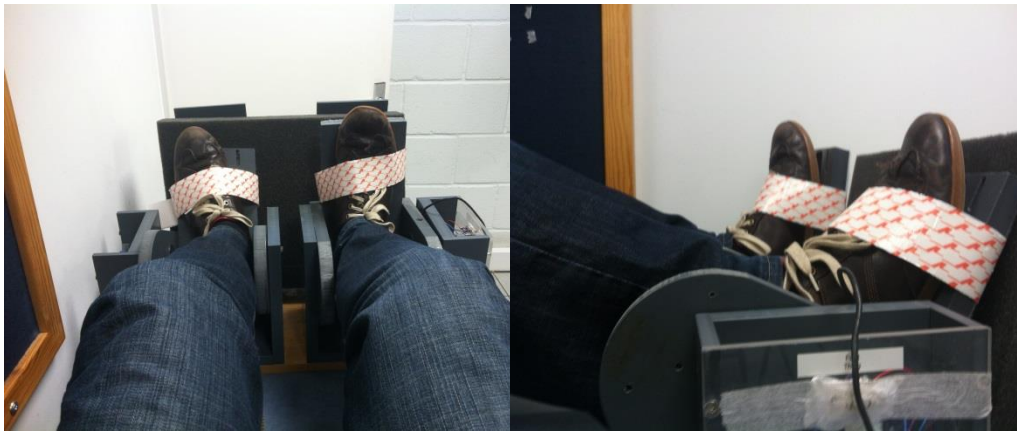
Eighteen included stroke survivors were invited to come to the Oxford Centre for functional MRI of the Brain (FMRIB). The study was approved by the local NHS Research Ethics Committee (REC reference: 12/SC/0403) and all participants gave

their informed consent to participate in the study according with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. Upon arrival, participants were briefed about all procedures and were given the opportunity to ask questions.

Each stroke survivor underwent a 40 minute scan including a structural MRI, a task-fMRI, a Diffusion Tensor Imaging (DTI) scan and an fMRI resting scan. The DTI and fMRI resting scan were conducted for use in a parallel project which was not part of the work described in this thesis. An overview of all scans and their duration is given in Table 6.1. During the structural -, DTI - and FMRI resting scan, stroke survivors were instructed to lay as still as possible. During the entire scan, the participant's feet were attached to a MRI-safe bipedal device (see Figure 6.1a). For the sake of this chapter and thesis only the procedures and results of the structural - and task-fMRI scan are now further discussed.

Table 6.1. fMRI scanning sequence

Type of scan	**Duration**
Structural scan	**± 6 min**
Task - Functional MRI scan	**± 17 min**
Diffusion Tensor Imaging scan	**± 6 min**
Resting state scan Functional MRI scan during rest (with eyes open)	**± 6 min**



A

B

Figure 6.1 Pedal device and rocker switch A. Top and side view of bipedal device. Left and right pedals move independent from each other. B. Top and side view of Rocker switch used to indicate response on cognitive tasks during task-fMRI scan.

6.2.2 Experimental procedure

The task-fMRI scan took place after the structural scan was completed. During the task-fMRI the stroke survivor was instructed to perform tasks requiring them to pedal up and down, execute a cognitive task using a small rocker switch (Figure 6.1b) or perform the bipedal foot movements and the cognitive task at the same time, i.e. dual task.

Each task was repeated 4 times and had a duration of 30 seconds followed by a 20 second rest period in which the stroke survivor was instructed to keep their feet still and focus on the word “Rest” presented on the screen. The order of tasks was in a fixed random order to prevent the participant from anticipating on the next task starting after a rest period. Each task block was preceded by a 2 second instruction about the upcoming task. Five different tasks were performed during the task-fMRI scan: Number Stroop Task whilst laying still (NS), Pedalling at self-selected frequency, Picture-planning task whilst lying still (PP), Number Stroop task whilst pedalling (NS-DT) and the Picture-planning task whilst pedalling (PP-DT).

All cognitive tasks were practiced beforehand, outside the scanner and whilst lying on the scanner bed to make sure participants had a good understanding of each task and were able to move the pedals. When required to pedal, an image of a moving foot was presented on the left side of the screen. The participant was asked to pedal at a self-selected frequency until the foot-image disappeared from the screen.

The NS task is a variant of the widely used Stroop task, designed to assess selective attention and executive function. During the NS task, participants viewed visual stimuli, presented on the screen they faced whilst laying in the scanner. Each stimulus consisted of a set of two numbers which were presented for 2 seconds after which the next stimulus was presented. The numbers were presented vertically, one above the other and differed in magnitude. In addition the two numbers also differed in font size. The object of the task was to indicate the biggest number in magnitude, regardless of font size (Algom, Dekel et al. 1996).

The PP was identical to the task used in the study described in chapter 2 and 3. Stimuli consisted of two pictures presented one above the other (more details in paragraph 4.2.2).

Responses to the stimuli presented in both the NS and PP tasks were given with a rocker switch held in the dominant hand.

The stroke survivors were instructed to respond “top” or “down” by moving the rocker switch in the matching direction of the correct answer (top number/picture or bottom number/picture). After the switch was pushed up or down the numbers (NS) or pictures (PP) disappeared and a new stimulus was presented after the stimulus duration had finished (2 seconds for NS and 5 seconds for PP). Both tasks were presented on the right side of the screen. During dual task conditions, NS-DT and PP-DT, on the left side of the screen the same foot-image as during the pedalling was presented to stimulate the stroke survivor to move their feet whilst executing the cognitive task. Figure 6.2 shows an overview with screen-shots of the different tasks and the rest-condition.

6.2.1 **fMRI equipment and processing**

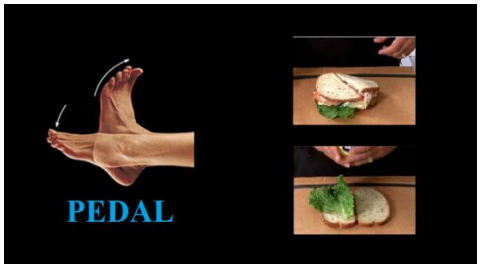
All scans were performed on a 3 Tesla Verio scanner (SIEMENS, Erlangen, Germany) using a 32-channel head coil. The task-fMRI scan was acquired during a T2* weighted Echo planar imaging (EPI) sequence, using the following settings: flip angle = 90°, TR = 2000ms, TE = 30ms, matrix size = 64 x 64, FOV = 192mm, slice thickness 3.0mm, voxel size = 3.0 x 3.0 x 3.0mm and 36 slices per volume. 512 measurements were taken during the scan with partial coverage of the cerebellum. Next to the task-fMRI a T1 weighted structural image was acquired using the following settings: flip angle = 8°, TR = 2040ms, TE = 4.7ms, matrix size = 192 x 192, FOV = 192mm, slice thickness 3.0mm, voxel size = 1.0 x 1.0 x 1.0mm.

A

B

C

D



E

F

Figure 6.2 A. Screenshot of stimuli presented during the pedalling task. B. Example of stimulus-screen during Number Stroop task. C. Example of stimulus-screen during Picture-planning task. D. Example of stimulus-screen during Number Stroop whilst pedalling task. E. Example of stimulus-screen during Picture-planning whilst pedalling task. F. Screenshot of rest-screen presented inbetween task blocks.

6.2.2 **Analyses and pre-processing**

Analyses of scan images was performed using FMRIB Software Library (FSL) (Version 5.0.8, FMRIB, Oxford UK). To enable comparison between stroke survivors, image files of stroke survivors with left sided lesions were flipped so all lesions appeared in the right hemisphere. Binary lesion masks were created to optimize registration.

Non brain tissue was removed from the structural image and fieldmap using FSL Brain Extraction Tool (BET) (Smith 2002) and the fieldmap unit was transformed to rad/s for use in FMRI Expert Analysis Tool (FEAT). EPI images were registered using Motion Correction with FMRIB's Linear Image Registration Tool (MCFLIRT) (Jenkinson, Bannister et al. 2002). Spatial smoothing with full width half maximum was set at 5mm and a high pass temporal filter, Gaussian-weighted within the line, was set with cut-off period of 120 seconds. Fieldmap unwarping was done using FSL's Boundary Based Registration (BRR) (Greve and Fischl 2009).

Due to the nature of the task, the images were susceptible to greater than normal levels of noise due to physical motion. Extra steps in the pre-processing were therefore taken in order to reduce the signal generated from motion contributing to the task signal. FSL motion outliers tool was ran to generate a confound matrix with a motion confound parameter to add to the GLM for statistical analysis. Furthermore ICA component analysis performed by FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) was performed to split the data into artefactual and non-artefactual components. Two trained researchers (Daan Meester, MSc and Dr. Andrea Dennis) individually went through the MELODIC output and identified components showing artefacts based on temporal and spatial features as described in Salami-Korshidi et al. (2014). After both researchers completed identification, the

component selection was discussed to verify which components were removed for further analyses.

6.2.3 **Statistical models and analyses**

Statistical procedures were carried out in FEAT with FMRIB's Improved Linear Model (FILM) which used a local autocorrelation correction (Woolrich, Ripley et al. 2001). A first level analysis of within-subject data was performed using FMRIB's Linear Optimal Basis Set (FLOBS) to generate basis functions with optimal efficiency for hemodynamic response function (HRF) convolution (Woolrich, Behrens et al. 2004). For this analysis, each task was modelled as a separate explanatory variable (EV) (see Figure 6.3). After first level analysis had run, registration was rerun with binary lesions masks to optimize fit around brain boundaries and ventricles. Rerunning of registration was performed using FSL's linear registration tool FLIRT (Jenkinson, Bannister et al. 2002) followed by the non-linear tool FNIRT (Smith, Jenkinson et al. 2004). For group level analyses only the canonical HRF regression parameter estimates were used.

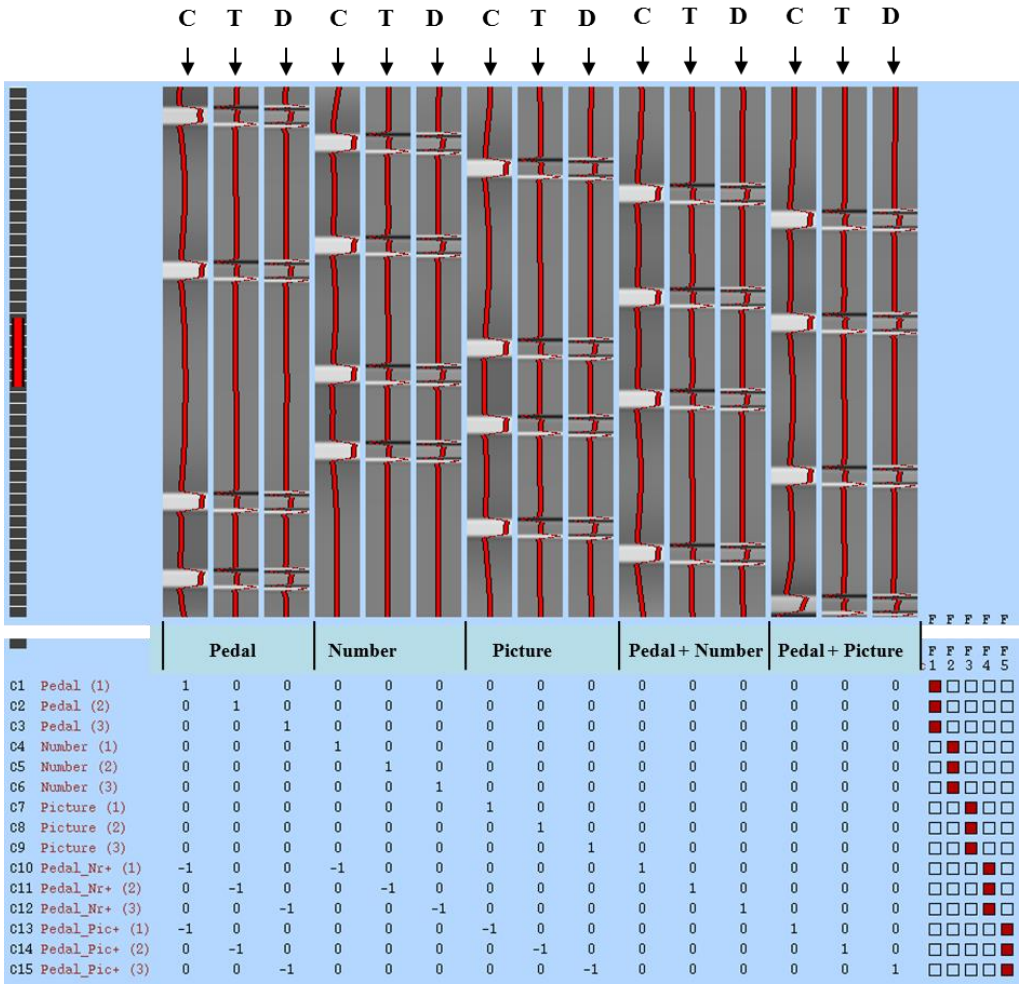


Figure 6.3 GLM design used in lower level analyses in FEAT with each task modelled separately. For each explanatory variable the toolkit FLOBS generated a basis set with a canonical HRF (C), a temporal derivative (T) and a dispersion derivative (D).

Mean activation during task execution was explored for all included subjects at baseline with treadmill speed as covariate to correct for differences in walking ability and explore relationships between treadmill speed and task related brain activation (see Figure 6.4). Training effects between groups were investigated by creating between visits contrasts for additional activation or deactivation at post-training compared to baseline and follow-up compared to baseline and to explore whether those contrasts differed significantly between groups. Finally task related

activation changes, within the dual task group and over time, were compared to behavioural changes in gait performance within the dual task group.

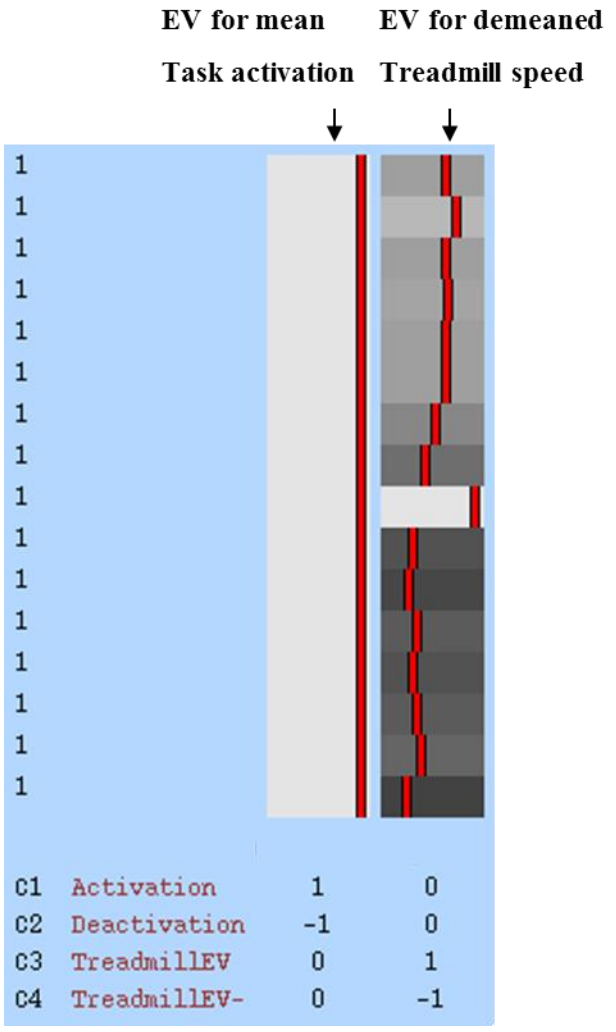


Figure 6.4 Example of GLM design used in higher level analyses with an EV (explanatory variable) for mean activation during task (e.g. pedalling) and an additional EV for the covariate of demeaned treadmill speed.

FMRI data sets typically contain over tens of thousands of voxels leading to many false positives when doing multiple comparisons. Significant activation of individual voxels was tested at a probability level of, $p < 0.05$. Correction for multiple comparisons was carried out using the 'cluster detection' approach which

takes into account the size of activated clusters when thresholding (Worsley 2001). First a z-statistic threshold of 2.3 was used to define contiguous clusters and then each cluster's estimated significance level (Gaussian field theory) was compared with the cluster probability threshold based on the cluster's size.

Max Z-stat coordinates of activated clusters were compared to the Harvard-Oxford atlas tool in FSL Eyes. In case of multiple areas being related to coordinates, the area showing the highest covered percentage was reported.

6.2.4 **Pedal and Cognitive data processing and statistical analyses**

Pedalling performance in the scanner was monitored through impedance meters on either side of the pedal device, which provide information about pedal frequency and amplitude. The signals from the impedance meters were influenced by the strong magnetic fields inside the scanner room and therefore amplitudes could not be derived from the signals. Pedal frequency however, was still readable and therefore used as the main behavioural measure for pedal performance.

For scoring on the NS and PP tasks, percentage of correct responses, reaction times and a composite score were calculated. The cognitive composite score took into account speed-accuracy trade-off and was calculated using the following formula:

$$Cognitive\ composite\ score = \frac{Correct\ responses\ \%}{Reaction\ time\ (s)} * 100$$

(Springer, Giladi et al. 2006)

DTE on pedal performance and cognitive composite scores was calculated using the formula below and used for statistical analysis.

$$DTE = = \frac{Dual\ task - Single\ Task}{Single\ task} * 100\%$$ (McDowd 1986)

Statistical analyses were performed in SPSS version 21. A Linear Mixed Models approach was used to explore changes DTE on cognitive scores over time and between the two training groups. An Unstructured, Autoregressive or Toeplitz covariance matrix was used to model fixed factors for time (baseline, post-training, follow-up) and training group (Dual Task, Control). An interaction term for Time*Group was added to the model only if this interaction was significant. Bonferroni corrections were used to explore changes between visits and groups.

6.3 **Methods fNIRS study**

Stroke survivors participating in the randomized controlled trial as described in Chapter 3, underwent functional fNIRS measurements of the prefrontal cortex (PFC) and premotor cortex (PMC) during treadmill walking at each time point. The treadmill test was executed following a block design in which participants performed one of five tasks for +/-30 seconds (s) alternated with 20s rest periods. Each task was repeated five times resulting in a total test-time of 21 minutes (min). The five tasks were: Auditory Stroop task whilst standing (AS), Walking at self-selected-walking-speed (W), Picture-planning task (PP), Auditory Stroop task whilst walking (AS-DT) and the Picture-planning task whilst walking (PP-DT). A detailed description of the treadmill test and task execution is given in paragraph 4.2.2.

6.3.1 **Instrumentation**

A continuous wave (782nm, 859nm) fNIRS instrument (Oxymon, Artinis Medical Systems, The Netherlands) was used to measure SMA, PMC and PFC activation. The system consisted of eight optodes (4 light sources, 4 detectors) which were set up in a 4-channel arrangement on the SMA and PMC a 2-channel combination on the PFC (see Figure 6.5). The source-detector pairs were set at an inter-optode-

distance of 30mm. The 4-channel optode holder on the SMA/PMC was set right in front of Cz covering an area between C_z and F_z according to the international 10-20 EEG which has been used as a reference for these areas in earlier NIRS studies (Miyai, Tanabe et al. 2001, Suzuki, Miyai et al. 2004). The 2-channel configuration on the Prefrontal cortex covered the left and right hemisphere with optodes at F7, Fp1, Fp2 and F8. To monitor haemodynamic responses, blood pressure and heart rate were measured before and after the treadmill exercise.

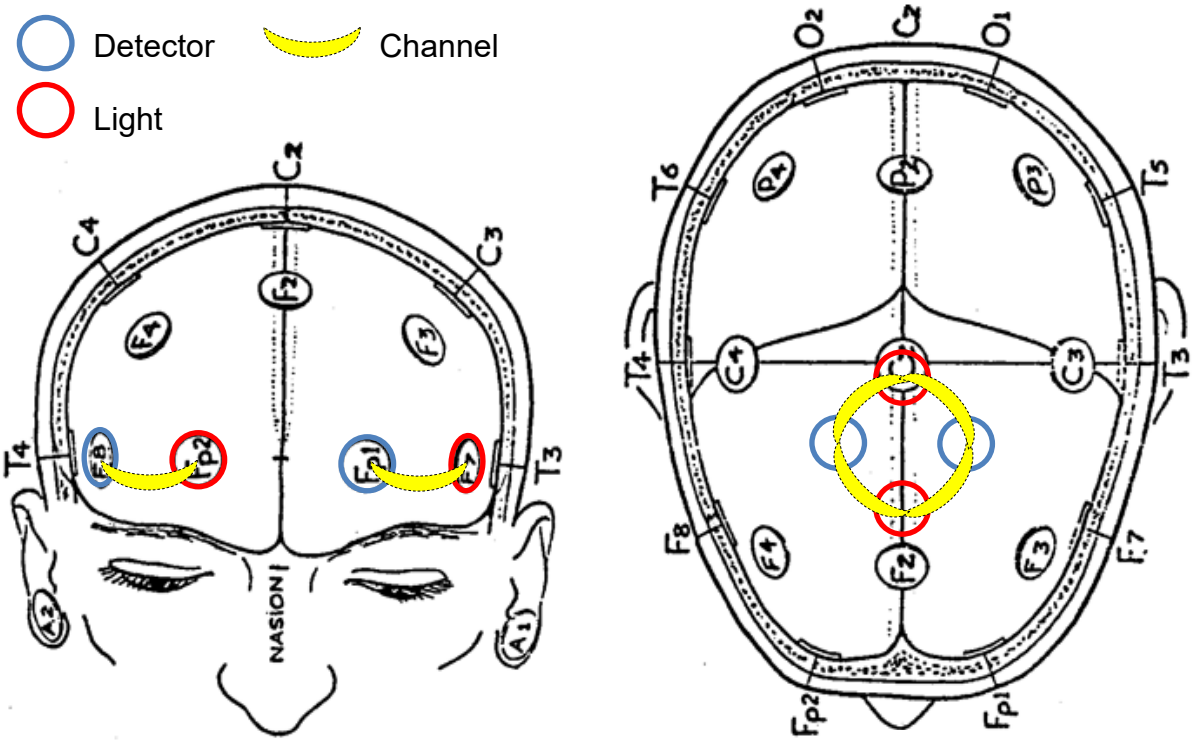


Figure 6.5 Frontal - and top view of fNIRS optode placement. 4 Detectors (blue circle) and 4 light sources (red circle) were placed over the SMA and PMC, resulting in 4 channels (yellow) which covered an area between Cz and Fz according to the international 10-20 EEG system. Two more detectors and light sources were used to create two separate channels which were placed over the left and right PFC covering an area between F7 and Fp1 and F8 and Fp2. Inter-optode-distance was 30mm.

6.3.2 **Data processing**

FNIRS data was collected using system software (Oxysoft 2.1.6, Artinis Medical Systems, The Netherlands). Light intensity changes sampled at 10Hz as measured with the Oxymon fNIRS instrument were used in the modified Beer-Lambert law (see paragraph 4.4) to calculate relative changes in HHb and OHb concentrations. A low pass filter of 0.7Hz was used to remove high frequency noise and enable visual inspection of signals for motion artefacts. Blocks of data containing motion artefacts, missing signals or other noise were removed from analyses. Traces were then filtered with a moving Gaussian filter (Molavi and Dumont 2012), using a width of 4s. Blocks included after motion artefact analysis and filter processing were detrended for the first 5 seconds preceding the task start and averaged for the task period and 20-second rest period after each task. For between subjects comparison, average signals for task and rest were normalized by dividing the whole average trace by the maximum concentration change within a channel and across tasks (Koenraadt, Roelofsen et al. 2014). The average relative concentration changes were calculated for the middle 10 seconds of both task and rest periods and used for statistical analyses. Data from the 4 channels on the PMC and SMA were averaged per two channels resulting in one for the left and one for the right hemisphere.

6.3.3 **Cognitive data processing**

Cognitive performance on the treadmill was calculated in the same manner as for the data collected in the fMRI study (6.3.5). For scoring on the AS and PP tasks, percentage of correct responses, reaction times and a composite score were calculated. The composite score took into account speed-accuracy trade-off and was calculated using the following formula:

$$Cognitive\ Composite\ score = \frac{Correct\ responses\ \%}{Reaction\ time\ (s)} * 100$$ (Springer, Giladi et al. 2006)

The composite scores from the single and dual task blocks were averaged and a dual task effect score was calculated for statistical analysis:

$$DTE = = \frac{Dual\ task - Single\ Task}{Single\ task} * 100\%$$ (McDowd 1986)

6.3.4 **Statistical analyses**

Statistics were performed in SPSS version 21. A Linear Mixed Models approach was used to explore changes in brain activation and DTE on cognitive performance over time and between the two training groups. An Unstructured, Autoregressive or Toeplitz covariance matrix was used to model fixed factors for time (baseline, post-training, follow-up) and training group (Dual Task, Control). An interaction term for Time*Group was added to the model only if this interaction was significant. Bonferroni corrections were used to explore changes between visits and groups.

6.4 **fMRI Results**

Figure 6.6 present the study flow diagram for the fMRI sub-study. Twenty participants were recruited for the fMRI sub-study of whom 18 were included at baseline. Randomization (as discussed in paragraph 5.2.5) resulted in 11 stroke survivors in the fMRI sub-study being allocated to the DT training - and 7 to the CT training group. Of those, 15 underwent the post-training scan and 14 the follow-up scan. Reasons for drop-out were: one stroke survivor felt too uncomfortable in the scanner, one stroke survivor dropped out of the training and study due to an unrelated injury and two more dropped out at follow-up due to artefacts in scan data and technical issues around the scanner.

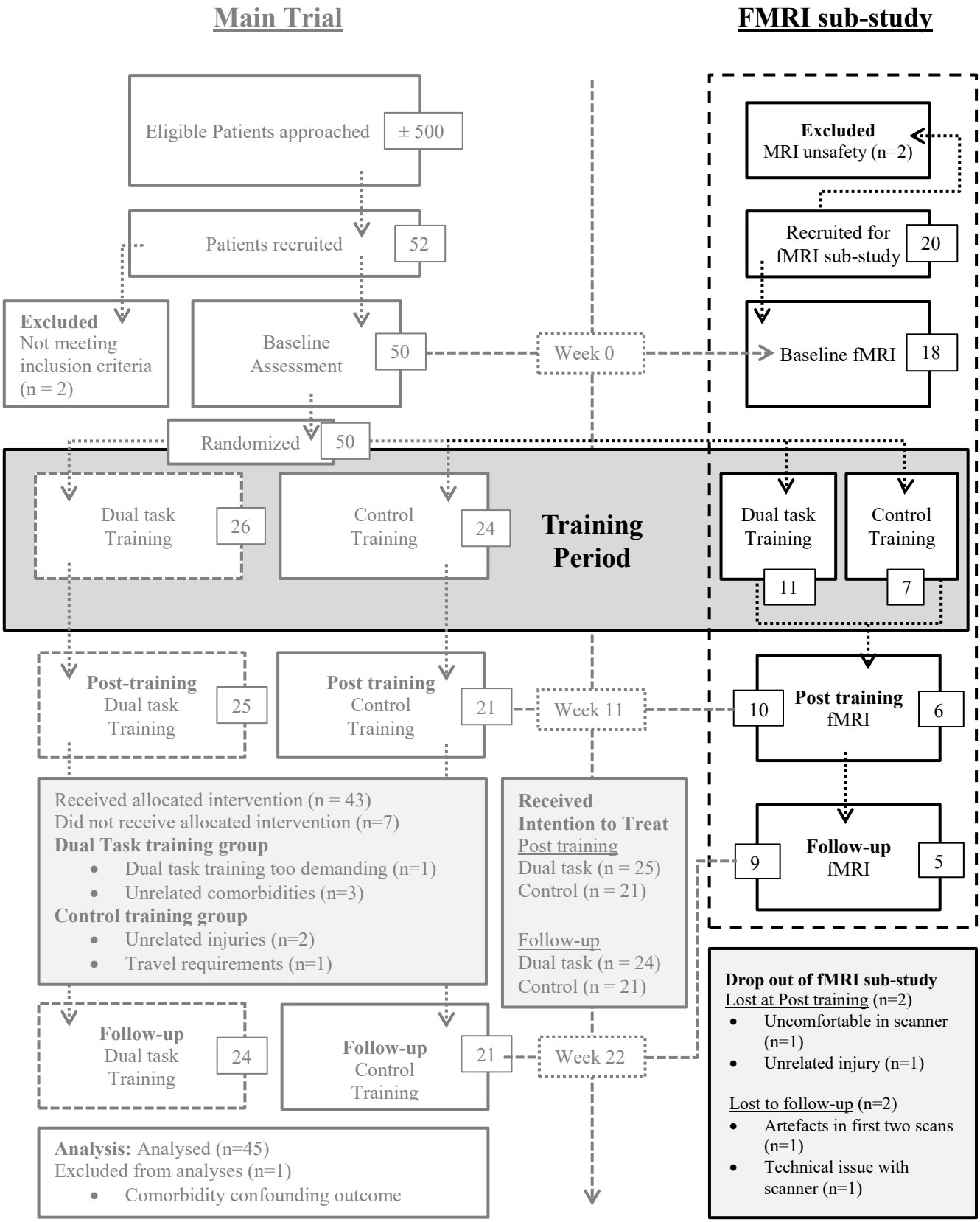


Figure 6.6 Flow diagram main trial and fMRI sub-study. One drop out from the main trial also dropped out in the fMRI sub-study (unrelated injury). Main trial is shaded grey as only the fMRI sub-study is discussed in this chapter.

Comparing baseline behavioural performance on walking parameters, significantly higher mean treadmill walking speeds and two-minute-walk distances were found for stroke survivors in the Control Training group (CT group) compared to the Dual Task group (DT group). Moreover scan data from two participants in the CT group contained too many movement artefacts. To be able to compare brain activation patterns between groups and over time for training groups with equal baseline walking abilities it was decided to remove 4 stroke survivors with the slowest treadmill walking speed from the DT training group for between group analysis. This resulted in a CT group with 5 stroke survivors and a DT group with 7 stroke survivors whose baseline characteristics presented in Table 6.2. Mean treadmill speeds were 0.67 ± 0.28m/s and 0.57 ± 0.21m/s for the CT group and DT group respectively ($t = 0.660$, $p = 0.524$). Stroke onset was significantly different between groups ($t = -2.470$, $p = 0.033$) with an average log-10 value of 1.08 ± 0.37 for the CT group and 1.64 ± 0.39 for the DT group. There was also a trend ($t = 2.214$, $p = 0.051$) towards a higher physical activity scale score in the CT group compared to the DT group at baseline (see Table 6.2). No significant differences were found between groups for sex, age, handedness, stroke characteristics, clinical scores, cognition or walking performance.

To check whether the difference between groups in stroke onset could influence brain activation, an additional covariate was added for stroke onset to higher level GLM designs (see Figure 6.4 with treadmill speed as covariate). No significant correlations were found between task related activation and stroke onset, therefore stroke onset was not used as covariate in further analyses.

Table 6.2 Baseline descriptives for fMRI study participants with group comparison

Measure	All included at baseline (n = 18)	CT Training Group (n = 5)	DT Training Group (n = 7)	T-test (α = 0.05)
Demography				
Male / female	8/10	3/2	4/3	*0.1000*[b]
Age (years)	61.28 ± 12.76	66.60 ± 9.89	60.57 ± 13.53	*0.419*
Handedness: right / left / no preference	15/1/2	4/1/0	5/0/2	*0.470*[b]
Stroke details				
Right / Left / mid – brain	9/6/3	3/1/1	3/3/1	*0.773*[b]
Stroke onset (Log^{-10})	1.39 ± 0.50	1.08 ± 0.37	1.64 ± 0.39	***0.033***[*]
Clinical characteristics				
Barthel Index	19.4 ± 1.5	19.8 ± 0.5	19.1 ± 2.3	*0.542*
MOCA	25.1 ± 4.2	26.2 ± 2.6	23.7 ± 5.6	*0.378*
(mild) aphasia: yes / no	17/1	5/0	6/1	*1.000*[b]
Walking characteristics				
Walking aid: none / stick / personal support	8/9/1	4/1/0	4 / 3 / 0	*0.576*[b]
Step Activity per day	3772 ± 1675	5158 ± 1765	4165 ± 1107	*0.317*
TMW	95.84 ± 36.12	126.80 ± 19.78	109.82 ± 22.34	*0.219*
TMW_DT	85.57 ± 31.05	108.84 ± 20.43	99.43 ± 21.09	*0.474*
Treadmill walking speed (ms^{-1})	0.49 ± 0.27	0.67 ± 0.28	0.57 ± 0.21	*0.524*
Physical Activity Scale Elderly	88.8 ± 47.2	132.4 ± 33.8	72.3 ± 20.1	***0.051***[#]

CT: Control, DT: Dual Task, MOCA; Montreal Cognitive Assessment Scale, TMW; two-minute-walk test, TMW-DT; two-minute-walk test with distraction. P-value represents result of independent sample t-test to test difference between training groups, α = 0.05. b; Fischer's exact test.

6.4.1 **Baseline activation patterns**

This section describes what areas activated and deactivated during pedalling and cognitive tasks at baseline. Moreover the effect of dual task on brain activation in relation to single task activation is presented. Significant activated areas were seen in different areas during each of the single tasks compared to rest (Pedal, NS and PP). Moreover significantly deactivated areas relative to single task brain activation were seen during the NS task. Table 6.3 and Figure 6.7 summarise the clusters of the maximum z-statistics related to activation and deactivation in these areas.

Our main hypotheses concerned dual task conditions. When dual task related brain activation was compared to the single task activation significant decreases in the *left postcentral gyrus, right superior occipital cortex* and the *right inferior occipital cortex* were seen during the NS-DT. For the PP-DT, decreases were seen in the *right precentral gyrus, left superior occipital lobule* and the *left inferior occipital cortex*.

Table 6.3 Activated clusters during single and dual task blocks at baseline

Task	Anatomical region	Cluster size Voxels	Max z-score	MNI Coordinates x	y	z
Pedalling at self-selected frequency **Activation compared to rest**	Left Precentral Gyrus	3210	4.64	-14	-32	62
	Right Inferior Occipital Cortex	2406	4.79	48	-70	-6
	Left Inferior Occipital Cortex	2258	4.81	-52	-68	2
	Cerebellum	1588	4.87	0	-48	-2
Number Stroop **Activation compared to rest**	Left Precentral Gyrus	18545	5.35	-46	4	28
	Right Frontal Lobe	3118	4.27	50	42	8
	Right Superior Parietal Lobule	2135	4.41	42	-36	48
	Left Occipital Cortex	1419	4.38	-44	-74	0
Deactivated compared to rest	Bilateral Occipital Lobe	8274	5.39	20	-92	-4
Picture Planning **Activation compared to rest**	Right Inferior Occipital Cortex	35800	4.87	48	-64	-2
Pedal + Number Stroop (NS-DT) **Deactivation relative to single task**	Left Postcentral Gyrus	1983	3.74	-62	-14	18
	Right Superior Occipital Cortex	1629	4.01	30	-58	62
	Right Inferior Occipital Cortex	1616	4.01	44	-68	-8
Pedal + Picture Planning (PP-DT) **Deactivation relative to single task**	Right Precentral Gyrus	3495	4.01	54	6	12
	Left Superior Parietal Lobule	2993	4.15	-34	-42	70
	Left Inferior Occipital Cortex	1891	4.27	-60	-70	-2

Anatomical regions according to the Harvard-Oxford atlas. DT: Dual Task. Grey shaded rows show areas that deactivated during task execution compared to rest.

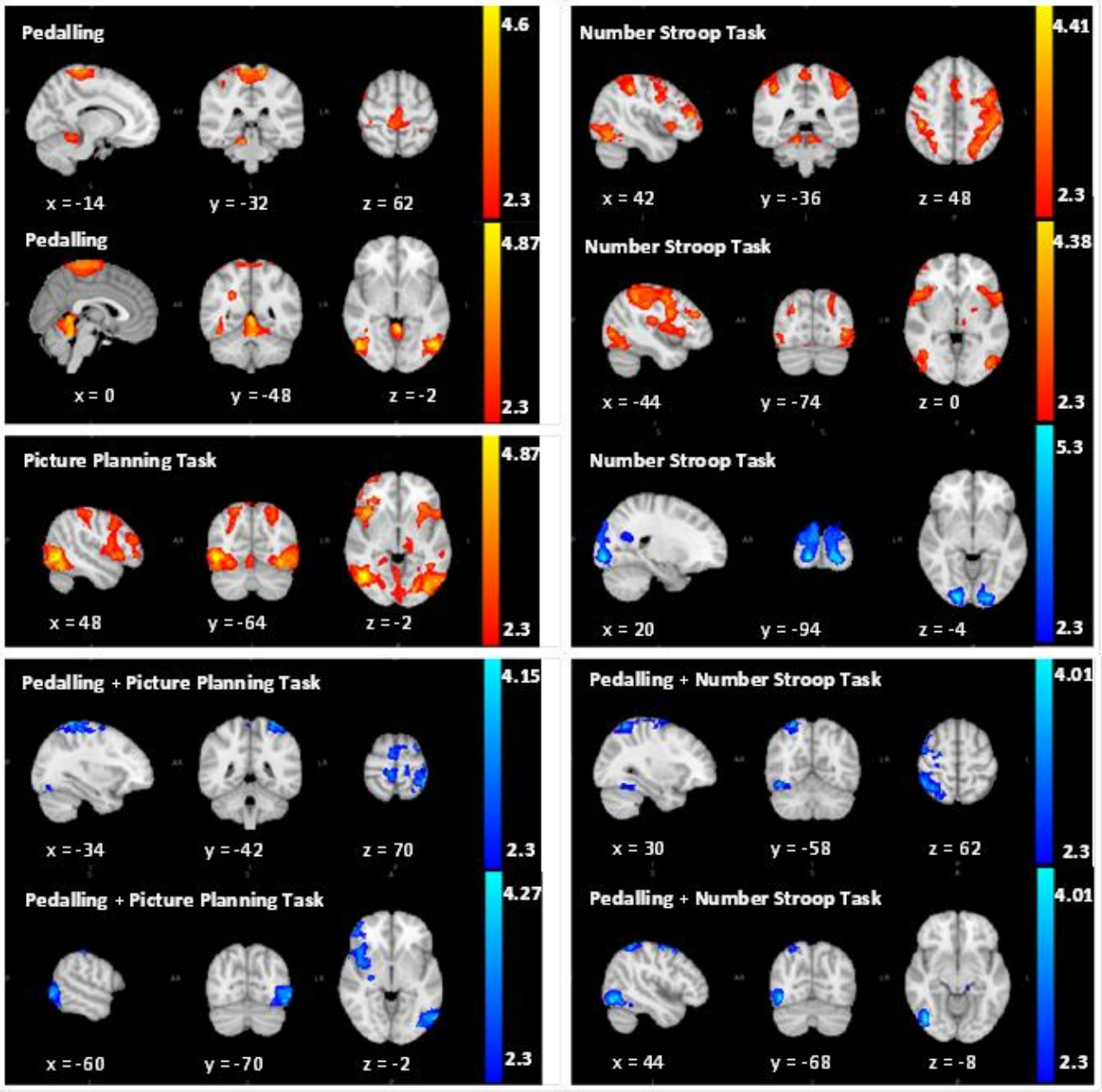


Figure 6.7 Mean activation patterns of 16 stroke survivors at baseline. Image presentation in radiological convention; left side of image is right side of brain and vice versa. Activation was seen in the *left precentral gyrus* **(Pedalling, Number Stroop),** *cerebellum* **(Pedalling),** *left occipital cortex* **(Number Stroop)**, *right inferior occipital cortex* **(Picture Planning). Deactivation was seen in the** *bilateral occipital lobule* **(Number Stroop),** *left postcentral gyrus* **and** *right inferior occipital cortex* **(Pedalling + Number Stroop)**, *right post central gyrus* **and** *left inferior occipital cortex* **(Pedal + Picture Planning).**

6.4.2 **Relationships between task related brain activation and treadmill speed**

Relationships between behavioural measures and task-related brain activation were explored. Treadmill speed related to strength of activation and deactivation during single - and dual tasks. Strength of activation in the *left middle frontal gyrus, left precentral gyrus* and *left cingulate gyrus* during pedalling correlated significantly positively with treadmill speed (top left Figure 6.8). During the NS, a positive correlation with treadmill speed was found for activation in the *left caudate*, *bilateral anterior cingulate gyrus and bilateral paracingulate gyrus* (top right Figure 6.8). Finally, areas that deactivated during both dual task conditions significantly correlated with increases in treadmill speed (bottom left and right Figure 6.8).

6.4.3 **Training group differences**

We predicted that dual task training would alter brain activity during dual task performance. However, we did not find any differences between training groups in change in dual task related brain activation over time. When comparing brain activation during the pedal task at follow-up compared to baseline a significant difference (cluster p-value < 0.001) was found between changes in activation over time between the CT and DT groups. From baseline to follow-up, activation in the *right superior occipital cortex* and *right occipital pole* increased in the CT group and decreased in the DT group (Figure 6.9). No other task contrasts showed changes over time that differed between training groups.

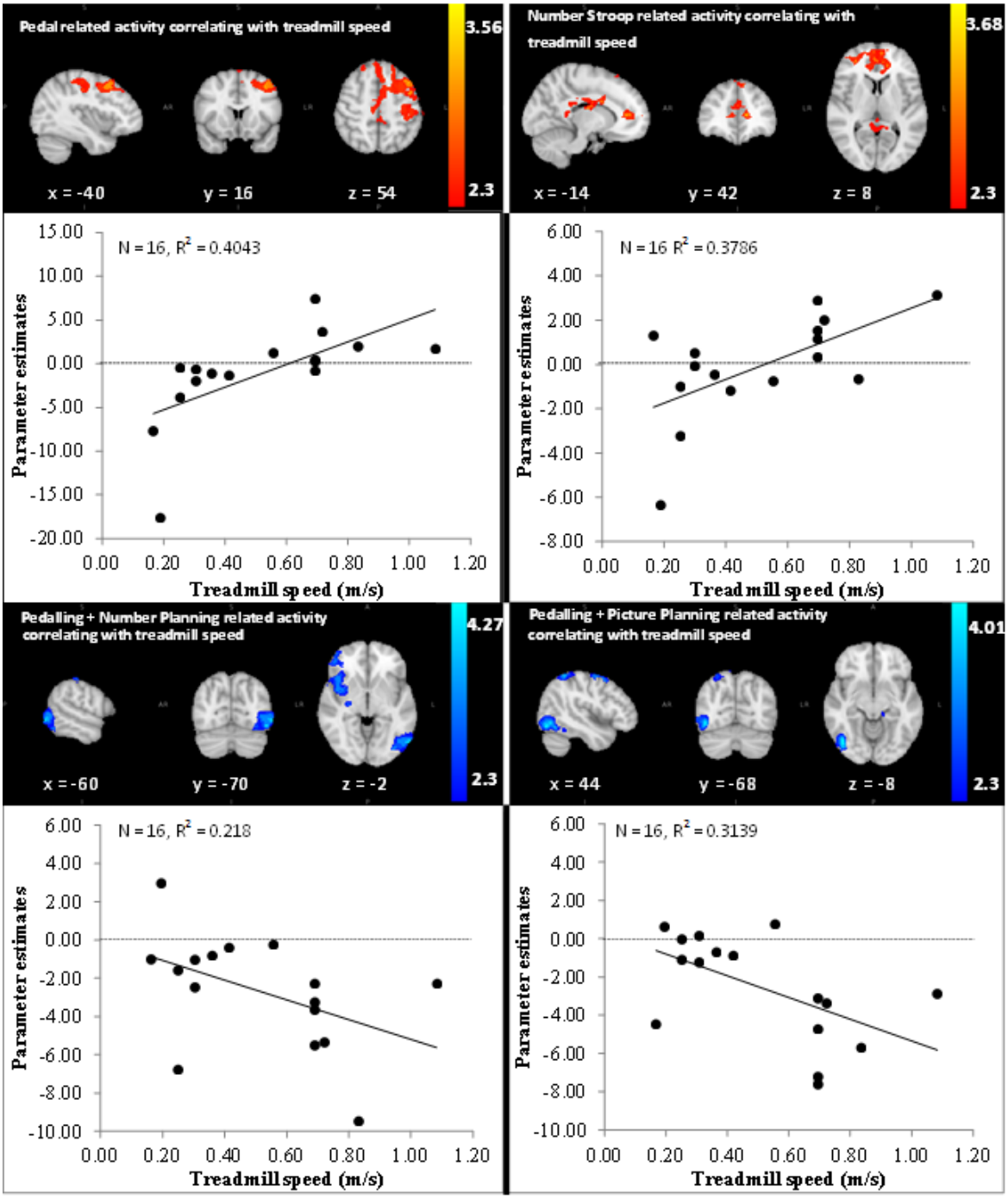


Figure 6.8 Relationship between baseline task activation and treadmill speed for pedalling (top left), Number Stroop (top right), Pedal + Number Stroop (bottom left) and Pedal + Picture Planning (bottom right). Activated areas that correlated with treadmillspeed were: *left middle gyrus* **and** *left cingulate gyrus* **(Pedalling)**, *left caudate* **and** *bilateral anterior cingulate gyrus* **(Number Stroop). Deactivated areas that correlated with treadmill speed were:** *left postcentral gyrus* **and** *right inferior occipital cortex* **(Pedalling + Number Stroop)**, *right post central gyrus* **and** *left inferior occipital cortex* **(Pedal + Picture Planning).**

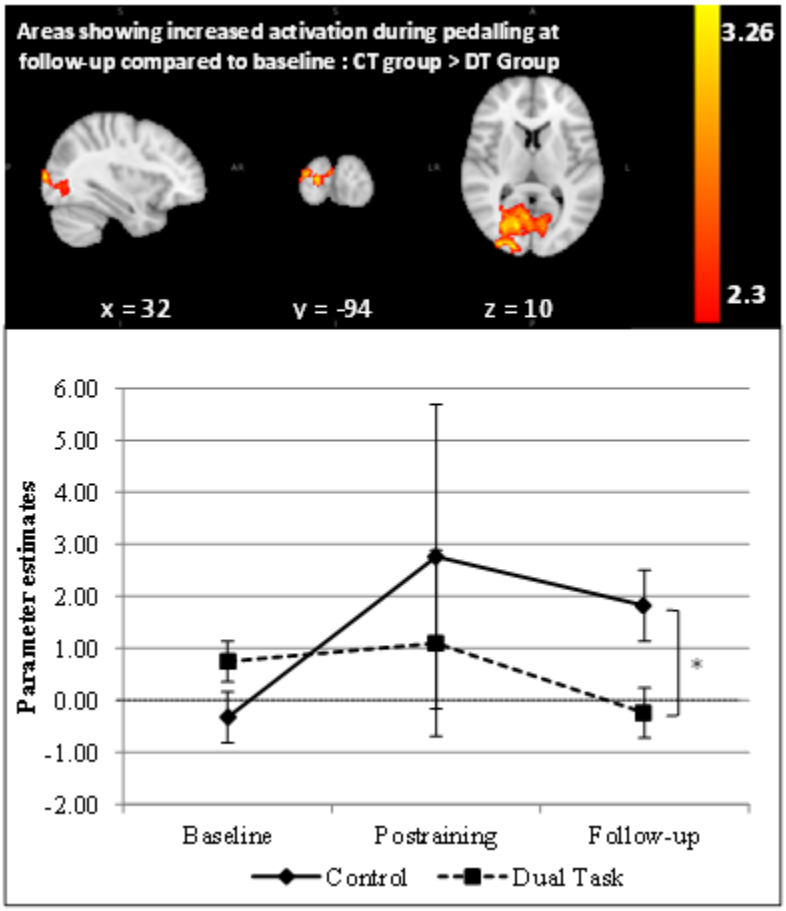


Figure 6.9 Change in activation during pedalling for both training groups. * Significant difference between the training groups for the change in activation from baseline to follow-up ($p < 0.001$). Differences in activation during pedalling between groups and over time were seen in the *right superior occipital cortex* **and** *right occipital pole*.

6.4.4 **Relationships between changes in brain activation and changes in walking performance within the dual task training group**

Consistent with our predictions, change in task related brain activity during pedalling and dual task related to changes in dual task walking performance. Specifically, from baseline to post-training activation during pedalling decreased significantly in the *left posterior cingulate gyrus* and the *left precuneus cortex.* In those areas change in activation from baseline to follow-up correlated negatively with increases in TMW-DT distance from baseline to follow-up (left, Figure 6.10). In addition, there was a positive correlation between brain activation increases during PP-DT at follow up compared to baseline in the *right frontal lobe* and *right superior and middle frontal gyrus* and increases in TMW-DT distance at follow-up compared to baseline (right, Figure 6.10). In other words, those who showed greater improvements in walking speed under dual task conditions showed greater decreases in single task pedal related activity and increases in prefrontal activity during dual task performance in the scanner.

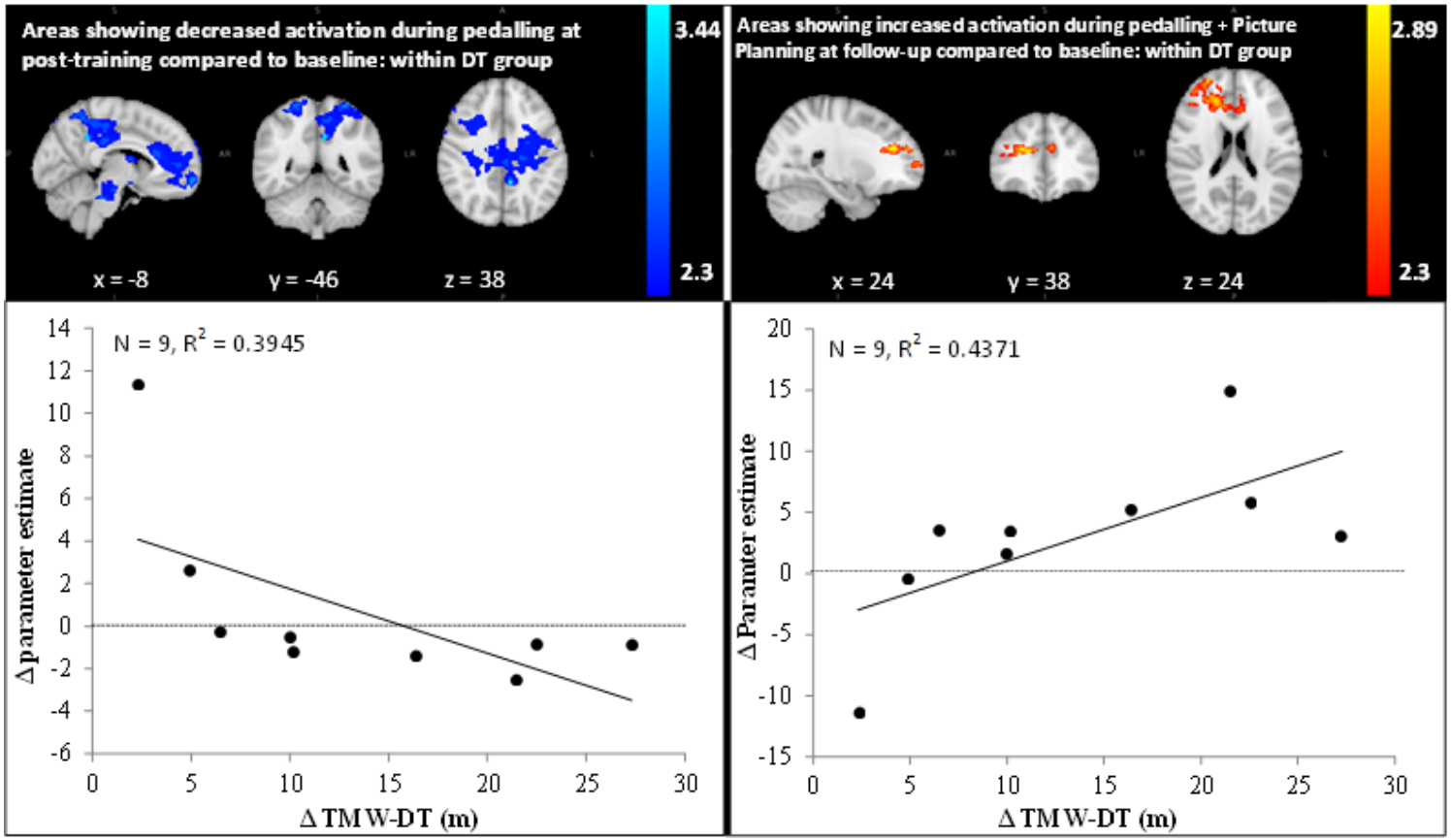


Figure 6.10 Relationships between change in brain activation during pedalling (left) and pedalling + Picture Planning (right) from baseline to follow-up and in walking distance on the two-minute-walk with dual task, within the Dual Task Training Group. Significant reductions in activations that related to change in TMW-DT were seen in the *left posterior cingulate gyrus* **and the** *left precuneus cortex***. During dual task significant increases in the** *right frontal lobe* **and** *right superior - and middle frontal gyrus* **related to increases in TMW-DT.**

6.5 fNIRS results

Figure 6.11 and Table 6.4 present the level of relative concentration change in OHb during treadmill walking and cognitive task execution in single and dual task conditions. Single cognitive tasks were associated with negative concentration changes in OHb compared to treadmill walking and the two dual task conditions which showed positive levels of OHb concentration changes. In both left and right PFC, relative changes in OHb during task period were significantly higher whilst treadmill walking compared to any of the other four task conditions. During treadmill walking, relative changes in OHb were 0.70mmol/L ± 0.28mmol/L and 0.79mmol/L ± 0.22mmol/L in left and right PFC respectively. In the left PFC there was a significant difference between PP and both DT conditions. In the right PFC both AS and PP showed significantly different OHb levels compared to both DT conditions. In the PMC areas, OHb levels during single cognitive task periods (AS and PP) were significantly lower compared to treadmill walking or any of the dual tasks.

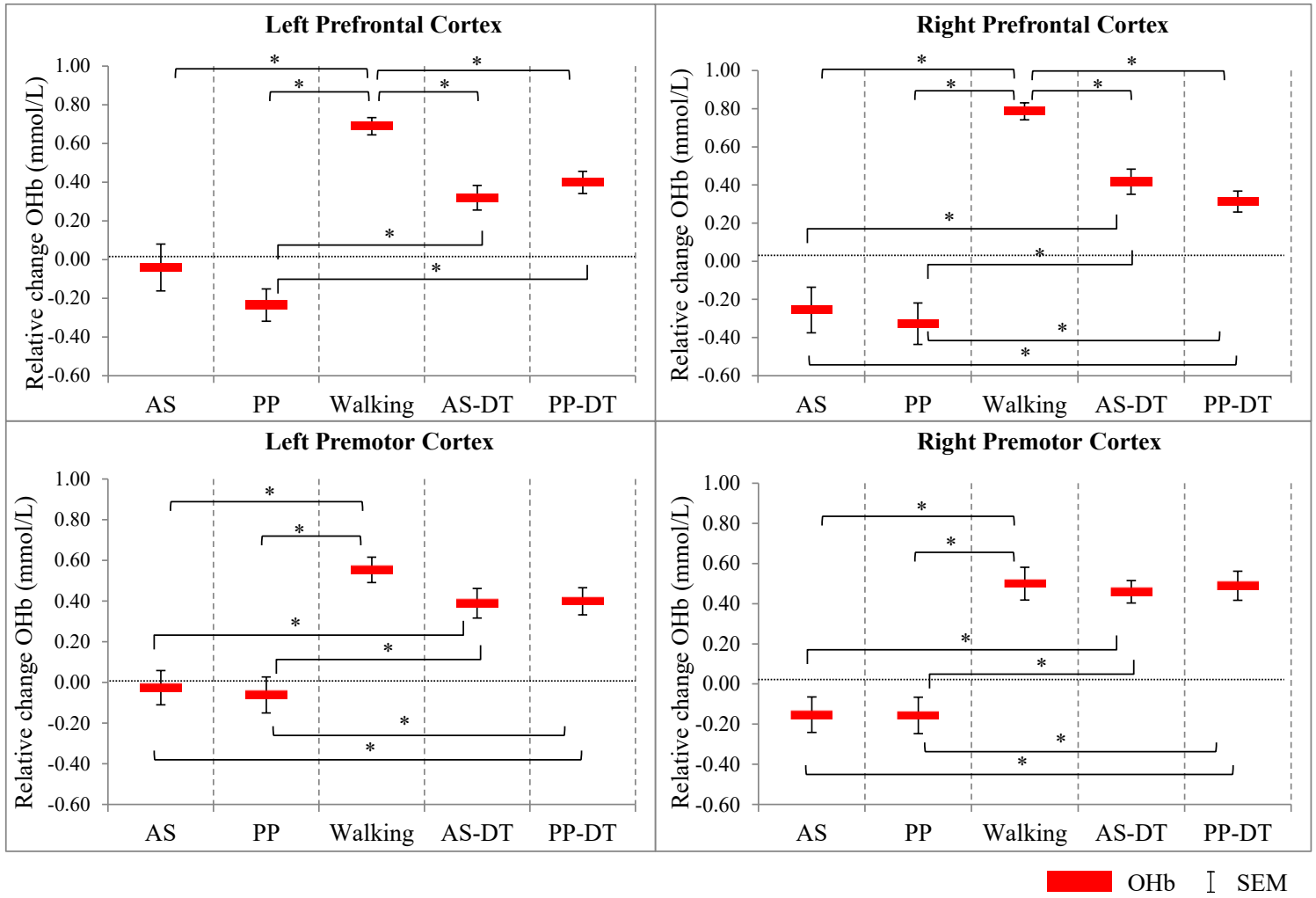


Figure 6.11 Average relative concentration change in oxygenated haemoglobin during single and dual task treadmill walking. OHb: oxygenated haemoglobin, SEM: standard error of the mean, AS: auditory Stroop, PP: Picture Planning, AS-DT: auditory Stroop task during walking, PP-DT: picture planning task during walking.

Table 6.4 Baseline brain activation during treadmill walking under single and dual task conditions.

Area (n)	Auditory Stroop	Picture Planning	Treadmill walking	Auditory Stroop-DT	Picture Planning-DT	Task difference
PFC (OHb in mmol/L)						
Left (34)	-0.04 ± 0.71	-0.24 ± 0.48	0.69 ± 0.26	0.32 ± 0.37	0.40 ± 0.33	***< 0.001*** [a,c]
Right (26)	-0.26 ± 0.61	-0.33 ± 0.55	0.78 ±0.29	0.42 ± 0.34	0.31 ± 0.28	***< 0.001*** [a,b]
PMC (OHb in mmol/L)						
Left (26)	-0.03 ± 0.43	-0.06 ± 0.45	0.55 ± 0.32	0.39 ± 0.37	0.40 ± 0.34	***0.001*** [b]
Right (30)	-0.15 ± 0.49	-0.16 ± 0.50	0.50 ± 0.45	0.46 ± 0.31	0.49 ± 0.40	***<0.001*** [b]

PFC; prefrontal cortex, PMC; premotor cortex, DT; dual task (task during treadmill walking). Post-hoc tests with Bonferroni corrections:

a. significant difference between treadmill walking and all other tasks

b. significant difference between single cognitive tasks (AS and PP) and treadmill walking, AS-DT and PP-DT

c. significant difference between PP and two DT conditions.

Table 6.5 Linear mixed model results for brain activation during treadmill walking between groups and over time.

Outcome measure	Group	Baseline	Post-training	Follow-up	Linear Mixed Model results			
Walking Task		Model means (SEM)	Model means (SEM)	Model means (SEM)	Effect	df	F	Sig.
Left PFC **(OHb mmol/L)**	Control	**0.76** (0.22)	**0.64** (0.48)	**0.59** (0.27)	Group	*43.317*	*0.039*	*0.845*
	Dual Task	**0.61** (0.30)	**0.62** (0.31)	**0.71** (0.24)	Time	*37.192*	*0.261*	*0.771*
					Group * Time	***37.192***	***3.264***	***0.049****
Right PFC **(OHb mmol/L)**	Control	**0.78** (0.24)	**0.68** (0.40)	**0.66** (0.28)	Group	*35.828*	*0.075*	*0.786*
	Dual Task	**0.77** (0.27)	**0.57** (0.33)	**0.75** (0.16)	Time	*57.437*	*1.906*	*0.158*
Left PMC **(OHb mmol/L)**	Control	**0.47** (0.32)	**0.68** (0.33)	**0.63** (0.63)	Group	*39.281*	*0.021*	*0.885*
	Dual Task	**0.56** (0.36)	**0.56** (0.30)	**0.62** (0.27)	Time	*62.574*	*1.063*	*0.352*
Right PMC **(OHb mmol/L)**	Control	**0.56** (0.32)	**0.65** (0.26)	**0.73** (0.22)	Group	*34.700*	*2.798*	*0.103*
	Dual Task	**0.41** (0.55)	**0.54** (0.28)	**0.61** (0.29)	Time	*58.440*	*1.819*	*0.171*

PFC: Prefrontal Cortex, PMC: Premotor Cortex, OHb: Oxygenated Haemoglobin, SEM: Standard error of the mean, df: degrees of freedom. Significance level for mixed model, α = 0.05.

Table 6.6 Linear mixed model results for brain activation during treadmill walking between groups and over time.

Outcome measure	Group	Baseline	Post-training	Follow-up	Linear Mixed Model results			
Walking + Audio Task Corrected for ST brain activation		Model means (SEM)	Model means (SEM)	Model means (SEM)	Effect	df	F	Sig.
Left PFC **(OHb mmol/L)**	Control	**-0.03** (0.72)	**0.01** (0.70)	**0.04** (0.55)	Group	*40.399*	*0.196*	*0.660*
	Dual Task	**-0.57** (0.92)	**-0.13** (0.42)	**-0.14** (0.65)	Time	*38.852*	*1.307*	*0.282*
Right PFC **(OHb mmol/L)**	Control	**0.06** (0.65)	**0.12** (0.50)	**-0.02** (0.48)	Group	*36.686*	*0.222*	*0.640*
	Dual Task	**-0.28** (0.64)	**0.00** (0.44)	**-0.21** (0.73)	Time	*49.335*	*1.778*	*0.180*
Left PMC **(OHb mmol/L)**	Control	**-0.02** (0.50)	**-0.29** (0.56)	**-0.29** (0.72)	Group	*37.763*	*0.000*	*0.992*
	Dual Task	**-0.17** (0.62)	**0.06** (0.94)	**-0.05** (0.49)	Time	*44.800*	*0.116*	*0.891*
Right PMC **(OHb mmol/L)**	Control	**0.13** (0.49)	**-0.18** (0.64)	**0.02** (0.63)	Group	*35.643*	*0.413*	*0.524*
	Dual Task	**0.10** (0.61)	**0.18** (0.55)	**-0.14** (0.64)	Time	*59.806*	*0.745*	*0.479*

PFC: Prefrontal Cortex, PMC: Premotor Cortex, OHb: Oxygenated Haemoglobin, SEM: Standard error of the mean, df: degrees of freedom.

Significance level for mixed model, $\alpha = 0.05$

Table 6.7 Linear mixed model results for brain activation during treadmill walking between groups and over time.

Outcome measure	Group	Baseline	Post-training	Follow-up	Linear Mixed Model results			
Walking + Picture Task Corrected for ST brain activation		Model means (SEM)	Model means (SEM)	Model means (SEM)	Effect	df	F	Sig.
Left PFC **(OHb mmol/L)**	Control	**0.14** (0.75)	**0.18** (0.57)	**-0.00** (0.44)	Group	*47.027*	*0.504*	*0.481*
	Dual Task	**-0.20** (0.40)	**0.17** (0.58)	**-0.10** (0.63)	Time	*66.059*	*2.480*	***0.092***[#]
Right PFC **(OHb mmol/L)**	Control	**-0.03** (0.50)	**0.20** (0.66)	**-0.21** (0.43)	Group	*35.550*	*3.367*	***0.075***[#]
	Dual Task	**-0.24** (0.59)	**0.05** (0.67)	**-0.05** (0.59)	Time	*43.920*	*2.096*	*0.135*
Left PMC **(OHb mmol/L)**	Control	**0.08** (0.69)	**-0.29** (0.70)	**-0.26** (0.63)	Group	*38.799*	*2.037*	*0.161*
	Dual Task	**-0.14** (0.67)	**0.10** (0.91)	**-0.02** (0.53)	Time	*52.122*	*0.092*	*0.912*
Right PMC **(OHb mmol/L)**	Control	**0.32** (0.84)	**-0.22** (0.73)	**-0.11** (0.39)	Group	*28.919*	*1.472*	*0.235*
	Dual Task	**0.02** (0.87)	**0.29** (0.65)	**-0.02** (0.60)	Time	*45.879*	*0.818*	*0.447*

PFC: Prefrontal Cortex, PMC: Premotor Cortex, OHb: Oxygenated Haemoglobin, SEM: Standard error of the mean, df: degrees of freedom.

Significance level for mixed model, α = 0.05

Linear mixed model results of brain activation during treadmill walking and dual task treadmill walking are presented in Table 6.5 - 6.7. No differences between groups or over time were seen for PFC and PMC activation during treadmill walking without an extra task (Table 6.5). A significant interaction ($p = 0.049$) between time and group was seen for PFC activation in the left cortex. Over time, OHb levels during treadmill walking increased in the DT group from 0.61mmol/L ± 0.30mmol/L at baseline to 0.62mmol/L ± 0.31mmol/L at post training and 0.71mmol/L ± 0.24mmol/L at follow-up. In the CT group, levels decreased from 0.76mmol/L ± 0.22mmol/L at baseline to 0.64mmol/L ± 0.48mmol/L and 0.59mmol/L ± 0.27mmol/L at post-training and follow-up respectively. The other areas did not show significant interactions. No relationships were found between brain activation as measured with fNIRS and behavioural measure such as treadmill speed, TMW distances or clinical characteristics like stroke onset.

6.6 Behavioural measures during fMRI scan and treadmill walking

6.6.1 Dual task effect on pedal frequency during fMRI scan

Pedal frequency increased during the NS during dual task for both groups and at all time points (Table 6.8). The strength of the DTE was higher in the CT group compared to the DT group ($p = 0.022$). In the CT group, at baseline the pedal frequency during NS-DT task was 6.70 % ± 11.70 % higher compared to just pedalling. This percentage increased to 11.40 % ± 5.00 % and 21.10 % ± 5.80 % at post-training and follow-up. In the DT group increases of pedal frequency during dual task with the NS were +6.7 % ± 8.20 %, +1.60 % ± 3.40 % and 4.30 % ± 3.80 % at baseline, post-training and follow-up. For the DTE on the pedal frequency during the PP-DT task, a similar difference between the two training groups was seen. The DTE in the CT group changed from -3.40 % ± 9.40 % at baseline to +6.50 % ± 6.90 % at post-training and +20.60 % ± 4.50 % at follow-up whilst the

DTE on pedal frequency during the PP-DT in the DT group changed from +3.40 % ± 6.70 % to +1.60 % ± 4.90 % and +4.00 % ± 3.00 % respectively. This led to a significant difference between groups ($p = 0.043$) and a trend towards a significant group * time interaction ($p = 0.093$).

6.6.2 Dual task effect on cognitive performance during fMRI scan

Cognitive performance for both the NS and PP did not change significantly during dual task compared to the single task condition. Moreover there were no significant DTE differences between groups or changes over time (see Table 6.8).

6.6.3 Dual task effect on cognitive performance during treadmill walking

DTE on cognitive performance on the AS task were small and did not change over time or differ between stroke survivors. On average for both groups and over all three time points, DTE on composite scores during dual task varied from +1.00 % ± 3.20 % to +3.70 % ± 2.50 % (see Table 6.9). For the PP task, DTE on cognitive performance showed a significant decrease in score at baseline with -9.00 % ± 4.20 % in the CT group ($t = 3.099$, $p = 0.005$) and -10.70 % ± 4.00 % in the DT group ($t = 2.990$, $p = 0.007$). These DTE percentages changed at post-training to +5.60 % ± 4.90 % and -7.50 % ± 4.40 % for the CT - and DT group with a significant DTE for the DT group ($t = 2.858$, $p = 0.009$). At follow-up, DTE was +1.10 % ± 5.30 % or the CT group and -3.90 % ± 4.90 % for the DT group.

Table 6.8 Linear mixed model results for cognitive performance during single and dual task treadmill walking and pedalling inside the scanner between groups and over time.

Outcome measure	Group	Baseline	Post-training	Follow-up	Linear Mixed Model results			
Task		Model means (SEM)	Model means (SEM)	Model means (SEM)	Effect	df	F	Sig.
fMRI Pedal frequency **Number Stroop DTE (%)**	Control	**+6.70 %** (11.70)	**+11.40 %** (5.00)	**+21.10 %** (5.80)	Group	***8.781***	***7.653***	***0.022****
	Dual Task	**+6.70 %** (8.20)	**+1.60 %** (3.40)	**+4.30 %** (3.80)	Time	*9.646*	*1.868*	*0.206*
fMRI Pedal frequency **Picture Planning DTE (%)**	Control	**-3.40 %** (9.40)	**+6.50 %** (6.90)	**+20.60 %** (4.50)	Group	*12.974*	*0.426*	*0.526*
	Dual Task	**+3.40 %** (6.70)	**+1.60 %** (4.90)	**+4.00 %** (3.00)	Time	***12.081***	***4.141***	***0.043****
					Group * Time	***12.081***	***2.904***	***0.093****
fMRI Cognitive score **Number Stroop DTE (%)**	Control	**+3.40 %** (3.90)	**-5.60 %** (9.90)	**+11.90 %** (7.40)	Group	*11.813*	*0.114*	*0.741*
	Dual Task	**+4.70 %** (3.00)	**+8.00 %** (7.00)	**+9.90 %** (5.50)	Time	*13.686*	*1.233*	*0.322*
fMRI Cognitive score **Picture Planning DTE (%)**	Control	**+4.60 %** (13.00)	**-8.60 %** (11.70)	**-0.90 %** (12.90)	Group	*9.369*	*0.000*	*0.988*
	Dual Task	**+0.90 %** (8.70)	**-5.10 %** (8.20)	**-2.50 %** (9.60)	Time	*10.230*	*0.285*	*0.758*

DTE: Dual task effect, SEM: Standard error of the mean, df: degrees of freedom. Significance level for mixed model, α = 0.05. * significant change over time, # Trend towards significant Group*Time interaction.

Table 6.9 Linear mixed model results for cognitive performance during single and dual task treadmill walking and pedalling inside the scanner between groups and over time.

Outcome measure	Group	Baseline	Post-training	Follow-up	Linear Mixed Model results			
Task		Model means (SEM)	Model means (SEM)	Model means (SEM)	Effect	df	F	Sig.
fNIRS **Auditory Stroop Composite score DTE (%)**	Control	**+2.00 %** (2.30)	**+3.70 %** (2.50)	**+2.20 %** (2.70)	Group	*44.862*	*0.010*	*0.921*
	Dual Task	**+3.60 %** (2.70)	**+1.00 %** (3.20)	**+3.20 %** (2.50)	Time	*43.717*	*0.051*	*0.950*
fNIRS **Picture Planning Composite score DTE (%)**	Control	**-9.00 %*** (4.20)	**+5.60 %** (4.90)	**+1.10 %** (5.30)	Group	*42.793*	*2.802*	*0.101*
	Dual Task	**-10.70 %*** (4.00)	**-7.50 %** (4.40)	**-3.90 %** (4.90)	Time	***81.471***	***2.926***	***0.059***$^{\#}$

DTE: Dual task effect, SEM: Standard error of the mean, df: degrees of freedom. Significance level for mixed model, α = 0.05. *significant percentage change as tested with paired T-Test, # Trend towards significant change over time.

6.7 Discussion

6.7.1 Dual task effect on brain activation during simulated and real walking at baseline

This study set out to explore brain activation patterns during single and dual task gait in chronic stroke survivors. Moreover, this is the first randomized trial to explore brain activation changes in response to dual task walking training in stroke. At baseline, it was hypothesized that during dual task, brain activation in areas involved in cognition and motor control would increase significantly more compared rest and when corrected for single task activation as a results of increased demands on prefrontal cortex areas for cognitive - and motor control. On the contrary, no areas showed additional activation during dual task gait during the fMRI paradigm or the treadmill walking with fNIRS. Instead, during the NS-DT and PP-DT, BOLD-signal in the occipital cortex and parietal lobule decreased relative to single task related brain activation. In addition, PFC and PMC activation as measured with fNIRS decreased during the AS-DT and PP-DT compared to treadmill walking on its own. Only in the PFC this reduction in brain activity was significantly lower compared to single task treadmill walking.

DTE on brain activation was not accompanied with reduced or increased behavioural performance during pedalling and cognitive task execution inside the fMRI scanner at baseline. During the PP-DT on the treadmill, cognitive performance decreased significantly compared to PP whilst standing, but these decreases did not correlate with DTE on brain activation.

In our study, during simulated walking inside the scanner, pedal frequency was left self-selected and wasn't paced. In contrast, Al-Yahya et al. (2015), used a pedal frequency inside the scanner that presented 80% of the rate that stroke survivors were able to produce outside the scanner. In our study, stroke survivors may have pedalled at frequencies lower than their normal speed in both single and dual task

blocks. Moreover, even though practice runs were done to familiarise the stroke survivor with the cognitive tasks and leg movement, moving their feet whilst lying down was not a familiar and simple movement on itself for most participants. Therefore the pedal task on itself could have been perceived as difficult and have led to high activation levels which already led to full capacity.

In comparison with previous work, one study by Beurskens et al. (2014) did also find decreases in the PFC activity in healthy older adults whilst dual task walking. Other studies reported increases in PFC, SMA and PMC activation during dual task walking in healthy young and older adults overground (Holtzer, Mahoney et al. 2011, Lu, Liu et al. 2015) and in healthy younger and older adults and stroke survivors whilst dual task treadmill walking (Meester, Al-Yahya et al. 2014, Al-Yahya, Johansen-Berg et al. 2015). In addition, some studies found concurrent increases and decreases during dual task paradigms involving cognition and tactile processing (Merabet, Swisher et al. 2007), two concurrent cognitive tasks (Salo, Rinne et al. 2015) and imagined walking while talking (Blumen, Holtzer et al. 2014).

The differences and similarities in findings between our study and previous work can be discussed in relation to study population, walking paradigm and type of task. In their study, Holtzer et al. (2011) found increases in PFC with dual task, but showed that the magnitude of change was modulated by age. Older adults showed less PFC increase during dual task walking compared to younger adults. Still the direction of change is opposite to our findings. In contrast, Al-Yahya et al. (2015) found increases in PFC activation in stroke compared to healthy age-matched adults. These results together suggest decreases of dual task related PFC activation with age, but increases post stroke.

Exploring the similarities and differences between the study of Al-Yahya et al. (2015), Holtzer (2011) and Lu (2015) it shows that two of the three have used serial subtraction as an extra task and the third has used a task in which participants

were asked to recite alternate letters of the alphabet. In comparison, both our study and the study of Beurskens et al. (2014) used a cognitive task which required visual attention and found decreases with dual task. The serial subtraction task and the alphabet reciting task are both tasks which require memory and processing. Moreover they are internally stimulated, i.e. the continuation of the task is driven by the tested subject. In contrast the AS task, PP task and check test (Beurskens, Helmich et al. 2014) are driven by external stimuli and may therefore demand less cognitive resources resulting in lower activation of the PFC in combination with increased activations of other areas like visual cortex and the caudal anterior cingulate cortex (Haupt, Axmacher et al. 2009).

Some other important differences between the study of Al-Yahya et al. (2015), Holtzer et al. (2011) and Lu et al. (2015) and our study were the (simulated) walking paradigms and the amount of instruction. In our study stroke survivors walked on a treadmill which didn't enable them to change their walking speed in response to distraction. Furthermore subjects were not instructed about how to perform the dual task. In both the studies of Holtzer et al. (2011) and Lu et al (2015) subjects were walking overground and were instructed to distribute equal attention to both walking and the extra task or to focus on the execution of the cognitive or additional motor task (Lu, Liu et al. 2015). The use of instructions may have stimulated the cognition and upregulated prefrontal cortex activation. Moreover overground walking would have enabled to slow down in walking speed. In addition, our study used 30 seconds task blocks in which stroke survivors walked continuously on the treadmill, whereas the other two studies had subjects performing dual task walking overground on a track of 15 feet causing the subjects to make turns. This inclusion of turns may have increased the task difficulty and in turn increased cognitive demands.

Finally, the type of analyses for exploring DTE on brain activation may have been of influence. A review by Szameitat et al. (2011) argued that differences in DT imaging studies could be attributed to different models of analysing the data.

In our study, DTE on brain activation was explored by subtracting the sum of single task activation from the activation or deactivation seen during dual task blocks (Szameitat, Schubert et al. 2011). Therefore, only activation or deactivation specifically linked to dual task activation would emerge. The study by Al-Yahya et al. (2015) used a slightly different statistical model to explore dual task activation by looking at the interaction between a cognitive task and pedal activity. In this case, activation apparent in both single task blocks will also be attributed to dual task activation. Others (Holtzer, Mahoney et al. 2011, Lu, Liu et al. 2015) lack the correction for brain activation related for one or both single tasks limiting the ability to attribute dual task related brain changes to performance change.

6.7.2 **Relationships, differences between groups and changes over time**

Relationships between pedal-induced brain activation and treadmill speed were apparent in the left middle frontal gyrus, left precentral gyrus and left cingulate gyrus, areas which are known to be involved in walking control (Fukuyama, Ouchi et al. 1997, Hanakawa, Fukuyama et al. 1999, Suzuki, Miyai et al. 2008). Significant clusters correlating with treadmill speed during execution of the NS task were situated in the left caudate, bilateral anterior cingulate - and bilateral paracingulate gyrus. The cingulate gyrus has been reported before as an area active during incongruent stimuli and performance monitoring (Cohen, Botvinick et al. 2000, MacDonald, Cohen et al. 2000). These relationships suggest that stroke survivors walking at faster speeds have increased activation in motor control areas. In addition, the scatter plots (figure 6.8) show that stroke survivors walking at speeds < 0.4ms have a negative activation pattern in the areas involved in motor

control and performance monitoring. Possibly one explanation for reduced walking abilities might be the lack of 'normal' brain activation patterns and therefore an impaired walking control system. The relationships were different for dual task activation, showing larger decreases in stroke survivors walking at higher treadmill speeds. Almost all individuals showed a decrease with dual task which may relate to the single task activation which was subtracted from dual task blocks. Therefore the stronger decrease in better walkers is likely to be related to higher increases in those walkers during single task blocks.

There was a small difference between training groups in pedal related activation in the occipital cortex at follow-up compared to baseline. Stroke survivors who had received DT training showed reduced occipital cortex activation compared to stroke survivors in the CT training. Decreases in brain activation related to stroke recovery of hand function have been reported before in different areas including the occipital lobe (Ward, Brown et al. 2003). The interesting difference between the two groups could be explained by a reduced sensory control in the DT group compared to the CT group. This reduction in sensory control might relate to an increased automated walking control through for instance central pattern generators (Belda-Lois, Mena-del Horno et al. 2011). However, much more neuroimaging research, especially in stroke, is needed to help understand these underlying changes in control of movement in response to rehabilitation.

Next to relationships at baseline we found that within the DT group decreases in the posterior cingulate from baseline to follow-up correlated negatively with improvements on the TMW-DT from baseline to follow-up. Moreover, increases in prefrontal cortex activation during PP-DT at follow-up compared to baseline correlated positively with improvements on the TMW-DT. These two relationships might tell us that dual task training increased automaticity of motor control of walking and therefore brain activation decreased during single task walking and the

role of the prefrontal cortex increased during dual task walking. However no change in cognitive performance was observed that correlated with these improvements.

FNIRS data showed no clear differences between the CT and DT groups for brain activation changes over time. There was a significant interaction between group and time for left PFC activation during treadmill walking, which could indicate an upregulated PFC in DT group participants in response to training compared to the CT group. However, the changes over time were very small and baseline values were slightly different between groups for left PFC activation which makes the argument for upregulated PFC activation only small and further research should be conducted to investigate this pattern.

This is the first study in stroke to use fMRI and show correlations between gait improvement and brain changes in response to dual task training. In previous studies relationships between change in brain activation and DT effect were seen in stroke (Al-Yahya, Johansen-Berg et al. 2015) and activation in the premotor, parietal cortices and cerebellum correlated with improved function in the upper limb (Johansen-Berg, Dawes et al. 2002). Others have shown that increases in motor output for tibialis anterior with transcranial magnetic stimulation of the unaffected hemisphere correlated with functional improvement (Yen, Wang et al. 2008) and increases in motor output of the first dorsal interosseous and map volume in the affected hemisphere correlated with functional improvement on motor scales (Koski, Mernar et al. 2004).

Both fMRI and fNIRS have proven to be feasible techniques to use in dual task paradigms in stroke. Preferably we would have liked to include more stroke survivors into the fMRI sub-study, but were unable due to a large amount of haemorrhagic stroke survivors (haemorrhagic strokes were an exclusion criteria for fMRI study to prevent an additional stratification factor) and other study

participants with contraindications for safe participation in fMRI scans. Means and standard deviations for stroke characteristics, walking ability and physical and mental health showed a heterogeneous population. This will have contributed to the high variability in the data and therefore decreased the chances of detecting statistical significant differences between groups and over time in certain comparisons. However, this larger heterogeneity also allows for a broader interpretation of the findings as it is more likely to have meaning for a large amount of the national and international stroke population.

Although fNIRS is a valid technique and has found increased use in walking experiments in healthy (Suzuki, Miyai et al. 2008, Holtzer, Mahoney et al. 2011, Kurz, Wilson et al. 2012, Koenraadt, Roelofsen et al. 2014, Meester, Al-Yahya et al. 2014, Mirelman, Maidan et al. 2014) and neurological populations (Miyai, Yagura et al. 2002, Fujimoto, Mihara et al. 2014), limitations are still present. The system used in our study consisted of 8 channels which limited the amount of areas that could be covered. Based on previous studies, other areas, such as the parietal cortex (Bakker, De Lange et al. 2008), but also subcortical areas (Luft, Macko et al. 2008), which cannot be measure with fNIRS, are likely to have been activated by our walking paradigm. In addition, in our study about one third of the fNIRS data had to be excluded due to motion artefacts or incomplete data.

6.8 **Conclusions**

Changes we found within our DT group and in comparison to the CT group showed that DT training was related to decreased activation during normal walking and increased activation during DT walking after 10 weeks of training. This suggests that, compared to CT training, DT training had a larger effect on training related brain plasticity. Moreover, dual task training may be more effective than just treadmill walking when influencing the central control of walking as indicated

by the decreased activation during single task walking in the DT group. The extent to which plasticity took place and how this relates to increased dual task ability, better walking control and plasticity as seen in early stages after stroke (Grefkes and Ward 2014) needs to be further explored in future trials with larger participant numbers and more optimized testing paradigms.

This study together with previous work shows that the use of neuroimaging techniques in randomized controlled trials conducted in stroke is useful and helps to improve rehabilitation programs especially around dual task training, where the current knowledge around neural correlates of training is in the early stages.

Chapter 7. Discussion and future directions

This final chapter summarizes and discusses the findings of the studies described in this thesis. The work in this thesis shows novel research in the area of community walking after stroke and may provide handles to continue research in this field and eventually improve rehabilitation programs. Future directions are discussed in light of improvements to current work and the use of other techniques and study designs to explore recovery of community walking after stroke.

Community walking after stroke was the recurring topic in this thesis. Although it has always been important to stroke survivors, it has only in recent decades become more studied and taken into account in rehabilitation programs. As mentioned at the end of chapter 1 and start of chapter 2. The ICF core sets for stroke have been used as a framework for rehabilitation research in stroke (Geyh, Cieza et al. 2004, Robinson, Shumway-Cook et al. 2011). The increasing research on community walking after stroke indicates an increasing focus on the recovery of functions that relate to participation in society rather than just improving the impaired body functions and structures that fall under activities in the ICF. This started with Perry et al. (1995) who defined walking disability after stroke in relation to community walking. After this work was published, others added information about what factors relate to community walking, with a focus on gait speed (Patla and Shumway-Cook 1999, Shumway-Cook, Patla et al. 2002, van de Port, Kwakkel et al. 2008, Ada, Dean et al. 2009, Andrews, Chinworth et al. 2010, Bijleveld-Uitman, van de Port et al. 2013, Robinson, Matsuda et al. 2013). In addition, studies have explored and discussed what tools could be used to measure

community walking (Lord, McPherson et al. 2004, Lord and Rochester 2005, Robinson, Shumway-Cook et al. 2011).

7.1 Summary of work

7.1.1 Dual task ability in relation to community walking

This thesis started with a cross-sectional study in 50 chronic stroke survivors where DTE on gait and cognition was compared between limited - and moderate-to-full community walkers (LCW and FCW respectively) (Chapter 2). Average overground walking speeds of $0.52ms^{-1}$ and $1.13ms^{-1}$ for LCW and FCW in our population respectively, were lower than speeds of age-matched healthy older adults (Bohannon 1997). Measures of dual task ability and community walking showed a reduced cognitive response in LCW during overground walking and lower confidence about walking in the community. In contrast, FCW showed relatively larger reductions in walking performance during dual task walking overground and in cognitive performance during dual task treadmill walking. In summary, both types of community walkers showed walking and dual task walking deficits, but the LCW felt significantly less confident about walking in the community.

Differences in responses to distraction during walking between LCW and FCW suggest that there is more than one strategy for coping with distraction. One could reason that a reduction in cognitive response indicates that individuals required full attention for control of walking and that LCW would therefore find difficulty during community walking. In contrast, FCW were able to lower their walking speed and continue a safe walk which in turn enables them to walk safely in communities where cognitive attention is required during walking. Which strategy is used (consciously or unconsciously) may depend on gait speed, cognitive ability and type of cognitive distraction.

The extent to which results of DTE tests can be related to community walking is challenging. Recently, Yang et al. (2016) tested the validity and reliability of dual task measurements and showed good reliability for DTE on mobility measures, but only poor to fair reliability of DTE on cognition. Moreover, assessing community walking also brings difficulties, for instance, measures being questionnaire-based which require a good memory from the person that is filling out the questionnaire. Particularly in neurological populations, cognitive deficits or memory loss could give difficulties when you want to interview someone about their community walking.

7.1.2 **Dual task training after stroke**

In chapter 3 a randomized controlled trial was presented which explored to what extent chronic stroke survivors could benefit from 10 weeks of dual task treadmill training versus treadmill training without any distraction. The trial was performed in 50 stroke survivors using a single-blinded randomization, control training with the same intensity and frequency as the dual task training and a one-on-one training approach tailored for each study participant. Furthermore multiple measures were used to assess dual task walking and community walking. Together, this was the first well-controlled trial to explore dual training in chronic stroke survivors. Training showed positive effects on walking performance and small effect sizes for dual task treadmill training compared to treadmill training without distraction. Moreover, increases in walking distance and speed were retained at follow-up and overall the trial showed good feasibility with good adherence to training sessions and only 10% drop-out for intention to treat analysis. Some effects of training on community walking were seen, with an increase in confidence about walking in the community in both groups. At follow-up, there was a trend towards a higher community walking score on the modified UAB Life Space Assessment

questionnaire in the DT training group compared to the CT group which may be related to increased cognitive responses on the TMW-DT. On the other hand, trends showed a larger DTE on walking distance over time in the DT group, which was not expected.

Again it is difficult to make direct connections between the changes in DTE on measures and changes in community walking ability of study participants. Importantly, the dual task training in this study was very feasible and small trends in larger improvements on the overground walk with distraction and the modified UAB Life Space Assessment questionnaire compared to the CT group give promise for the use of dual task training in clinical settings and the effect on community walking. However, at the same time, the small differences between outcomes in both training groups also show the need for a larger trial to optimize the training techniques and examine the effect in a larger group of participants.

7.1.3 **Neuroimaging of dual task walking control after stroke**

Measuring both behavioural and mechanistic factors helps to increase understanding around the process of recovery and how the brain and body adapt and may be manipulated in early and chronic phases after stroke. Behavioural measures, such as walking performance and cognitive performance were used and described in the studies in Chapter 2 and 3 to understand the impact and outcome of dual tasks on behaviour and real life situations. Mechanistic measures, such as brain activity and muscle reflexes, provide additional information on what occurs in the control mechanisms of dual task walking.

Neuroimaging techniques have been introduced in rehabilitation trials to measure brain activation during motor tasks, but also to assess recovery of brain tissue and change in brain activation patterns over time (Carey and Seitz 2007). Moreover in combination with for instance neuro-stimulation, neuroimaging may identify

biomarkers which attribute to development of neurorehabilitation programs (Seitz and Donnan 2010).

The final part of this thesis (Chapter 6) focussed on results from fMRI and fNIRS measures that were taken during the clinical trial to explore brain activation patterns during single and dual task locomotor movements and compared results between the two training groups. At baseline, decreases in brain activation were seen in prefrontal cortex areas during dual task treadmill walking which may relate to decreased dual task ability in these chronic stroke survivors. Moreover fMRI during pedal movements with a concurrent cognitive task showed decreased brain activation compared to pedal movement alone. Levels of activation and deactivation correlated with treadmill speed showing different levels of central control between stroke survivors with different walking abilities.

Activation during pedalling decreased in response to training in the DT group compared to the CT group. No strong conclusions can be drawn from this difference in activation between groups, but it suggested a slightly larger effect of training on brain activation in the DT group. When focussing on the DT group (without the comparison to CT group), stroke survivors showed reductions in brain activation during normal walking and increases in activation during dual task walking in response to training. These changes in activation correlated with increases in walking distance on the TMW-DT and could indicate a recovery of the automaticity of control of normal walking as a result of dual task training.

However the numbers of included fNIRS-data and participants in the fMRI were small. Results from both neuroimaging tools cannot be compared, but showed similar patterns. Development of fNIRS systems can help to improve data signals and comfort of the measured subjects which are currently the main reasons for data exclusion. The neuroimaging data presented in this thesis help to understand how motor control mechanisms change in response to training and provides handles to further examine brain plasticity as a result of dual task training in chronic stroke.

7.2 **Future directions**

This thesis covered community walking and dual task ability in stroke survivors and aimed to produce work that covered different aspects including clinical and behavioural relationships, training feasibility of dual task walking and neural mechanisms. Overall, solid methodology, data management, data processing and statistics were used. Nonetheless, in stroke populations, even if a homogeneous population is tested, data often shows large variation. For a large part, this can be explained by the fact that a stroke can occur in any location in the brain at any given time in life and that early recovery after stroke is influenced by many factors which vary hugely amongst individuals. To improve rehabilitation, it is therefore useful to use measures in stroke research that can also be informative on an individual basis. Especially when measuring community and someone's ability to participate in the society.

One of the difficulties when assessing community walking is that it relates to performance in real life. Ideally you would like to be with a person when they are walking in the community, to be able to assess a person's community walking ability. In a study by Park et al. (2011) time taken to walk a 300 meter community walk was used to assess community walking ability. Such measures are coming much closer to reality than a walk on a treadmill or a walk overground on a set out trajectory. Another method of measuring community walking more directly could be through the use of a body camera that monitors a person's physical activity and the same time can provide an image from a first person perspective to give information about where the activity takes place (Doherty, Hodges et al. 2013). Such a device could provide very detailed information about where and when someone is walking, (e.g. how busy is the surrounding). In this detailed information lies a huge ethical concern, as the data collected by these cameras contain personal and private information which should be handled with extremely

carefulness (Mok, Cornish et al. 2015). Some research has been done in healthy young adults (O'Loughlin, Cullen et al. 2013), but further research and debates are needed to assess the possibility of using these systems in older and neurological populations.

Similar to behavioural measures, mechanistic measures such as the neuroimaging tools that have been used in this study could be used in community based settings or use testing paradigms that come closer to real-life settings. There are already fNIRS systems that can be used in freely moving subjects whilst walking or even cycling (Piper, Krueger et al. 2014). Wearing such a system will always be a distraction to the subject being tested, but it does allow for use in different testing environments. An fMRI scanner cannot be moved into community settings, but high-resolution scanners and development of software do allow for measurements during larger movements and the use of novel paradigms that relate more to daily life situations.

Sub-populations of stroke survivors, for instance selected based on community walking speeds, may benefit from different types of training programs to improve functional walking and to have an effect on brain control mechanisms. Therefore, continuing the use of neuroimaging in walking rehabilitation research will further develop neurorehabilitation in stroke.

8. Appendices

8.1 Appendices Chapter 2

8.1.1 Appendix 2.A Dual task effect on gait parameters during overground walking tests

Table 2.A1 Change in gait parameters during single task and dual task condition during two-minute-walk tests.

Gait measure	Single Task	Dual Task	DTE (%)	P-value
Two-minute-walk	**(n = 50)**	**(n = 50)**		
Distance (m)	85.23 ± 41.73	73.95 ± 35.36	- 12.17 ± 9.57	***< 0.001***
	(n = 44)	**(n = 44)**		
Cadence (steps/min)	95.49 ± 23.46	90.85 ± 23.03	- 4.80 ± 7.86	***< 0.001***
Stride time ratio				
High/low	1.02 ± 0.03	1.02 ± 0.02	+ 0.14 ± 3.34	*0.903*
Step Frequency (Hz)	1.49 ± 0.41	1.39 ± 0.44	- 6.24 ± 14.36	*0.490*
Step time (s)	0.70 ± 0.20	0.73 ± 0.22	+ 5.11 ± 9.28	***0.002***
Step time variability (s)	0.09 ± 0.08	0.11 ± 0.11	+ 22.67 ± 43.60	***< 0.001***

DTE; dual task effect. P-value represents result of paired sample t-test to test difference between single - and dual task condition, α = 0.05.

Table 2.A2 Dual task effect on gait measures during two-minute-walk tests per type of community walker

Gait measure	DTE (%) LCW	DTE (%) FCW	P-value
Two-minute-walk	**(n = 23)**	**(n = 21)**	
Distance (m)	-9.76 ± 8.85	-14.83 ± 9.92	*0.068*
Cadence (steps/min)	+4.87 ± 9.92	+4.81 ± 6.60	*0.742*
Stride time ratio			
High/low	+3.00 ± 3.13	-0.50 ± 3.81	*0.739*
Step Frequency (Hz)	-9.09 ± 18.77	-3.10 ± 6.19	*0.240*
Step time (s)	+5.91 ± 11.30	+4.19 ± 6.68	*0.546*
Step time variability (s)	+21.00 ± 49.22	+24.62 ± 37.81	*0.787*

DTE; dual task effect, LCW; limited community walkers, FCW; moderate-to-full community walker. P-value represents result of independent sample t-test to test difference between values for LCW and FCW, α = 0.05.

8.1.2 Appendix 2.B Dual task effect on gait parameters during treadmill walking

Table 2.B1 Gait parameters (mean ± stdev) during treadmill walking with and without additional tasks and the effect of dual task

Gait Measure	Walking	AS-DT	PP-DT	Audio DTE change (%)	P-value	Picture DTE change (%)	P-value
Treadmill assessment	**(n = 48)**	**(n = 48)**	**(n = 48)**				
Cadence (steps/min)	75.65 ± 17.00	76.93 ± 16.71	77.64 ± 17.19	+ 2.18 ± 7.27	*0.057*	+ 3.18 ± 9.31	***0.020***
Stride time ratio							
High/low	1.03 ± 0.05	1.04 ± 0.05	1.03 ± .05	+ 0.52 ± 4.74	*0.484*	- 0.19 ± 3.84	*0.841*
Step Frequency (Hz)	1.13 ± 0.34	1.16 ± 0.35	1.13 ± 0.34	+ 5.22 ± 17.28	*0.148*	- 2.20 ± 23.17	*0.975*
Step time (sec)	0.88 ± 0.21	0.85 ± 0.18	0.85 ± 0.18	- 2.93 ± 6.91	***0.005***	-3.11 ± 6.48	***0.002***
Step time variability (s)	0.15 ± 0.11	0.17 ± 0.12	0.15 ± 0.11	+ 14.09 ± 47.30	*0.163*	+ 12.04 ± 49.60	*0.949*

AS-DT; auditory Stroop task during walking, PP-DT; picture planning task during walking, DTE; dual task effect. P-value represents result of paired sample t-test to test difference between single - and dual task condition, α = 0.05.

Table 2.B2 Dual task effect on gait measures during treadmill walking per type of community walker

Gait Measure	AS-DT DTE (%) LCW	AS-DT DTE (%) FCW	P-value	PP-DT DTE (%) LCW	PP-DT DTE (%) FCW	P-value
Treadmill assessment	**(n = 25)**	**(n = 23)**		**(n = 25)**	**(n = 23)**	
Cadence (steps/min)	+1.80 ± 5.74	+2.57 ± 8.69	*0.718*	+0.00 ± 10.24	+2.78 ± 8.93	0.323
Stride time ratio						
High/low	+0.08 ± 4.12	+1.17 ± 5.42	*0.435*	-0.96 ± 3.37	+0.52 ± 5.25	0.247
Step Frequency (Hz)	+4.72 ± 15.41	+5.78 ± 19.48	*0.834*	-2.04 ± 17.60	-2.00 ± 17.74	0.994
Step time (sec)	-2.54 ± 0.78	-3.22 ± 5.83	*0.338*	-4.80 ± 20.17	-0.30 ± 6.44	0.312
Step time variability (s)	+13.64 ± 49.23	+14.48 ± 46.17	0.952	+10.80 ± 76.09	+6.65 ± 43.55	0.820

AS-DT; auditory Stroop task during walking, PP-DT; picture planning task during walking, DTE; dual task effect. P-value represents result of independent sample t-test to test difference between values for LCW and FCW, α = 0.05.

8.1.3 Appendix 2.C Dual task effect on cognitive performance during treadmill walking

Table 2.C1 Cognitive task scores (mean ± stdev) during treadmill walking with and without additional tasks and the effect of dual task

Cognitive measure	Single Task	Dual Task	DTE (%)	P-value
Auditory Stroop	**(n = 47)**	**(n = 47)**		
% correct	91.45 ± 12.59	92.79 ± 10.93	+ 1.98 ± 6.95	*0.067*
Reaction Time (ms)	1402 ± 215	1404 ± 270	+ 0.09 ± 8.88	*0.916*
Composite score	0.67 ± 0.15	0.68 ± 0.16	+ 2.87 ± 10.84	*0.074*
Picture Planning	**(n = 46)**	**(n = 46)**		
% correct	90.87 ± 10.76	81.07 ± 0.13	- 10.17 ± 14.13	***< 0.001***
Reaction Time (ms)	1980 ± 420	1985 ± 401	+ 0.91 ± 11.75	*0.905*
Composite score	0.48 ± 0.12	± 0.12	- 9.80 ± 19.52	***< 0.001***

DTE; dual task effect. P-value represents result of paired sample t-test to test difference between single - and dual task condition, α = 0.05.

Table 2.C2 Cognitive scoring during single and dual task per type of community walker

Measure	LCW	FCW	P-value
Auditory Stroop	**(n = 25)**	**(n = 22)**	
Score (%)	90.80 ± 12.57	92.18 ± 12.87	*0.712*
Reaction time (ms)	1371 ± 210	1438 ± 221	*0.290*
Composite score	0.68 ± 0.17	0.65 ± 0.14	*0.518*
Audio Stroop DT			
Score (%)	92.68 ± 11.26	92.91 ± 10.80	*0.944*
Reaction time (ms)	1393 ± 318	1417 ± 209	*0.765*
Composite score	0.70 ± 0.18	0.67 ± 0.13	*0.537*
Picture planning	**(n = 24)**	**(n = 22)**	
Score (%)	86.29 ± 12.82	95.86 ± 4.21	***0.002***
Reaction time (ms)	2104 ± 476	1846 ± 307	***0.034***
Composite score	0.43 ± 0.12	0.53 ± 0.09	***0.002***
Picture planning DT			
Score (%)	78.88 ± 13.85	83.45 ± 10.96	*0.223*
Reaction time (ms)	2042 ± 408	1924 ± 394	*0.325*
Composite score	0.40 ± 0.11	0.45 ± 0.13	*0.119*

LCW; limited community walkers, FCW; moderate-to-full community walker, ST; single task, DT; dual task. P-value represents result of independent sample t-test to test difference between values for LCW and FCW, α = 0.05.

Table 2.C3 Dual task effect on cognitive performance per type of community walker

Cognitive measure	LCW DTE (%)	FCW DTE (%)	P-value
Auditory Stroop	**(n = 25)**	**(n = 22)**	
% correct	+2.56 ± 7.82	+1.32 ± 5.92	*0.547*
Reaction Time (ms)	+1.20 ± 11.33	-1.18 ± 4.79	*0.365*
Composite score	+2.48 ± 12.54	+3.32 ± 8.79	*0.795*
Picture Planning	**(n = 24)**	**(n = 22)**	
% correct	-7.67 ± 16.28	-12.91 ± 11.08	*0.212*
Reaction Time (ms)	-1.83 ± 12.90	+3.91 ± 9.76	*0.098*
Composite score	-4.58 ± 21.68	-15.50 ± 15.38	*0.057*

LCW; limited community walkers, FCW; moderate-to-full community walker, DTE; dual task effect. P-value represents result of independent sample t-test to test difference between values for LCW and FCW, α = 0.05.

8.2 **Appendices Chapter 3**

8.2.1 **Appendix 3.A Modified University of Alabama study of Aging Life-Space Assessment for walking in the community**

Life-space level			**Frequency**				**Independence**	**SCORE**
During the past four weeks have you been **WALKING** in.....			**How often did you get there?**				**Did you use aids, equipment or help from another person?**	Level X Frequency X Independence
Live-Space Level 2 *An area outside your house, such as your porch, deck or patio, hallway or garage, in your own yard or driveway?*	Yes 2	No 0	Less than 1/ week 1	1-3 times /week 2	4-6 times /week 3	Daily 4	1 = Personal Assistance 1.5 = Equipment only 2 = independent	***16*** Level 1 score
Score	_***2***_ x		_***4***_ x				__***2***__ =	
Live-Space Level 3 *Places in your neighbourhood, other than your own yard or apartment building?*	Yes 3	No 0	Less than 1/ week 1	1-3 times /week 2	4-6 times /week 3	Daily 4	1 = Personal Assistance 1.5 = Equipment only 2 = independent	***18*** Level 2 score
Score	_***3***_ x		_***3***_ x				__***2***__ =	
Live-Space Level 4 *Places outside your neighbourhood, but within your town?*	Yes 4	No 0	Less than 1/ week 1	1-3 times /week 2	4-6 times /week 3	Daily 4	1 = Personal Assistance 1.5 = Equipment only 2 = independent	***12*** Level 3 score
Score	_***4***_ x		_***2***_ x				___***1.5***___ =	
Live-Space Level 5 *Places outside your town?*	Yes 5	No 0	Less than 1/ week 1	1-3 times /week 2	4-6 times /week 3	Daily 4	1 = Personal Assistance 1.5 = Equipment only 2 = independent	***7.5*** Level 4 score
Score	_***5***_ x		_***1***_ x				___***1.5***___ =	
							TOTAL SCORE	***53.5*** Sum of Levels

8.2.2 Appendix 3.B Scatterplot for community walking at follow-up

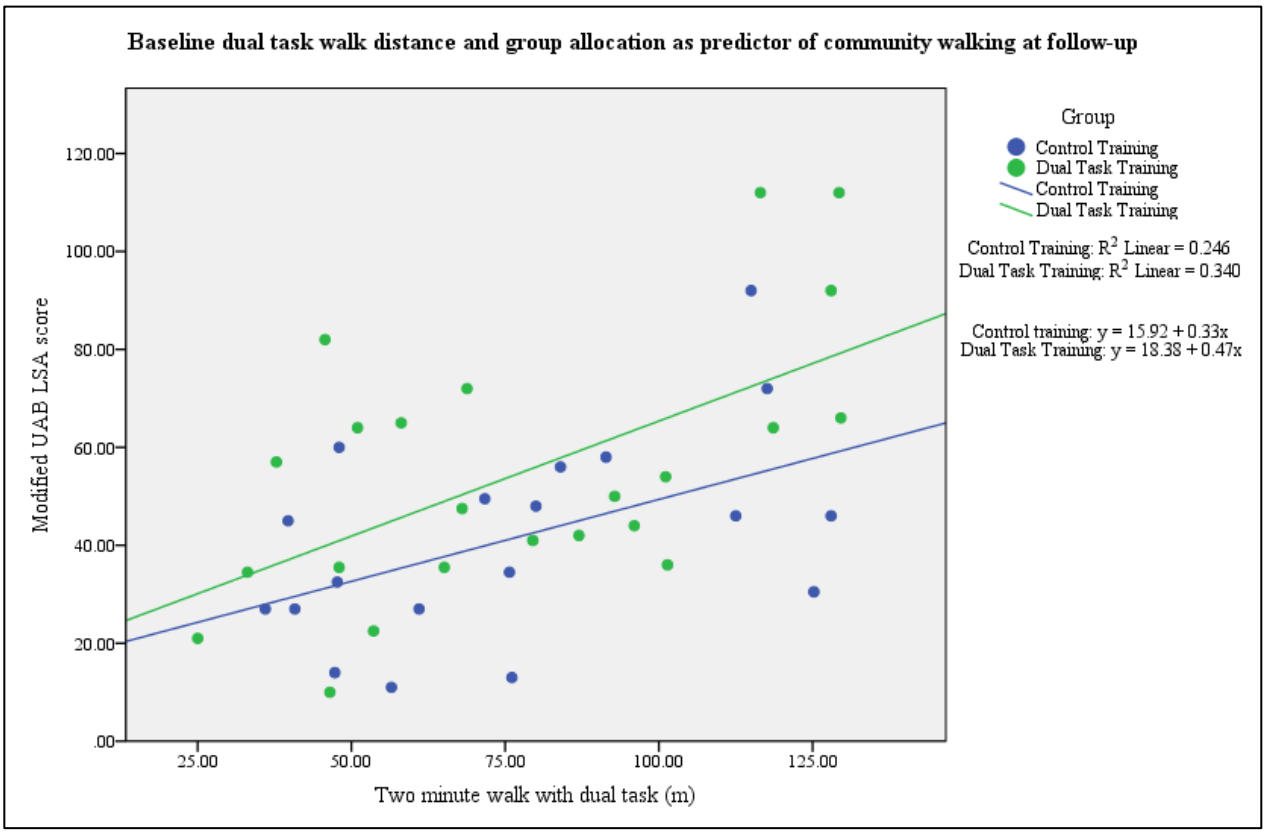


Figure 3.B1 Scatterplot of baseline two-minute-walk with dual task distance and UAB Life Space Assessment at follow-up, with separated slopes for scores of CT and DT group.

8.2.3 **Appendix 3.C Description of in-training progression and feasibility of training methods of the trial presented in Chapter 3**

This appendix contains a paper which was written up with help of one of the professional trainers who was involved in providing the training to the stroke survivors who took part in the trial described in Chapter 3. This person was not involved in the design of the trial and content of the training, but purely delivered the training as given by the protocol. In addition he analysed and wrote up a report of the data that was collected during the dual task and control training and described feasibility of the training methods. The data that was used for this report differs from the data that has been reported in Chapter 3 as it was collected during the training sessions and not during the assessments.

Description of training progression during a cognitive dual-task and single-task treadmill walking intervention for chronic stroke patients: secondary analysis from a randomised controlled trial.

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Abstract

Objective

To describe a cognitive dual-task and single-task treadmill training intervention for chronic stroke patients, including description and comparison of training progression.

Design

Secondary analyses of intervention training data from both a dual-task and a control group in a randomized controlled trial.

Subjects

Fifty stroke patients, at least six months from a stroke with a clear gait impairment resulting in a reduced two-minute-walk distance.

Intervention

Ten weeks of bi-weekly aerobic treadmill training for up to 45 minutes. The control group walked undistracted and the dual-task group walked whilst performing cognitive tasks.

Setting

Community exercise rehabilitation facilities

Main Measures

Treadmill speed (km/h), training duration (min) and relative heart rate (%). Performance on the cognitive tasks (rating) in the dual-task group.

Results

Forty-three participants (86%) were included in the analyses with a mean (SD) age of 62 ± 14. There were no differences between the control group (n = 21) and the dual-task group (n = 22) for mean (SD) change in treadmill speed (+0.8 ± 0.6km/h vs. +1.0 ± 0.7km/h, P = 0.23), mean (SD) change in training duration (+13 ± 11min vs. + 12 ± 8min, P = 0.69) or mean (SD) relative heart rate (61 ± 1% vs. 62 ± 1%, P = 0.97).

Conclusion

The dual-task treadmill training protocol is safe and well tolerated. Both groups increased their training doses, with no difference between groups. Some cognitive tasks used in the dual task training showed potential, but scoring needs modification for effective analysis in future studies.

Keywords

Stroke, gait, walking, dual task, cmi, cognitive motor interference, treadmill, exercise, aerobic exercise

Introduction

Community walking levels and cardiovascular fitness remain low in stroke patients compared with healthy sedentary people (Davenport, Dennis et al. 1996, Michael, Allen et al. 2005). Treadmill training is an attractive intervention which can improve functional mobility and walking (Harris-Love, Forrester et al. 2001, Andrews, Chinworth et al. 2010) and increase cardiovascular fitness (Macko, Ivey et al. 2005, Polese, Ada et al. 2013). Walking in the community presents a unique set of challenges after a stroke because attentional demands need to be divided between control over walking and external distractions such as other people, obstacles, changes in surfaces and traffic. These normal demands are accentuated in stroke patients, because walking requires more attention (Smulders, van Swigchem et al. 2012, Al-yahya 2015) and cognitive performance may be adversely affected (Andrews, Halford et al. 2013, Andrews, Halford et al. 2014).

Dual task training during walking has been studied (An, Kim et al. 2014, Kim, Han et al. 2014, Choi, Kim et al. 2015, Choi, Lee et al. 2015, Song and Park 2015) with approaches mainly exploring the simultaneous performance of motor (Choi, Lee et al. 2015) or cognitive tasks (An, Kim et al. 2014, Plummer, Villalobos et al. 2014, Choi, Kim et al. 2015). Whilst the findings are promising for improving gait and balance function for stroke in the short term (Wang, Pi et al. 2015), there is limited evidence that supports long-term benefits. Different cognitive tasks have been found to have varying effects on gait speed (Plummer, Villalobos et al. 2014), indicating that some may be more effective than others for improving walking. However, there is a lack of description of training protocols and their progression which limits replicability and the development of newer, more effective protocols. This paper describes how chronic stroke patients performed in a randomised trial which compared undistracted treadmill walking with treadmill walking whilst

performing cognitive tasks. The Template for Intervention Description and Replication (TIDier) guidelines (Hoffmann, Glasziou et al. 2014) has been used.

Method

The data presented is a secondary analysis from a randomised controlled trial (Trial registrations: ISRCTN 50586966, MREC N° 12/SC/0403, UKCRN ID 13923), approved by the local NHS Research Ethics Committee (REC reference: 12/SC/0403). It only reports training data; the study protocol and results are available through the above trial references. All participants gave their informed consent to participate in the study according with recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Patients

Fifty stroke patients were recruited from hospitals, GP practices, stroke clubs and via advertisement in local newsletters and magazines. To be included in the study, they had to be at least 6 months post haemorrhagic or ischemic stroke, have a clear walking deficiency that manifested as a reduced two-minute-walk distance, be able to walk safely on a treadmill and provide informed consent. Participants were excluded from the study if they had concurrent other neurological conditions, a mental state that precluded safe participation as stated by a GP, psychological disorders and aphasia that severely limited communication and being able to respond to dual tasks, or any other contra-indications to safe participation in an exercise intervention.

Before beginning the training protocol, participants were assessed at an exercise rehabilitation facility where they were given an explanation of the testing protocol and received an informed consent form. After giving consent, participants were

asked to complete a series of questionnaires, supported by the researcher. Information about the stroke (type, location and date of stroke), current medications and medical history were recorded.

Formal measures included:

- Cognitive ability, measured using the Montreal Cognitive Assessment (MOCA) (Nasreddine, Phillips et al. 2005).
- Independence in daily activities assessed using the Barthel Index (Collin, Wade et al. 1988).
- Health and wellbeing were measured using Short-Form-36 (SF-36) (Ware and Sherbourne 1992).
- Before the physical performance assessments, a Physical Activity Readiness Questionnaire (Shephard 1988) was completed to assess ability to safely perform exercise.
- Two two-minute-walk tests along a 16m long track set out on a corridor, marked by cones at each end. They were instructed to walk along the track at a self-selected walking speed until the researcher informed them to stop and the distance was recorded. The order of these two tests was randomized between patients.
    - One test was performed as a normal two-minute-walk test where the participant walked on their own.

During the other test the researcher distracted the participant with verbal questions. The questions focused on planning normal daily activities in the subject's lives e.g. *"Can you tell me how your day started today?"*

After completing the assessment, participants were randomized into a control or intervention group by a blinded assessor using a minimization technique. Both

groups performed 10 weeks of bi-weekly treadmill walking sessions administered one-to-one by an exercise professional/physiotherapist for 20 aerobic training treadmill sessions in a community gym facility. The principles of aerobic training, using a treadmill, for people with neurological conditions were adhered to (ACSM 2009).

Treadmill training

Before and after the treadmill training, participants had their blood-pressure measured using an electronic blood pressure monitor (Carescape V100) to ensure that it was within safe limits to exercise (systolic ≤ 170, diastolic ≤100). Participants wore a heart rate monitor (Polar TI31 chest strap) during exercise and heart rate was recorded every 5 minutes. Training sessions lasted a maximum of 45 minutes, of which there were 5 minutes to warm-up at the start and 5 minutes to cool down at the end using slower, comfortable walking speeds. Training sessions were of shorter duration if the subject or exercise professional determined that they could not safely complete 45 minutes of training on that day. The treadmill speed was self-selected and was increased when the subject felt comfortable doing so. Increasing training duration was prioritized, until the subject was performing the maximum duration and then speed increases were prioritized to ensure heart rate (intensity) was maintained within an aerobic zone (55%-85% age predicted maximum i.e. 220-age). Short rest periods of approximately one to two minutes were allowed if they were requested by participants and it was determined that it allowed a participant to exercise for significantly longer than they otherwise would be able to. As they progressed, they would attempt to walk for longer duration between rest periods. The rest could be seated or standing.

The treadmill was inclined when participants walked fast enough that they could not progress further without running. When two training sessions could not be

completed in a week due to illness or other reasons, another session was scheduled. In some cases, this meant that they protocol took up to 12 weeks to complete the full 20 sessions, although for logistical reasons this meant that some participants performed less than 20 sessions. Treadmill speed and incline were recorded every five minutes during the session and training duration would be recorded as the total time spent walking on the treadmill, excluding rest periods. Participants in the control group were minimally distracted during their training, with the main communication being to check their well-being and suitability of training speed. Those administering the exercise conferred before training and observed each other administering the treatment during a session to ensure uniformity in treatment. For participants taking the beta blockers bisoprol or timolol, heart rate was adjusted up by 15% and 10% respectively to correct for the medication's effect on heart rate.

Cognitive tasks

Participants in the dual-task group performed cognitive tasks whilst treadmill walking after they completed their warm-up. Each session had a variable set of tasks which included two blocks of 5 minutes of planning tasks, 10 minutes of radio tasks and a combination of the clock face task, counting task, audio Stroop task (McClain 1983), a word task, an alternative uses task or a creativity task each performed twice (Table 1. and Table 2). Cognitive task performance was recorded in all sessions. Cognitive task performance was analysed at session 1, 18 and 20, as these days contained the same set of tasks (planning, radio, counting backwards and clock task). The word task, alternative uses task and creativity task were excluded from cognitive performance analyses as these tasks had a scoring system which did not provide sufficient quantification of task performance to determine progression over the training period. Moreover the latter tasks were unintentionally not sufficiently standardized across sessions.

Table 1. Cognitive task description and scoring method

Task	Objective	Scoring
Planning	A random assortment of daily tasks of varying complexity to plan e.g. how would you make a cup of tea	0 = no attempt 1 = performed poorly 2 = minor problems 3 = little or no problems
Radio	A radio fragment is played through speakers followed by a conversation with the subject about the fragment to distract them	0 = no attempt 1 = performed poorly 2 = minor problems 3 = little or no problems
Clock face	A time is given verbally to the subject and they must state whether the corresponding hands on a clock are on the left, right or both sides of the clock.	0 – 9 for no. of correct answers
Counting backwards	Participants are asked to count backwards from a number between 290 and 300 in steps of either 3, 4 or 7	0 -4 for no. of series of numbers with no mistakes
Audio Stroop	A randomized series of the word “High” and “Low” are played through speakers at a high or low pitch. The subject must state the pitch of the word that was just said	0 = no attempt 1 = some correct 2 = about half correct 3 = mostly correct
Word	A letter of the alphabet is given and the subject must name as many words as they can	No. of words in 1 minute
Alternative uses	The name of an object is given and the subject must list as many possible uses for that object as they can	No. of uses in 1 minute
Creativity	Participants must name as many objects as they can which has a certain attribute e.g. objects that can be described as being tall	No. of objects in 1 minute

Table 2. Cognitive tasks performed each session with cumulative frequency

Session No.	Clock	Counting	Planning	Radio	High/Low	Naming Words	Alternative Uses	Creativity
1	X	X	X	X				
2			X	X	X	X		
3		X	X	X			X	
4	X		X	X				X
5			X	X	X		X	
6		X	X	X	X			X
7	X		X	X				
8	X		X	X		X		
9		X	X	X	X			
10		X	X	X			X	
11	X		X	X	X			
12	X		X	X				X
13			X	X	X	X		
14	X	X	X	X				
15		X	X	X	X			
16	X		X	X			X	
17	X		X	X	X			
18	X	X	X	X				
19		X	X	X	X			
20	X	X	X	X				
Frequency	11	10	20	20	9	3	4	3

***X = task performed**

Analysis

Feasibility of adhering to the prescribed treadmill training program and cognitive program was assessed through the dropout rate, reasons for dropouts, compliance (no. of sessions completed), the differences in training parameters between groups and amount and quality of cognitive tests performed. Any tailoring and modification of the intervention is described. How well the planned intervention was carried out was recorded by the trainers using a training diary. Checks of fidelity to training were carried out by researchers not blinded to group allocation by regular site visits for observation and discussions with the trainers regarding

training and its progression. End values of training parameters were obtained by taking the highest value from the participant's final 3 training sessions. The age predicted maximum heart rate was calculated using the formula (220 – age) and was used to calculate the relative heart rate. Statistical tests were performed in Microsoft Excel 2010 and SPSS v19. Means were compared using paired and independent Student T-tests as applicable and correlations were analysed using Pearson Correlation. Cognitive task scores were compared using Wilcoxon Signed Rank tests.

Results

Of the 50 participants who went through the initial assessment, 43 (86%) were included in the final analysis (Figure 1). Stroke onset ranged from 6 months to 17 years and 8 months with a mean (SD) of 43 ± 52 months. Baseline measures for included participants are displayed in Table 3. There were 21 participants left in the control group and 22 in the dual-task group for the analysis. Of the analysed participants, the mean (SD) number of sessions completed was 19 ± 2 sessions and 36 out of 43 participants (84%) completed the full 20 sessions. One participant in the control group completed training for the full 10 weeks, but had the frequency of training reduced to one session per week half way through, giving only 13 sessions. This was done to help manage fatigue. The decision was made for this participant's data to be included, because they had trained for the full 10 weeks and the protocol had otherwise been successfully followed. Table 3 shows the baseline measures for the included participants. The mean (SD) two-minute-walk-distance of 88 ± 37m was substantially lower compared to normative values for similar age groups (Bohannon, Wang et al. 2015). The mean (SD) undistracted two-minute-walk distance of 89 ± 37m was higher than the mean (SD) two-minute-walk-distracted distance of 78 ± 32m ($P < 0.01$).

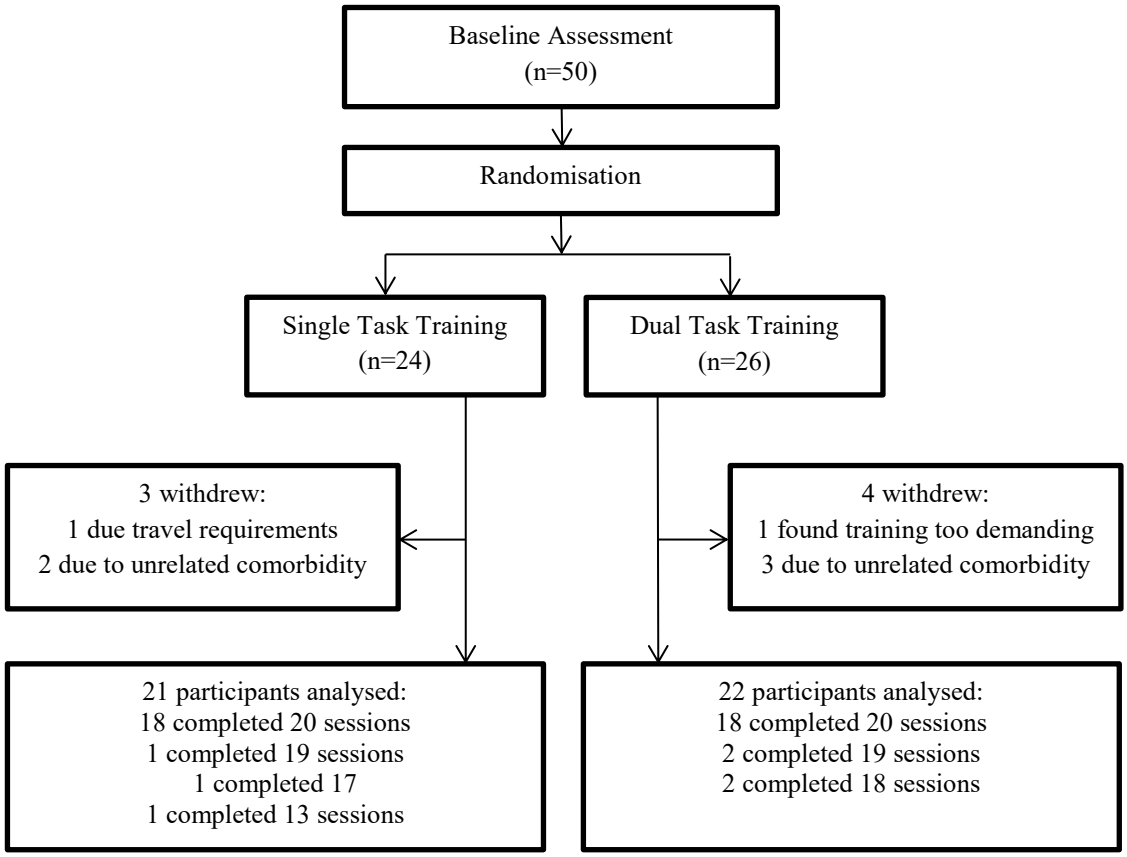

Figure 1. Participant flow post-recruitment

Table 3. Baseline measures for participants included in the analysis (n = 43)

	Mean ± SD	**Range**
Age (years)	62 ± 14	18 - 84
Barthel Index	19 ± 2	12 - 20
MOCA	25 ± 4	10 - 30
SF36 Total Score	59 ± 18	16 - 87
SF36 Mental Health Score	63 ± 20	21 - 93
SF36 Physical Health Score	53 ± 17	15 - 85
Two-minute-walk (m)	89 ± 37	28 - 162
Two-minute-walk-distracted (m)	78 ± 32	25 - 130

Effects of cognitive dual tasks on training treadmill performance

Across both groups, seven participants were walking at the maximum duration of 45min at the start of training, meaning that most participants had the possibility to increase both their time and their speed during training. Forty-two out of 43 improved their walking speed from their session one speed to their end speed. Means of these measures improved with training along with their product – distance, indicating that both endurance and gait speed were able to be improved. The mean relative heart rate for both groups were within the target range of 55-85% with a mean (SD) relative heart rate of 61 ± 1% for the control group and 62 ± 1% for the dual-task group (P = 0.97) (Table 4.). There were no differences in training parameters between the control group and the dual-task group with respect to starting values, end values and change in values (P > 0.05).

Table 4. Training parameters for the control group vs. dual-task group

	Control (n = 21) (Mean ± SD)	**Dual-Task (n = 23) (Mean ± SD)**	**P Value**
Mean speed - week 1 (km/h)	2.2 ± 1.6	2.5 ± 1.3	0.52
End speed (km/h)	2.9 ± 1.5	3.4 ± 1.6	0.32
Change in speed (km/h)	+0.8 ± 0.6	+1.0 ± 0.7	0.23
Mean training duration – week 1 (min)	29 ± 11	31 ± 9	0.46
End training duration (min)	41 ± 7	42 ± 6	0.68
Change in training duration (min)	+13 ± 11	+12 ± 8	0.69
Mean distance walked - week 1 (km)	1.2 ± 1.2	1.3 ± 0.9	0.77
End distance walked (km)	2.1 ± 1.2	2.3 ± 1.2	0.54
Change in distance walked (km)	+0.9 ± 0.6	+1.0 ± 0.6	0.62
Mean relative heart rate – week 1 (%)	60 ± 10	61 ± 10	0.76
End relative heart rate (%)	66 ± 9	62 ± 13	0.34
Change in relative heart rate (%)	+7 ± 8	+4 ± 10	0.18

Cognitive task performance in the dual-task group

Missing data for session 20 meant that session 18 was used as the end point for the analysis. Subjects improved their cognitive task score during training, with a mean (SD) aggregate score of 92 ± 8% at session 18, which was higher than the session 1 mean (SD) of 80 ± 17% (n = 15, P = 0.02). MOCA scores correlated positively with several session 1 task scores including the radio task score (n = 20, R = 0.61, P < 0.01), the planning task score (n = 22, R = 0.64, P < 0.01) and the clock task score (n = 22, R = 60, P < 0.01). MOCA scores correlated positively with the session 18 clock task score (n = 19, R = 0.53, P = 0.20) and radio task score (n = 18, R = 0.75, P < 0.01). No baseline measure or training parameter correlated with changes in cognitive task performance (P > 0.05).

The mean (SD) session 18 clock task score of 94 ± 17% was higher than the session one mean of 82 ± 23% (P = 0.03). The mean session 18 radio task score of 98 ± 8% was higher than the session one mean of 88 ± 21% (P = 0.02). The mean (SD) session 18 counting task score of 69 ± 30% was not different to the session one mean (SD) of 61 ± 40% (P = 0.26). There was no variation in the planning score at session 18 with every subject scoring 100% compared to the session 1 mean (SD) of 93 ± 14%.

Clinical experience accumulated

We found that asking the participants how fatigued they felt after each training session was useful for determining their ability to progress to a higher speed. Some participants experience abnormal levels of fatigue after exercise, which can interfere with their functional ability during their daily routine. To maintain high levels of compliance, accumulating fatigue across sessions should be avoided and participants should ideally have at least one day rest between sessions. For one participant, we halved the training frequency to one day a week at around half-way

through the training program to give this person more time to recover between sessions. It can be helpful to find out what other forms of physical activity participants perform during the week and this should be taken into account when trying to space out exercise. Some participants could perform the treadmill training on the same day as their normal exercise routine with no negative effects, illustrating the wide range of ability to recover from exercise.

Another strategy used to combat fatigue, was to take breaks during exercise. These breaks would last a minute or two and the time spent exercising between rests would vary between around five and thirty minutes depending on the individual's capabilities. To rest, the treadmill would be stopped and if necessary a chair would be place on the treadmill to allow the participant to sit and unload their leg muscles. This strategy was very effective in increasing the total dose of exercise for participants who would otherwise have to cease exercising after a short duration. Walking with hemiparesis can cause extra strain on particular muscles and localized fatigue in a specific area of muscle was a common reason for needing rest. This was not limited to lower limb muscles, as upper limb muscles would also fatigue from use of the handrails. For a couple of participants, rest periods were required more due cardiovascular fitness factors and in these cases the bouts of exercise were generally longer between rests. One of the participants with more severe gait impairment increased their training duration from 8½ at session one to 22½ minutes at session thirteen, despite exercising for only 2½ minute between rests. Unfortunately, the participant dropped out due to unrelated comorbidity, but nevertheless showed how training dose can be increased through the use of rest periods.

We found that participants reacted differently to being asked to perform cognitive tasks. Some participants treated it like an exam and appeared to be very focused on getting as many correct answers as possible, whilst others were more relaxed and treated it as normal conversation. This was particularly the case on the counting

backwards tasks, as there was a higher variation in mathematical ability and this could cause some anxiety. It was helpful to talk through the tasks that would be performed that day before beginning the training. This allowed them to memorize the instructions without the distraction of walking and reduced the anxiety from not knowing what tasks they would be performing that session. After several sessions, the participants were generally more relaxed about answering questions and became more fluid in their responses.

The systolic blood pressure readings were over the 170mmHg limit on a several occasions, which meant that exercise could not be performed. However, we found that the readings would often reduce to within a safe range within a couple of minutes of sitting and remained safe if retested in the middle of exercise. For some this appeared to be related to the method of travel they had used to get to the facility and the level of stress that this incurred. Participants generally preferred using local volunteer car services instead of taxis, as they would often be driven by the same volunteer drivers throughout the entire protocol. The volunteer drivers would get to know the participants and their particular needs, including any assistance they needed getting in and out of the car and where was best to park to minimize the challenge of getting into the facility. From a study feasibility perspective, another benefit of volunteer car services over taxi services was the considerably lower costs allowing for inclusion of patients who lived further from the community gym facilities and who could not arrange for their own transport.

Discussion

The 10 week exercise protocol was a feasible and safe method to improve walking performance. There were no adverse health outcomes as a result of the training and adherence could be considered to be high. Apart for the one participant who had their frequency deliberately reduced, those who were included in the analyses

without completing 20 sessions, completed fewer sessions due to logistical reasons. Whilst five participants dropped out due to unrelated comorbidity, this was to be expected given the age of the participants and the effects of having a stroke combined with the relatively long period in which they took part in the study. There was a large range in two-minute-walk distances, showing high variation in the level of gait impairment and/or fitness of the participants.

The increase in mean relative heart rate during training shows that the participants were working harder towards the end of the 10 week protocol. This could mean that the participants improved their tolerance to fatigue or that they were not training at their full capacity at the start of training. The latter seems to be a likely factor, given that many of the participants were not performing regular exercise and had not participated in an exercise program prior to the study. Those who did not participate in exercise prior to the study would have had lower levels of fitness, but perhaps also less confidence in their ability to perform exercise. Time of cessation of exercise and treadmill speed was determined largely by the subject, their sense of fatigue and willingness to continue training. Therefore, psychological factors and not just physiological factors may have influenced who improved the most. Use of incline with some participants was necessary for progression, but adds an additional layer of complexity to the analysis as different participants began using the incline at different speeds.

Despite an observed deficit between the two-minute-walk and two-minute-walk-distracted distances measured at baseline, neither training group appeared to train at a greater intensity than the other. The differences between these results may be due to differences between overground and treadmill walking. For example, most of the subjects elected to use the handrails on the treadmill, with some using the front handrails and some using the side handrails. Kang et al (Kang, Lee et al. 2015) found that the use of both the front and side handrails produced changes in the gait of stroke patients compared to the use of no handrails, although they

suggest that this is of benefit to gait training. Increased stability and decreased demands on attention from the lack of obstacles and level, consistent walking surface would leave more attention for the cognitive tasks during treadmill training. The cognitive tasks served their purpose as a form of distraction with dual-task participants having a high level of engagement with the tasks. Participants significantly improved on some of the cognitive tasks alongside improvements in gait speed that were similar to those improvements seen in the control group. However, the cognitive task scoring methods made it difficult to differentiate between scores on the planning and radio tasks. This was particularly evident on the planning tasks, where at session 18 all participants scored maximally. Furthermore, the dose of cognitive task training varies between participants due to the differences in training duration and this means that with the current design participants with lower training duration will practice certain tasks more than others. This makes comparison between participants problematic. On the counting task in our study, it was apparent that some participants were much more adept with number tasks than others and this made it difficult to devise a scoring system that reflected the full spectrum of performance due to the issue of errors carried forwards when counting sequentially.

Using the same tasks across all participants can be difficult due to the variation in cognitive abilities between participants. Plummer et al (Plummer, Villalobos et al. 2014) attempted to overcome the problem of variation in cognitive abilities between subjects by utilizing several levels of difficulty within each task. However, in their gait activities they allowed for variable gait speed according to the difficulty of each tasks. Hegeman et al. (2012) noted that task prioritization during obstacle avoidance dual tasking may be dependent on the instructions given and the implied importance of one task over the other. In our study, gait speed was more likely to be prioritized as the treadmill speed is likely to remain fixed after the warm-up before the cognitive tasks begin. This will decrease the likelihood that

speed will vary between tasks, although variation in other gait parameters such as cadence was not recorded during training. MOCA scores were some indication of initial cognitive task performance and this may be useful in selecting the appropriate difficulty for tasks in future research.

Conclusion

In conclusion, the 10 week treadmill training protocol was well tolerated with a low dropout rate and high compliance. There were improvements in treadmill walking performance in both groups and there were no detectable differences in training performance between groups. Therefore any differences in outcome measures using this protocol cannot be attributed to differences in training intensity in this study. Modification of the cognitive tasks used would be necessary to effectively analyse cognitive performance in a future study. This could give more insight into the importance of individual cognitive tasks.

Clinical messages

- Performing cognitive dual task treadmill training does not hinder training progression compared to single task training in those with chronic stroke.
- Future cognitive dual task research should consider the choice of cognitive tasks and the ability to assess performance on the specific tasks.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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