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Does walking speed predict change in cognitive function late after head injury?

AND

Clinical Research Portfolio

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Submitted in partial fulfilment of the requirements for the degree of Doctorate in Clinical Psychology

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Chapter 1. Systematic literature review

Walking speed and cognition following acquired brain injury:

A PRISMA review

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Abstract

Background

Severe head injury (HI) has been shown to be a trigger for neurodegeneration (Gupta, 2016) while research into predictors of cognitive decline has found walking speed to be a useful predictor of changes in cognition over time. It is therefore important to explore what we know about whether walking speed could predict cognitive decline in this 'at risk' group after a head injury. Little research has been reported on HI and this review is broadened to include any acquired brain injury (ABI).

Research Question

Can walking speed screen for cognitive function in people who have experienced an ABI?

Methods

A systematic search of the literature was conducted to identify available literature which explored an association between cognition and walking speed in those who had experienced an ABI.

Results

The search identifies five articles that meet inclusion criteria; four include participants with a stroke, and one, participants with head injury (HI). The papers are evaluated for quality and a narrative synthesis is used to combine and interpret the results. There is not enough evidence to reach conclusions about people who have experienced a HI, however some evidence suggests that walking speed could be a useful predictor of cognition over time following a stroke. The importance of considering time post stroke and the use of walking speed as part of a dual task are discussed.

Significance

Walking speed offers the potential of a quick, easy and naturalistic method of detecting risk for cognitive change, hence exploring the potential role of walking speed in predicting this risk may have important clinical and research implications.

Keywords: walking speed; dual task; ABI.

Introduction

Head injury and cognitive decline

It has been argued that severe head injury (HI) is a major global health and socioeconomic problem which can act as a trigger for neurodegeneration and cognitive impairment (Gupta, 2016). Dunning et al (2016) conducted a meta-analysis of 21 studies, in HI survivors. When compared to controls, those with a HI had significant deficits in memory and visuospatial skills. Fann et al (2018) conducted a nationwide population based observational cohort study in Denmark using national data on 2,794,852 people. They found that head injury was associated with an increased risk of dementia when compared to those without HI and this enhanced risk can cause ongoing concern to the individual and their loved ones.

There is currently a great deal of interest around the neuropathology of HI and cognitive decline. Iverson et al (2015) completed a review of chronic traumatic encephalopathy (CTE) which is considered a type of dementia associated with repeated head injuries and repeated episodes of concussion. They reported that it was still unclear whether it is HI that leads to cognitive decline, where the neurotrauma itself causes cognitive impairment, or whether the HI is instead associated with reductions in cognitive reserve which make the person then vulnerable to an earlier expression of a degenerative disorder. This leads to controversy around whether CTE is a separate disease process or a contributor to a known disease process. Alternative theories also suggest that there may be an independent third factor of importance; a risk factor which increases a person's chance of having both a HI and cognitive decline. McMillan et al (2014) found that poorer health prior to injury was associated with mortality late after mild HI and so there may be health related factors which make people more vulnerable to both HI and cognitive decline. Gupta argues that there is a need to understand this process more fully with improved accuracy of clinical diagnostic criteria for HI induced diseases.

Gait and cognitive decline

Research into predictors of cognitive decline has explored the importance of gait, in particular walking speed. Miekle et al (2012) conducted a large population-based study (n=1478) on walking speed as a predictor of cognitive decline. They found that faster walking speed was associated with better performance in memory, executive function and

global cognition when followed for 20 years. This is in line with findings from other studies showing an association between walking and cognition (Callisaya et al, 2015 & Verghese et al, 2007).

Buracchio et al, (2010) explored the trajectory of gait speed preceding mild cognitive impairment (MCI) and found that gait speed slowed up to 12 years before MCI. They argue that motor function may be useful in early detection of dementia when the benefits of intervention would be greatest.

Research has tried to explore why walking speed might predict cognitive decline. Some theories suggest that the changes to the brain which lead to cognitive decline affect walking speed early in the process. Magnetic resonance imaging scans have been found to show periventricular white-matter sensitivities which are associated with slower of walking speed (Camiciolio et al, 1999). Walking speed therefore could be an indicator of a neural problem associated with future cognitive decline. Montero-Odasso & Hachinski (2014) argue that brain cortical control of both gait performance and cognitive function such as executive function share the same brain networks. They argue that these brain networks are highly susceptible to microvascular damage, thus affecting both cognition and gait. While Hausdorff (2005) argues that the processes involved in walking are automatic, requiring little cognitive input. They argue that when this automaticity is impaired, for example if someone has a degenerative disease, then walking is impaired. Alternative theories suggest the potential importance of a common shared factor affecting both walking speed and cognitive decline. Alfaro-Acha et al (2007) describe one potential third factor as muscle strength. Muscle strength has been shown to be highly correlated with walking speed in disabled older women (Rantanen et al, 1998), as well as blood markers which have been shown to contribute to cognitive decline in Alzheimer's Disease (Hogervorst et al, 2004).

Measuring walking speed

In addition to looking at walking speed alone, some studies also investigate walking speed as part of a dual task procedure. A dual task (DT) procedure requires an individual to perform two tasks simultaneously, and can be compared to performance in single task (ST) conditions (McCulloch, 2007), allowing by subtraction, a response cost to be calculated. An example would be asking someone to walk (ST), then count backwards from 100 in 3s (ST) then do them both at the same time (DT). Reduced performance in the DT condition is described as dual task cost (calculated as DT-ST/ST). Dual task cost may represent

impaired capacity to share cognitive resources between walking and an attention demanding task. Measures of dual task were developed following clinical observation that some frail elderly patients would stop walking when they were talking, and this was associated with falls risk (Lundin-Olsson et al, 1997). A recent review demonstrated the ecological validity of dual task measures (McFadyen et al, 2017), while others have argued that short walking tests alone are redundant (Dobkin et al, 2006).

Gait and head injury

Biomechanical deficits are common following HI (van Donkelaar et al, 2006). Williams et al (2009) aimed to identify the most common gait abnormalities in this group. They recruited 41 ambulant participants who were receiving therapy for gait abnormalities following HI. They found that the most common abnormalities were related to trunk and pelvic movements. They also compared the sample to healthy controls and found that those with HI walked significantly slower than the controls, due to a reduced rhythm and a shorter step length. The higher prevalence of walking difficulties in this population leads to an interesting theoretical question around whether this impacts the potential usefulness of walking speed as a predictor of cognitive decline in this group. If it were established that walking speed predicts cognitive change in this at risk group, then it could be used as a tool to triage patients presenting in primary care to further screening of neuropsychological assessment. This would help ensure they received an appropriate intervention as quickly as possible.

Aims

This review sought to explore the available evidence exploring an association between cognition and walking speed in those who have experienced an acquired brain injury (ABI). Walking speed offers the potential of a quick, easy and naturalistic method of detecting risk for cognitive change hence exploring the potential role of walking speed in predicting this risk has important clinical and research implications. Although it would be too restrictive to only include studies which utilised a dual task procedure, studies which included walking speed as part of a dual task are of particular interest for this review.

Research Questions:

1. Is there an association between walking speed and cognitive function in people who have experienced an ABI?
2. Can walking speed screen for cognitive function in people who have experienced an ABI?
3. Can walking speed/cognition dual task screen for cognitive function in people who have experienced an ABI?

Methods

Search strategy: Studies were identified using the following electronic databases: Medline, EMBASE, Psych Info, Cochrane Library, Psychology and Behavioural Sciences and CINAHL. All databases were searched on 2.10.17, with no time limit. The search was carried out using subject headings and keywords (in title, abstract and keyword) separately and then combined. The following search terms were used (Table 1):

Table 1. *Search strategy*

	1. Walking speed	**2. Acquired Brain Injury**	**3. Cognition**
Subject headings	• Walking • Gait • Ambulation • Walking speed	• Brain injury • Head injury • TBI • ABI • Stroke • cardiovascular accident • CVA • Hypoxia • Encephalitis	• Cognition • Cognitive decline • Cognitive change • Cognitive deterioration • Cognitive impairment • Cognitive dysfunction • Cognitive function
Keywords	((walk* or gait) N5/ adj5 (speed or pace))	((brain or head) N2/adj2 injur*) or TBI or ABI or stroke or cardiovascular accidentor CVA or hypox* or encephal*	(cognit* N5/adj5 (chang* or declin* or deteriorat* or impair* or dysfunction* or function*))

The three searches in Table 1 were conducted separately and then combined (1 AND 2 AND 3). The final search strategy was individualised to ensure suitability across each of the databases and was developed with the support of a librarian.

Selection criteria: Following completion of the search and removal of duplicate articles, studies identified were screened in line with the following inclusion and exclusion criteria.

To be included, the paper had to include a sample of adults (aged over 15 years) who had experienced an ABI, defined as any single neurological event injury of acute onset. The participants must have undergone a measure of walking speed and a measure of cognition, and so all had to be able to walk a short distance. In addition, the paper had to provide (or be made available upon request to the research team) analysis exploring relationships between walking speed and cognition. The paper had to be published in the English language in a peer reviewed journal.

Articles were excluded if they did not meet inclusion criteria or if including participants with congenital (e.g. Down's syndrome) or neurodegenerative conditions (e.g. dementia or multiple sclerosis). For those with an ABI, studies with participants who had brain damage as a result of long term decline, for example, due to alcohol use were also excluded.

Search Results: After removing duplicates, 911 articles were identified. Of these, 803 were excluded on the basis of title, and a further 73 by abstract. Thirty-five articles were read in full. Of these, 30 were excluded because they did not include data exploring an association between cognition and walking speed. Five studies were included in the qualitative synthesis. Data were extracted using a data extraction form (see appendix 1.2). This aimed to extract key information on participants, interventions, comparators, and outcomes (PICO). The reference lists of these five papers were then read, but no additional articles that met the inclusion criteria were identified at this stage. The search was re-run on 3.5.18, to search for articles published from 2017 onwards and no further articles that met the inclusion criteria were identified. Hence five studies were included in the final review (see figure 1).

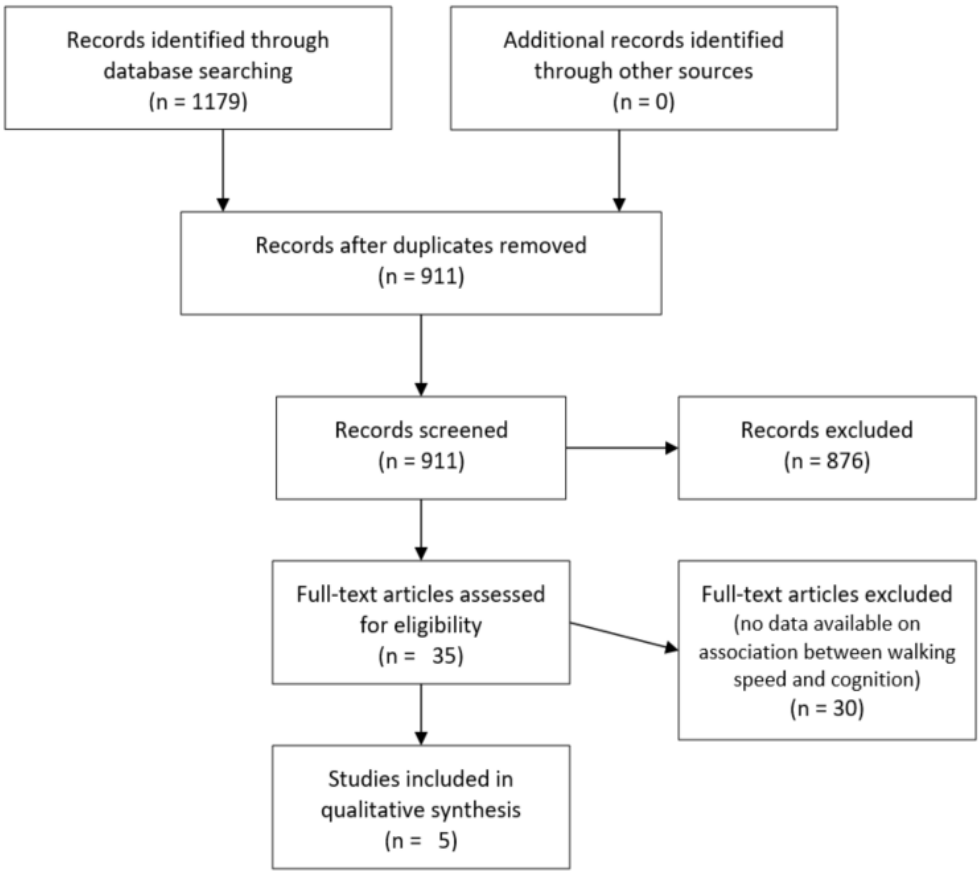

Figure 1. PRISMA flowchart

Rating risk of bias: Papers selected for inclusion were systematically rated for methodological bias using criteria developed for observational studies in epidemiology (Sanderson et al, 2007) in six key domains (see appendix 1.3). This method was used by Moynan & McMillan (2017) in their systematic review exploring the prevalence of head injury and associated disability in prisoners. The following defines low risk of bias for each domain:

Methods for selecting study participants

- Inclusion and exclusion criteria are clear and adequate assurance they meet criteria of having experienced an ABI. The sample is representative of the ABI population group it includes.

Methods for measuring exposure and outcome variables

- Use of standardised measures for both walking speed and cognition.

Design specific sources of bias

- Appropriate methods outlined to deal with any design specific issues such as biased loss to follow up or blinding.

Methods to control confounding

- Appropriate consideration of potential confounders on the relationship between walking speed and cognition.

Statistical methods

- Appropriate use of statistical analysis.

Conflict of interest

- Declarations of conflict of interest and identification of funding sources.

Each paper was assessed by two independent raters in each of the six domains as having a 'high' or 'low' risk of bias. In cases where it was unclear, e.g. no details provided on blinding, but unclear whether blinding would be necessary, were rated as 'unclear'. Raters were both trainee clinical psychologists and interrater concordance was 27/30 (90%), with the three discrepancies resolved with discussion.

Results

All the studies consist of a sample of people who have had a stroke, apart from Cantin et al (2007) which has a HI sample. Table 2 shows the risk of bias across each of the five included studies. Apart from low bias in Ben Assayag et al (2015), risk of bias was mixed for the other domains. Table 3 documents characteristics of the participants while table 4 provides information about the study methods and results.

There was a range of ages included, with the mean age ranging from 37.7 to 70 years (individual sample age ranges not always provided). There was a higher percentage of men in each of the studies. This is likely to reflect the higher prevalence of HI in men than women in the wider population (Frost et al, 2013), and the higher prevalence of men than women (aged under 75) who have a stroke (Rosamond et al, 2007).

Table 2. *Risk of bias*

Authors (year)	Methods for selecting participants	Methods for measuring exposure and outcome variables	Design specific sources of bias	Methods to control confounding	Statistical methods	Conflict of interest
Arsic et al (2015)	High	Low	Unclear	Low	Low	Low
Ben Assayag et al (2015)	Low	Low	Low	Low	Low	Low
Cantin et al (2007)	High	High	Unclear	High	Low	Low
Sagnier et al (2017)	Low	Low	High	Low	Low	Low
Taylor-Pillae et al (2012)	Low	Low	High	High	Low	Low

Table 3. *Data extracted from included studies- Participants*

Author (Year)	ABI	Sample size (ABI)	Time since ABI	% male	Mean (SD) age (years)
Arsic et al (2015)	Ischemic stroke patients in subacute phase with hemiparesis	50	Range unknown. All had undergone early rehabilitation and were continuing with further rehabilitation.	52	69.9 (7.71) Range: 50-80 years
Ben Assayag et al (2015)	First ever, mild-moderate ischemic stroke or transient ischemic attack	298	Neuropsychological data at point of hospital admission (within 72 hours of symptom onset)	62	66.7 (9.6)
Cantin et al (2007)	Moderate or severe HI, mean (SD) Glasgow Coma Scale = 7.6 (2.6)	10	Time since injury: Range= 30-861 days, Mean (SD)= 5.4 (8.4) months	80	37.7 (13.7)
Sagnier et al (2017)	Supratentorial ischemic stroke. Large-artery atheroscelorosis (14%), Cardioembolism (26%), small vessel disease (9%), other (4%), undetermined (47%).	212	Recruited at hospital admission. Baseline data 24-72 hours from onset.	71	64 (13)
Taylor-Pillae et al (2012)	68% ischemic stroke, 31% hemorrhagic stroke	100	Months post stroke Range= 3-356 Mean (SD)= 39 (49)	54	70 (10)

Table 4. *Data extracted from included studies- methodology and results*

Authors (year)	Key inclusion/exclusion criteria	Measures	Key findings
Arsic et al (2015)	*Inclusion*-stroke patients with hemiparesis who had received early rehabilitation	*Walking speed*-The Functional Ambulation Categories (FAC) is a functional walking test that includes a measure of walking speed; m/s over 3 metres. *Cognition*-MMSE	Mean (SD) MMSE score- 22.72 (3.33) Mean speed of gait (m/min)- 75.46 (23.1) MMSE is not significantly correlated with walking speed (r=.228, p>0.05).
Ben Assayag et al (2015)	*Inclusion*- First ever, mild-moderate ischemic stroke or TIA. *Exclusion*- if they had haemorrhagic stroke, stroke resulting from trauma or invasive procedures, severe aphasia, CD/dementia, or were unlikely to be discharged from hospital or participate in hospital. Patients with gait dysfunction were also excluded.	*Walking speed*- Speed over 20 metres *Cognition*-MoCA and Neurotrax (computerised battery)	Mean (SD) 6 month MoCA score- 25.3 (3.3) Mean (SD) 6 month walking speed (m/s)- 1.3 (1.8) Walking speed correlates significantly with MoCA scores 6 months (r=.509, p<0.01) and 24 months (r=.470, p<0.01) post stroke. 46 participants (15.4%) developed clinically significant cognitive decline during 2 year follow up. Walking speed predicts cognitive decline over 24 months (Relative Hazard Ratio=4.61 95 % confidence interval: 2.19-9.67, P<0.001*).
Cantin et al (2007)	*Inclusion*- Experienced only 1 HI with severity ratings of moderate to severe on the Glasgow Coma Scale. Able to walk with a minimum speed of 0.7m/s without any walking device or assistance. *Exclusion*- subjects with skull fractures or perforations, severe cognitive or behavioural problems adversely affecting	*Walking speed*- Included in locomotor patterns assessment *Cognition*- trails, SDMT, Digit span, STROOP, D2 test, Brown Peterson test, letter number sequencing	Mean (SD) scores for Trails A (seconds), 41 (22.49), Trails B (seconds), 110.56 (51.21), digit span forward (number), 8.9 (2.6), digit span backward (number), 5.3 (2.11), Stroop colour (seconds), 74.89 (8.82), Stroop word (seconds), 56.9 (7.33), Stroop interference (seconds), 123.4 (24.47), spatial span forward (number), 8.7 (2), spatial span backward (number), 8 (1.63), SDMT (number), 38.2 (6.32), letter-number sequencing (number), 8.8 (2.49), D2 test (number)

	the ability to participate, or musculoskeletal problems affecting locomotion.		total, 381.9 (63.65), errors, 23.3 (32.06), Brown Peterson Test (number), 13.2 (4.85). "no significant relationships were shown between walking speeds and results on neuropsychological exams"- no statistical analysis provided
Sagnier et al (2017)	*Inclusion*- adults diagnosed with a supratentorial ischemic stroke between 24 hours and 72 hours from onset and with a National Institute of health stroke score comprised between 1 and 15. *Exclusion*- pre-stroke modified Rankin scale >1, pre-stroke dementia, axis 1 psychiatric disorder, history of chronic disease compromising patient's follow up at 1 year, and incapacity to perform the tests due to severe hemiplegia or aphasia.	*Walking speed*- 10m walking test (10-MWT) *Cognition*- MoCA	Mean (SD) MoCA score -baseline- 22.1 (6.3) -3 months -24.3 (4.6) -one year - 25 (4.1) Mean (SD) 10-metre walking time (seconds) - baseline – 11.9 (3.7) - 3 months – 9.7 (3.9) -12 months – 9.9 (4.9) Change in walking speed is associated with change in MoCA score at 1 year post stroke (estimate β= 0.2, (-0.24; -0.07), $p<0.01$))
Taylor-Pillae et al (2012)	*Inclusion*- community-dwelling stroke survivors. First 100 to enrol in an exercise intervention study	*Walking speed*-4m gait speed test *Cognition*- MMSE	Mean (SD) MMSE score- 27.9 (2.2) Mean (SD) gait speed (m/s)- 0.7 (0.3) Walking speed correlates weakly but significantly with MMSE (r=0.2, $p<0.05$).

MMSE- Mini Mental State examination, MoCA- Montreal Cognitive Assessment, SDMT- Symbol digit modalities test, CD- cognitive decline, TIA- Transient ischemic attack

*This result is not identified as significant in the published paper. Correspondence with the author confirmed a typing mistake and confirmed this as a significant result.

Summary of studies

Arsic et al (2015) explored whether there was an association between walking speed and cognition in 50 stroke patients. They found no significant correlation between walking speed and Mini Mental State Examination (MMSE) score. There was however a high level of bias in recruitment of participants, all of whom had undergone early rehabilitation post-stroke. The paper does not state exclusion criteria, or provide any details around the larger sample from which it is recruited or recruitment rates. It is therefore unknown how representative it is of the wider stroke population. The modest sample size also limits confidence in interpretation. Walking speed during a dual task procedure was not included.

Ben Assayag et al (2015) explored both how gait speed and cognition were correlated after stroke and if gait speed could predict cognitive decline in the two years following a stroke. They found that gait speed and Montreal Cognitive Assessment (MoCA) scores had moderate correlations at both 6 and 12 months post stroke and that gait speed predicted cognitive decline. There was no evidence of risk of bias in this study. This study also utilised a dual task procedure, where people were asked to walk while counting backwards from 100 in 3s. They found that using this procedure, the number of correct responses given during this dual task significantly correlated with MoCA scores 6 and 24 months after stroke and predicted cognitive decline over 2 years.

Cantin et al (2007) explored correlations between gait speed and cognition in 10 patients following a traumatic brain injury. They did not provide any specific results for this analysis but reported that no significant associations were found across a range of cognitive measures. There was a high risk of bias noted in this study, with a small sample size, no global measure of cognition, and no evidence that potential confounders on the relationship had been considered. Walking speed during a dual task procedure was not included in this study.

Sagnier et al (2017) reported significant associations between changes in walking speed and changes in MoCA scores one year after stroke. High risk of bias however was noted in this study when considering loss to follow up. Although the study included data from 212 participants, the study only included results for participants with complete longitudinal data. It is therefore unknown how representative this is of the larger stroke population and some of the factors which may have led to participants not remaining in the study. Walking speed during a dual task procedure was not included in this study.

Taylor-Pillae et al (2012) explored how walking speed and cognition were associated in 100 patients who had experienced a stroke. They found a weak correlation between walking speed and MMSE score. There were potential sources of bias noted however; high levels of missing data, only including those with complete data and not including age as a potential confounder. Walking speed during a dual task procedure was not included in this study.

Overall, these studies provide a range of results around a potential association between walking speed and cognition following ABI. Findings are difficult to generalise because the study designs vary, as do the participants they include, the measures they use and the questions they attempt to answer and so it is not possible to combine results to explore overall results across studies. Of particular interest are studies which include a measure of walking speed as part of a dual task procedure, however only one study included this.

Discussion

A systematic search of the literature to identify articles which explored a potential association between walking speed and cognition in a sample of people who had experienced an ABI found five articles which met inclusion criteria. With due consideration of potential sources of bias, the results can be interpreted to help us answer the research questions.

Is there an association between walking speed and cognitive function in people who have experienced an acquired brain injury?

Together the studies comprised 660 participants who had experienced a stroke and ten participants who had experienced a HI. There is insufficient evidence to come to any definite view about HI. It is clear that this is an area which requires further research given interest in long term decline after HI (Millar et al, 2003).

Research on stroke participants suggest a link between walking speed and cognition. Ben Assayag et al (2015) included the largest sample and had the least risk of bias and found evidence for a moderate correlation at both 6 and 24 months post stroke. Of note, the association was smaller after 24 months than 6 months which may reflect a reduction in the strength of the association over time. Arsic et al (2015) did not find a correlation between MMSE and walking speed after stroke. However, this study included people at varying times after experiencing a stroke and did not consider this potentially important factor in

their analysis. Their lack of significant findings may be a reflection of the importance of length of time following a stroke when considering study results. Delaveran et al (2017) conducted a study suggesting that the MoCA may be more suitable than MMSE to detect long-term post stroke cognitive impairment, as it was found to have increased sensitivity and did not have a ceiling which was found in the MMSE. This finding may be important when interpreting our results and may explain the larger effect seen in studies using the MoCA as opposed to the MMSE. With the limited number of studies available, it is not possible to fully explore the impact of the cognitive measure used or the impact of the length of time following injury. Future research would need to explore these issues more fully before conclusions can be drawn.

Can walking speed screen for cognitive function in people who have experienced an acquired brain injury?

Two studies explored longitudinal data. These studies explored whether walking speed predicts cognitive change over time following stroke. Ben Assayag et al (2015) found that gait speed 6 months after stroke predicted cognitive decline (cognitive impairment or dementia) 2 years after stroke, while Sangier et al (2017) found that changes in walking speed were associated with changes in MoCA one year after a stroke.

Overall, both studies had reasonable sample sizes (200+) and included participants who had experienced a minor stroke (Median National Institutes of Health Stroke Scale (NIHSS) score of 2 in Ben Assayag et al, 2015, and a mean NIHSS score of 3.7 in Sagnier et al, 2017). Although both studies utilised different methods, they are consistent in finding that walking speed is a useful measure of cognitive function up to 2 years following a stroke. Of particular note, the study by Sagnier et al (2017) only included participants who completed all measures, with no evidence that drop out was considered. This is in contrast to the study conducted by Ben Assayag who compared the participants who completed the study with those who did not and found no significant difference between the groups. This is important and provides us with important evidence that their results are likely to be representative of the original sample. Overall, this evidence suggests that walking speed may be a useful indicator of cognitive decline following a stroke. These studies only include follow up for two years, and so future research should explore whether walking speed is useful at predicting longer term outcomes for these patients.

Can walking speed/cognition dual task screen for cognitive function in people who have experienced an acquired brain injury?

One study (Ben Assayag et al, 2015) used a dual task procedure in addition to the single task analysis. The number of correct responses during the dual task significantly correlated with MoCA scores 6 months (r=0.295, p<0.05) and 24 months (r=0.279, p<0.05) after stroke and predicted cognitive decline over 2 years (relative hazard ratio; 2.39 (1.16-4.93), p<0.05). It may be that future research should explore the potential for walking speed as part of a dual task procedure to be used as a predictor for cognitive decline in those who have experienced a head injury.

Results in context

When considering these results within the wider context, it is important to consider how they compare with studies in other participant groups and in what way an ABI sample may be similar or different.

Miekle et al (2012) conducted a large population based study (n=1478) on walking speed as a predictor of cognitive decline, in adults from the general population aged 70-89 years. They found that faster walking speed was associated with better performance in memory, executive function and global cognition when followed for 20 years. Callisaya et al (2015) included a sample of 284 adults aged 60-85 years, to explore how gait speed was associated with cognitive decline over three years. They found that a decline in executive function was associated with a decline in gait speed, with a stronger association where participants were already showing signs of cognitive impairment at baseline. Verghese et el (2007) conducted a community based study with 399 participants aged over 70 years old. Over five year follow up, 33 participants developed dementia and this study found that those participants had significantly slower walking speed at baseline when compared to the group who did not develop dementia during follow up.

These studies provide evidence that walking speed can be associated with cognition over time. All participants in these studies were recruited from the general population which marks a clear difference from those included in this review; all of whom had an ABI. The studies in this review were predominantly on people who had experienced a stroke- with variability in time between the stroke and the assessment. This review aimed to explore the potential utility of walking speed as a predictor of cognitive change over time; however these studies may include people who experience a rapid change in cognitive function

following initial assessment. When considering the impact of a stroke on an individual it is likely that many would show cognitive improvement following an early initial assessment. This contrasts with population based studies that include older adults, where it would be unlikely for a person to show cognitive improvement over time. It may be that, given the range in outcome following a stroke, it will be harder to unpick the usefulness of walking speed as a predictor of later cognitive function in this sample. In addition, the picture is further complicated by the walking difficulties experienced by many following a stroke. Factors which affect the person's walking speed are far more complex in someone who has experienced a stroke than in the general population, with sufferer's commonly experiencing muscle stiffness, weakness or complete lack of muscle control. For future research it seems important to consider when the baseline assessment takes place. Consideration will need to be given to when one might expect walking speed following an ABI to be a useful indicator of the person's current or future level of functioning, with the majority of recovery occurring in the first three months post stroke (Skilbeck at al, 1983; Krakauer et al, 2015).

Limitations

There are limitations of this review which should be acknowledged. Although the primary goal of this review was to identify research with a HI sample, the findings showed that there was only one study including a HI sample. This particular paper had high risk of methodological bias and failed to provide any research data in support of their findings thus making it impossible to draw any meaningful conclusions about this population group. As it had been predicted that HI research would be limited, the search was extended to include participants with any ABI. The search however only identified studies including people who had experienced a stroke therefore making any conclusion about ABI more generally impossible. When reviewing the four papers that included participants who had experienced a stroke, risk of methodological bias was noted in three of the four. Although not a limitation of the review itself, this does lead to limitations around the reviews ability to answer the research questions with confidence. Conclusions about the usefulness of walking speed as a predictor of cognitive decline following ABI as well as the potential

impact of existing walking difficulties in this population cannot be drawn with confidence and so remain questions for future research.

Conclusions

This review aimed to identify articles which explored an association between walking speed and cognition following ABI. It sought to explore the evidence for an association between these factors and to explore whether walking speed could screen for cognitive function in people who had experienced an ABI. Review of the five included articles suggests an association between cognition and walking speed following a stroke but did not provide enough evidence about the utility of walking speed as a predictor of cognitive decline in this sample to form a conclusion. Evidence on HI was also insufficient for a view to be formed. The evidence that does exist is overall promising, and further research is required which should consider the use of walking speed as part of a dual task assessment.

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Does walking speed predict change in cognitive function late after head injury?

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Plain English Summary

Cognitive decline late after head injury

Background

When someone experiences a severe head injury, it is known that they are at increased risk of cognitive decline later in life (Gupta et al, 2016). This can often occur long after the head injury and so can cause ongoing worry. Research has tried to explore what may help predict who is at risk of cognitive decline. Findings show that slower walking speed can predict a decline in a person's cognitive ability (Buracchio et al, 2010). Although this has been shown in a number of studies, it has not been looked at in people who have had a severe head injury. As these people are already at increased risk of cognitive decline it is important to explore whether walking speed also predicts decline in this group.

Aims and questions

To determine whether walking speed is associated with cognitive change late after severe head injury. Will walking speed predict how a person's cognitive ability changes over the next two years?

Methods

This study included 48 participants who experienced a severe head injury 20-40 years previously and who took part in an initial assessment assessing their walking speed and cognitive ability. Participants were asked to consent to undergo a second assessment, 2 years later, to re-assess their walking speed and cognitive ability. Statistical analyses were used to explore whether walking speed at the first assessment predicted any change in cognitive ability between the first and second assessment.

Main findings and conclusions

This study found that over a 2 year period, the sample overall did not show cognitive decline. This made it difficult to know whether walking speed would have detected a change in cognitive ability in this group. As part of the walking task, participants were asked to count backwards from 100 in 3s while walking (dual task). The results showed that people who counted more slowly during this task were more likely to show decline in some of the cognitive measures. This shows that this dual task may provide us with

important information about ongoing cognitive functioning. As those with HI are at risk of cognitive decline, it is important that future research explores this further.

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Abstract

Background

Severe head injury (HI) can be a trigger for neurodegeneration (Gupta, 2016) and research into predictors of cognitive decline has found walking speed to be a useful predictor of changes in cognition over time. It is therefore of interest to explore whether walking speed could predict cognitive decline within this 'at risk' group.

Research Question

Can walking speed during dual task be used as an assessment for cognitive change late after severe head injury?

Methods

This study included 48 participants with a historic HI. All had been assessed two years previously, completing measures of both cognition and walking speed as part of a dual task. This study followed up these participants and repeated their baseline assessment. Regression analyses were used to explore whether the dual task measures at baseline predicted change in the cognitive measures between the baseline and follow up assessment.

Results

Overall the cognitive ability of the sample remained relatively stable over the two year follow up period. Although walking speed measures did not predict cognitive change, dual task counting and dual task cost (which include a measure of walking speed in their calculation) predicted change in the Mini Mental State Examination (MMSE) score and change in Symbol Digit Modalities score.

Significance

The dual task measure has potential to provide important information about ongoing cognitive functioning. Given that those who have experienced HI are at increased risk of cognitive decline, it is important that this potential is fully explored.

Keywords: Walking speed; dual task; Head Injury; Cognitive decline

Introduction

It has been argued that severe head injury (HI) is a risk factor for neurodegeneration late after injury (Gupta, 2016). Dunning et al (2016) conducted a meta-analysis of 21 studies, in HI survivors. When compared to controls, those with a HI had significant deficits in memory and visuospatial skills. The impact of HI may be long lasting and may put people at higher risk of cognitive decline later in life (Ozen et al 2015). Fann et al (2018) conducted a nationwide population based observational cohort study in Denmark using national data on 2,794,852 people. They found that head injury was associated with an increased risk of dementia when compared to those without HI. This large scale study with long term follow up clearly demonstrates the increased risk of dementia following HI and this enhanced risk can cause ongoing concern to the individual and their loved ones. There is currently a great deal of interest around the neuropathology of HI and cognitive decline. Iverson et al (2015) completed a review of chronic traumatic encephalopathy (CTE) which is considered a type of dementia associated with repeated head injuries and repeated episodes of concussion. They reported that it was still unclear whether it is HI itself that leads to cognitive decline or whether the HI is instead associated with reductions in cognitive reserve which make the person then vulnerable to an earlier expression of a degenerative disorder. Alternatively, there may be a third factor which makes people more vulnerable to both HI and cognitive decline, for example, poor health (McMillan et al, 2014).

Teasdale et al (1997) found that there may be genetic factors which affect outcome after HI, finding those who had an APOE genotype to be more likely to have a worse outcome 6 months after injury. Millar et al (2003) tried to explore whether this same genotype predicted cognitive decline after injury but concluded their sample with a mean age of 42 years was too young to reach conclusions, suggesting this be explored further as the sample aged.

Research into predictors of cognitive decline has explored the importance of walking speed. Some studies look at walking speed alone while others utilise it as part of a dual task whereby participants are asked to walk while doing another cognitively demanding task, for example, talking. Of the following six studies, two utilised a dual task procedure (Doi et al and Ben Assayag et al), whereas four looked at walking speed alone. Miekle et al (2012) conducted a large population based study (n=1478) on walking speed as a predictor of cognitive decline. They found that faster walking speed was associated with

better performance in memory, executive function and global cognition when followed for 20 years. This is in line with findings from a number of studies showing an association between walking and cognition (Callisaya et al, 2015 & Buracchio et al, 2010). This association has been shown in several diagnostic groups including those with mild cognitive impairment (Doi et al, 2014), stroke (Ben Assayag et al, 2015) and dementia (Verghese et al, 2007). Two of these studies (Doi et al, Buracchio et al) looked at an association between walking and a measure of cognitive function. The other four studies (Ben Assayag et al, Callisaya et al, Verghese et al, & Miekle et al) looked longitudinally at how walking was associated with cognitive decline over time.

Research has tried to explore why walking speed might predict cognitive decline. Some theories suggest that the brain damage or abnormality which leads to cognitive decline affects walking speed early on in the process while other theories attribute the link to a shared common factor, for example, muscle strength which has been shown to affect both walking speed in disabled older women (Rantanen et al, 1998) and blood markers which are linked to cognitive decline in Alzheimer's Disease (Hogervorst et al, 2004).

Biomechanical deficits are common following HI (van Donkelaar et al, 2006). Williams et al (2009) aimed to identify the most common gait abnormalities in this group. They recruited 41 ambulant participants who were receiving therapy for gait abnormalities following HI. They found that the most common abnormalities were related to trunk and pelvic movements. They also compared the sample to healthy controls and found that those with HI walked significantly slower than the controls, due to a reduced rhythm and a shorter step length. With participants who have experienced a HI being at higher risk of having gait abnormalities, it is not known whether the association between walking and cognitive change shown in other groups will also be evident in people who have experienced a severe HI.

Walking speed offers the potential of a quick, easy and naturalistic method of detecting risk for cognitive change. It is known that those with severe HI are at increased risk of cognitive change over time (Millar et al, 2003; Whitnall et al 2006); hence exploring the potential role of walking speed in predicting this risk has important clinical and research implications. If it were established that walking speed predicts cognitive change in this at risk group, then it could be used as a tool to triage patients presenting in primary care to further screening of neuropsychological assessment. This would help ensure they received an appropriate intervention as quickly as possible.

There are a number of methodological challenges associated with this area of work. When seeking to follow up those with HI over a long period of time, it must be acknowledged that this group is at risk of experiencing premature death. McMillan et al (2011) conducted a 13-year follow up study and found a death rate of 30.99 per 1000 per year in the head injury cohort, as compared to a rate of 13.72 per 1000 per year in the community control sample. In addition they are more likely to experience disability (Whitnall et al, 2006), which may also affect recruitment for research. This presents with a significant challenge when trying to follow up large samples over time, in particular when trying to obtain data from a representative sample.

This study is keen to detect cognitive decline. While research has shown that those with HI are at increased risk of cognitive decline later in life, it is not possible to predict when this decline will take place. Where a sample includes people covering a wide age range, it is likely that the risk of accelerated cognitive decline is not consistent across the sample. Research therefore can only capture a snapshot of time, with uncertainty around the level of cognitive decline which would be expected within such a sample. Any findings therefore must be interpreted with this in mind and with appropriate caution.

Aims and hypotheses

Aim

The aim is to explore walking speed during dual task as an assessment for cognitive change late after severe head injury. If an association between walking speed and cognitive change is found, then an additional aim will be to investigate whether a walking speed cut off can be established to capture those with cognitive decline (i.e. with good sensitivity and moderate/ good specificity).

Hypothesis

Walking speed at baseline (as measured by a dual task) is associated with cognitive change (as measured by the difference in cognitive scores between baseline and 2-year follow up).

Method

Study in context

Participants were recruited from two historical research cohorts that included people with a severe HI (Millar et al, 2003; Teasdale et al, 2005). The study conducted by Millar et al (2003) comprised of a database of 1133 patients who had sustained a severe head injury

and had been studied in the acute stage in the Department of Neuropsychology, Institute of Neurological Sciences at the Southern General Hospital, Glasgow between 1968 and 1985.

A cohort of 396 was then included in follow up study at a mean age of 18 years later. This follow up study was primarily exploring long term neuropsychological outcome after head injury in relation to genetic risk factors. The study conducted by Teasdale et al (2005) included a sample of 1094 patients following head injury admission to the same neuropsychological unit between 1996 and 1999. This study followed patients up for 6 months, again exploring the role of genetics in outcome after HI. Both of these studies were interested in the association between the APOE genotype and outcomes following HI and this remains an interest for ongoing research within this sample. Patients were recruited for further exploration into this possible association between 2015-2017. This provided a unique opportunity to explore the current research question around the potential role of walking speed as a predictor of cognitive decline and so dual task walking measures were included in the baseline assessments.

The study has ethical approval from the West of Scotland NHS Research Ethics committee (ref 14/WS/1145).

Participants

One hundred and three participants from the original two cohorts were recruited and assessed in the first part of this current study (2015-2017) and were eligible to be contacted for two-year follow up (2017-2019). A total of forty-eight participants were included in this study. They all undertook assessments in both 2015/2016 and then in a follow up study two years later, in 2017/2018. Recruitment is shown in the flowchart below (figure 1).

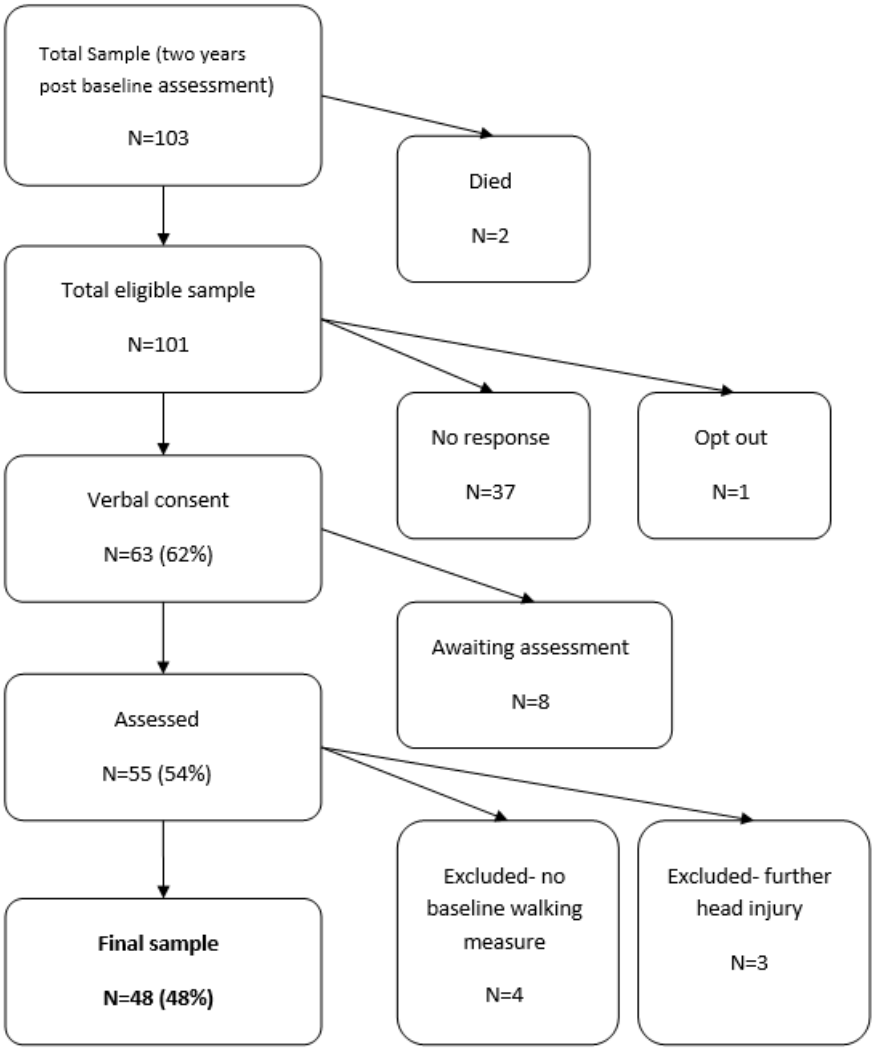

Figure 1. Recruitment flowchart

Inclusion and exclusion criteria

Participants were eligible to be included if they took part in the baseline assessment in 2015-17. All had a history of severe HI and baseline data on their cognitive ability and walking speed. All participants had to be considered capable of giving informed consent.

Participants were excluded if they had suffered a serious neurological event since the baseline assessment (e.g. a stroke or further HI), a physical injury affecting walking or were not capable of being assessed.

Design

The study was a longitudinal within group study. Walking speed at baseline was explored as a predictor of cognitive change at 2 year follow up.

Measures and materials

Background questionnaire: This included basic demographic data, including the participant's age, gender and occupation. In addition, it explored whether the person had experienced any significant life events since their previous assessment.

Walking measure

Dual task: A dual task (DT) procedure requires an individual to perform two tasks simultaneously, and can be compared to performance in single task (ST) conditions (McCulloch, 2007), allowing by subtraction, a response cost to be calculated. In this instance, participants will first be timed to walk 6 metres (ST) and then to count backwards from 100 in 3s for 30 seconds. In addition to completing these tasks singly, participants will also complete them simultaneously – the dual task (i.e. walking and counting at the same time). In the DT condition, poorer performance in either walking and/or counting could occur. Reduced performance in the DT condition is described as dual task cost (calculated as DT-ST/ST). Dual task cost may represent impaired capacity to share cognitive resources between walking and an attention demanding task.
A total of four scores were used from this test;
Dual task walking speed- Time taken (seconds) to walk 6 metres while counting backwards;
Dual task counting- The number of correct counting responses given while walking 6 metres divided by the time taken for each individual's dual task walk, resulting in the number of correct responses per second;
Dual task walking cost- (Time to walk 6m while counting– time to walk 6m without counting) divided by time to walk 6m without counting;
Dual task counting cost- (number of correct counting responses per second while walking-number of correct counting responses per second without walking) divided by number of correct counting responses per second without walking.

Disability Assessment

Glasgow Outcome Scale Extended (GOSE, Jennett & Bond, 1975): A global scale of functional outcome that uses a structured interview to rate patient status into one of eight categories of recovery. The GOSE has been shown to be a valid measure of outcome which is sensitive to change following both mild to moderate (Levin et al, 2001) and severe brain injury (Teasdale et al, 1998).

Cognitive measures

The choice of cognitive measures was limited by the need to use the same tests as those used in earlier studies with this cohort.

*Mini Mental State Examination (*MMSE, Folstein et al, 1975): A screening tool to assess general cognitive function. It includes items of orientation, registration, short term memory and language functioning. Participants are given a total score out of 30, with a score of 24 or above representing normal cognition. The MMSE has been shown to be a reliable measure of cognitive change in older adults (Hensel et al, 2007).

Logical Memory Test (WMS-R- Wechsler, 1987). The test involves reading 2 short stories aloud to the participant. The participant is asked to recall as much as they can about each story, both immediately and again after a thirty-minute delay. The score used in this current study is the total score combining their immediate and delayed recall. The logical memory test has been shown to help differentiate those with and without mild cognitive impairment (MCI) as well as predicting progression from MCI to Alzheimer's disease (Rabin et al, 2009).

STROOP test: A measure of inhibitory control where the participant is asked to name the colour a word is printed in when the word itself is the name of another colour. The score is the number of correct responses within a two-minute period. Slowing on the STROOP has been shown to relate to patterns of cognitive decline in adults with dementia (Koss et al, 1984).

Symbol digit modalities test (SDMT- Smith, 1982): A tool for measuring processing speed, which can be used to screen for cognitive impairment, the participant is asked to use a reference key to pair specific numbers with given geometric figures. Participants are asked to try to pair as many number/figures as they can within 90 seconds. The score is the number of correctly completed pairings. The SDMT has been shown as a valid and reliable measure of cognitive function (Sheridan et al, 2006).

Short-term Memory binding task (STMBT): This computerised task investigates the retention of shapes, colours or combinations of shapes and colours. Participants are shown two consecutive screens and asked to identify changes between the two displays. These

displays show shapes which change in either their shape or colour or both. When they change in both shape and colour this is a measure of shape-colour binding. Impairments in memory binding have been shown to differentiate between the performance of people with Alzheimer's disease and patients with major depressions (Parra et al, 2010). As a newly developed measure, lacking the same reliability and validity data as the other cognitive measures, it was not combined with the other cognitive measures within the composite cognitive score. Scores were calculated for accuracy when remembering the shape alone, accuracy when remembering the shape and colour (memory binding) and the difference between the two scores; representative of a specific difficulty with memory binding.

Procedure

All participants recruited to the first phase of this study were asked to take part in a follow up assessment, approximately two years after their last ('baseline') assessment. The follow-ups were carried out by the author from August/September 2017 alongside a research worker who was involved in the baseline study. The author completed 36 of these follow up assessments.

All potential participants (n=103) were contacted by letter from Professor McMillan with the study information (appendix 2.3), 2 years following their baseline assessment. They were asked to read the information and return the enclosed consent form (appendix 2.4) in a prepaid envelope if they wished to participate. They were then contacted by phone to ensure they met the inclusion criteria and to schedule the assessment. Research assessments took place in the Clinical Research Facility within Glasgow Royal Infirmary. They were provided with travel expenses and supermarket vouchers (£20) to compensate them for their time. The data was stored securely in line with the Data Protection Act.

Analysis

The primary research question was to explore whether walking speed during DT predicted cognitive change late after HI. Cognitive change was the primary outcome variable. A composite score for cognitive ability was created by combining Z scores for performance on Logical Memory, STROOP and Symbol Digit Modalities Tests. These were created using the mean and standard deviations of the whole sample at baseline for each test and subtracting the score for each participant from this and dividing by the standard deviation

of the sample. The z scores for these three tests were summed for each participant to give the composite score, a method used by Whitnall et al (2006) when exploring disability after HI. Composite scores were created for each of the two time points. Change in (i) this composite score, and (ii) change in MMSE score were the primary outcome variables measuring cognitive change. Patterns in the data were explored; assumptions to conduct regression were met (see appendix 2.5), and non-parametric tests were used as the data violated the assumption of normality.

Descriptive statistics were used to describe the sample at both baseline and follow up and the data were explored for changes between the two time points. Linear regression was used to explore whether the walking measures predicted change in cognitive scores over time. Those who showed decline in their walking speed were also compared with those who did not. Those who showed a decline in their GOSE were compared with those who did not show decline on their GOSE; t-tests were used to explore whether these groups differed on the walking measures. Following findings from the baseline data; additional analysis also used linear regression to explore walking measures as predictors of executive functioning.

Sample Size Estimation: Brace et al (2009), argue that as a rule of thumb at least 10 times as many participants as predictor variables are needed and so with 4 predictor variables (dual task walking speed, dual task counting; dual task walking cost and dual task counting cost) the sample size of 48 is sufficient.

Results

Participant Characteristics

The follow-up sample comprised 48 participants aged between 19-96 years (mean age 52.13, SD=15.82). Thirty-three were male (69%). They represented a range in educational level (10-22 years of education, mean 14.22 years, SD=3.40), and a range in socio economic status (SIMD quintiles; 1 (most deprived) =25%, 2=15%, 3=13%, 4=15%, 5 (least deprived) =32%).

All participants had a moderate or severe head injury, between 19 and 46 years previously (mean 29.71 years previously, SD=8.51). They showed a range in outcome after the head injury on the GOSE, as shown in table 1 below. Overall; at baseline 52% of the sample had made a 'good recovery' (7 or 8) and 48% were disabled (3-6). At follow up 40% had made a 'good recovery' (score of 7 or 8), and 60% were disabled (3-6).

Table 1. *GOSE scores at baseline and follow up*

GOSE category	Baseline	Follow-up
1- Dead	0	0
2- Vegetative state	0	0
3- Lower severe disability	4 (8.3%)	4 (8.5%)
4- Upper severe disability	2 (4.2%)	4 (8.5%)
5- Lower moderate disability	9 (18.8%)	9 (19.1%)
6- Upper moderate disability	8 (16.7%)	11 (23.4%)
7- Lower good recovery	15 (31.3%)	10 (21.3%)
8- Upper good recovery	10 (20.8%)	9 (19.1%)

Dual task scores

Participants were asked to count backwards from 100 in 3s (single task) and were then timed to walk 6 metres (single task). They were also asked to do both simultaneously (dual task). The results for both single and dual task are shown below (table 2).

Table 2. *Single task vs dual task scores*

Outcome	**Single task Median (IQR)**	**Dual task Median (IQR)**	**Difference**
Walking time (seconds)	4.82 (1.64)	5.84 (3.08)	**Z= -5.84, *p*<0.01**
Correct counting response rate (correct responses per second)	0.53 (0.29)	0.04 (0.39)	Z= -1.04, *p*=0.30

Participants were significantly slower at walking 6 metres when counting at the same time. Their counting rate was unaffected.

Is walking speed at baseline associated with cognitive change between baseline and 2-year follow up?

At baseline, participants ranged in their time to walk 6 metres from 2.59 seconds to 15.85 seconds (mean 6.68 seconds, SD 2.69).

Cognitive change was assessed as the difference between baseline and follow up on the MMSE, STROOP, Logical Memory and SDMT (table 3). In addition, the STROOP, Logical Memory and SDMT were combined to form a composite cognitive score. There was no significant change in the scores, except for Logical Memory where performance was significantly better at follow up compared to baseline.

Table 3. *Change in cognitive scores over two year follow up.*

Test	**Mean (SD)- Baseline**	**Mean (SD)- Follow up**	**Difference over time**
MMSE	28.81 (1.42)	28.77 (1.69)	t(47)=0.20, *p*=0.85
STROOP	83.91 (27.93)	90 (23.16)	t(42)=1.28, *p*=0.21
Logical memory	12.94 (7.67)	15.10 (9.10)	t(47)=2.81, ***p*<0.01**
Symbol Digit modalities Test	39.25 (11.13)	38.94 (12.47)	t(46)=0.80, *p*=0.43
Composite cognitive score	0.2 (2.16)	-0.04 (2.39)	t(42)=1.49, *p*=0.143

Linear regression was used to explore whether the dual task predicted a change in cognitive scores between baseline and follow up. Each dual task score (dual task walking

speed, dual task counting, dual task walking speed cost, and dual task counting cost) was explored as a potential predictor of change in cognition. The outcome was the change in cognition score (follow up score minus baseline score). Age and number of years of education were also added into the model. This was initially completed for change in MMSE score.

Table 4. *Dual task measures and change in MMSE scores. Univariate Regression analyses*

Variable	B	SE B	Significance
Dual task walking speed	-0.13	0.09	0.14
Dual task counting	2.46	0.81	***p*<0.01**
Dual task walking speed cost	-1.02	0.69	0.14
Dual task counting cost	-0.21	0.44	0.63

Table 4 shows that when entered individually, dual task counting is the only measure that predicts change in MMSE score. For every increase of 1 in the dual task counting score there is an increase in MMSE score of 2.46 points. The dual task variables were then entered together into the multivariable regression model (Table 5). Neither walking speed during dual task nor walking speed cost were significant predictors, but dual task counting and dual task counting cost were. When added in together, for every increase of 1 in the dual task counting rate we see an increase in MMSE score of 3.82 points and for every increase in the dual task counting cost, there was a decrease in MMSE score of 1.23 points.

Table 5. *Dual task measures and change in MMSE scores. Regression analyses variables combined.*

Variable	B	SE B	Significance
Dual task counting	3.82	0.89	***p*<0.01**
Dual task counting cost	-1.23	0.44	***p*<0.01**
Age	*-0.00*	*0.01*	*p=0.82*
Years of education	*0.62*	*0.62*	*p=0.32*
Baseline MMSE score	*0.47*	*0.14*	*P<0.01*

It was also of interest to explore whether dual task measures predicted change in the composite cognitive score using univariate analysis; none significantly predicted outcome (table 6).

Table 6. *Dual task measures and composite cognitive score. Univariate regression analysis*

Variable	B	SE B	Significance
Dual task waking speed	-0.05	0.07	0.47
Dual task counting	0.36	0.73	0.63
Dual task walking speed cost	0.00	0.53	0.99
Dual task counting cost	-0.28	0.32	0.38

Using ROC curves, it was found that none of the dual task measures could be used as screening tools for change in MMSE (as measured by a decrease in score by 1SD, 1.4 points). The area under the curve was poor to meaningless for each of the dual task scores (walking speed 0.35; counting rate 0.65; walking cost 0.42; counting cost 0.34) confirming that dual task scores were not able to screen for change in MMSE.

Is a reduction in walking speed between assessment and reassessment associated with a greater decline in cognitive test performance?

Walking speed during the dual task was assessed at both time points. Within the sample, 33 participants (73.3%) did not show a change in their walking speed between the two time points (scoring within 1 SD; 2.70 seconds across both time points). Seven participants walked faster (decreasing the time to walk 6m by 2.70 seconds, 1SD) at follow up than baseline, while the remaining 5 participants (11.1%) walked at least 2.7 seconds slower at follow up than at baseline.

Within the group who performed slower (n=5), reduction in walking speed was between 2.70 seconds and 40.94 seconds slower (Mean=11.78, SD=16.34).

Table 7 shows the group differences, when comparing those who showed a reduced walking speed between the two time points and those who did not. There are no significant differences between the groups on their change in MMSE score or composite cognitive score.

Table 7. *Change in cognitive measures and group differences between those who showed reduced walking speed and those who did not.*

	Same or improved walking speed N=40	**Decline in walking speed N=5**	**Difference between groups**
Change in MMSE score Mean (SD) Range	0.05 (1.43) -3 to 1	-0.80 (1.64) -4 to 3	t(43) = -1.23, *p*=0.22, *d*=0.55
Change in composite cognitive score Mean (SD) Range	-0.14 (1.07) -2.73 to 2.97	-0.50 (0.86) -1.43 to 0.27	t(38)=-0.57, *p*=0.57 *d*=0.66

Additional exploratory analysis

Short-term Memory binding task (STMBT)

The STMBT was used as an exploratory measure. It was of interest whether dual task measures were associated with scores on this measure recently developed as an assessment for early decline in cognitive function (Parra et al, 2010). The scores at both time points are shown below (table 8).

Table 8. *Short term memory binding task scores (accuracy) at baseline and follow-up*

STMBT score	Mean (SD)- baseline	Mean (SD)- Follow up	Difference over time
Shape memory	0.95 (0.09)	0.95 (0.07)	t(41) =0.13, *p*=0.90
Shape and colour (memory binding)	0.91 (0.11)	0.87 (0.14)	**t(41)= 2.45, *p*<0.05, *d*=0.32**
Difference	0.04 (0.09)	0.08 (0.11)	**t(41)= 2.19, *p*<0.05, *d*=0.40**

Memory binding score is measured as accuracy rate and so the results show that participants were significantly less accurate in completing the memory binding task at follow up when compared to baseline. The difference score indicates the difference between a person's performance on the shape memory task and their performance on the shape and colour memory task. A higher score indicates a higher level of specific memory binding difficulty and so it can be seen that the participants were more likely to show a memory binding difficulty at follow up when compared their performance at baseline.

Linear regression showed that none of the dual task scores at baseline predicted change in any of the STMBT scores between baseline and follow up (see Appendix 2.6).

Decrease in Glasgow Outcome Scale Extended Score

Table 9. *Change in GOSE score between time points (n=47)*

Change in GOSE score	N (%)
+1	7 (14.6)
No change	31 (64.6)
-1	5 (10.4)
-2	2 (4.2)
-3	1 (2.1)
-4	1 (2.1)

It was of particular interest to explore any potential role of dual task scores in those who have shown deterioration over the two year follow up. Nine participants had a lower GOSE score at follow up when compared to baseline (table 9). Exploratory analysis

considered whether there were any differences in walking variables between those who had deteriorated and those who had not.

Table 10. *Differences in baseline dual task measures between those who deteriorate on the GOSE and those who do not.*

Dual task measure	Deterioration in GOSE N=9	No deterioration in GOSE N=36	Difference between groups
Dual task walking speed Mean (SD)	6.86 (1.51)	6.59 (2.94)	t (45) =0.26, *p*=0.79, *d*=0.12
Dual task counting Mean (SD)	0.47 (0.13)	0.61 (0.27)	**t (43)= -2.30, *p*<0.05*, *d*=0.68**
Dual task walking speed cost Mean (SD)	1.05 (0.19)	0.98 (0.34)	t (45) = 0.59, *p*=0.56, *d*=0.25
Dual task counting cost Mean (SD)	0.29 (0.52)	0.08 (0.51)	t (43) = 1.07, *p*=0.29, *d*= 0.41

*equal variances not assumed

Table 10 shows that those whose GOSE decreased were significantly slower at counting during the dual task at baseline.

Baseline data analysis

During the analysis of these results, some additional data became available from the write up of the baseline study (n=125). McLean et al, (under review) report that an increase in dual task counting cost score predicts an increase in SDMT, STROOP and STMBDT scores, all considered measures of executive functioning.

Although STMBT scores have already been explored within this sample, regression analyses were used to explore dual task scores at baseline as predictors of change in the STROOP and SDMT individually (as opposed to as part of a composite measure).

Table 11. *Dual task and executive functioning. Univariate regression analysis*

	Variable	**B**	**SE B**	**Significance**
Dual task walking	SDMT	0.08	0.38	0.83
	STROOP	-1.29	0.85	0.14
Dual task walking cost	SDMT	0.47	2.99	0.88
	STROOP	-2.81	7.26	0.70
Dual task counting	SDMT	-2.55	3.77	0.50
	STROOP	15.59	9.40	0.11
Dual task counting cost	**SDMT**	**-4.28**	**1.69**	**<0.05**
	STROOP	-1.66	4.24	0.69

Dual task counting cost score at baseline predicted change in SDMT score between baseline and follow up.

Discussion

This study investigated whether walking speed measures predict cognitive decline in people who have experienced a HI. Although walking speed itself was not shown to predict cognitive change, dual task counting and dual task cost (which include a measure of walking speed in their calculation) were found to predict change in MMSE score and change in SDMT scores.

Previous research has highlighted the potential usefulness of walking speed in predicting cognitive decline, with longitudinal associations found both in the general population (Miekle et al, 2012) and in diagnostic groups including stroke and dementia (Ben Assayag et al, 2015; Verghese et al, 2007). This study explored whether walking speed predicts cognitive decline in a different group; those with HI, however this was not found. Walking speed showed no associations with cognitive decline within this HI sample. We cannot however conclude that walking speed is not a useful measure for people with HI, due to the limited cognitive change in the sample within the 2 year follow up period.

In terms of cognitive change, the only score where a change was observed was an improvement in logical memory, which may be explained by a learning/practice effect. It is therefore important to consider the possibility that cognitive change was not detected. It may be that there was a recruitment bias, and those showing cognitive decline were less likely to be recruited to follow up. Ongoing follow up will recruit more participants by offering home visits or phone interviews in addition to outpatient assessments. This will allow this possibility to be explored more fully. It is also possible that the tests were not sensitive enough to pick up cognitive decline. This may be unlikely, due to the use of standardised measures, which have shown cognitive decline in older adults with and without cognitive impairment (Hensel, et al 2007; Rabin et al, 2009 & Koss et al, 1984). It is therefore likely that the cognitive decline shown by participants is either too small or in too few participants to show cognitive change in the sample overall. Ozen et al (2015) argued that a historic HI may place older adults at risk of accelerated age related cognitive decline later in life. With the average age within this sample being 52 years it may be that they have yet to enter the period of accelerated cognitive decline.

Interpretation of dual task scores

Dual task measures include both a walking and a counting task component. When asked to do these at the same time, it is expected that either or both walking and counting will slow. When asked to complete two tasks simultaneously, without instruction, the person has to make a decision about which task to prioritise. This study found that the participants were more likely to prioritise the cognitive task during dual task and in fact managed to maintain their counting rate between single and dual task counting, at the expense of walking speed. This is in line with what would be expected from previous research (Li et al, 2012).

The results showed that although it was walking speed that was affected during the dual task, the dual task counting rate was more predictive of outcomes at follow up. As there was no difference between single task and dual task counting rate, the results showing the dual task counting rate as predictive of future outcomes are best understood as a reflection of the importance of the cognitive task itself, as opposed to how it is affected during the dual task. It seems that being able to count backwards in 3s is predictive of later changes in cognition.

Although not significant on its own, dual task counting cost became significant when added into a regression model alongside dual task counting rate. It appears that a better picture of counting cost can be observed when counting rate is adjusted for. Dual task counting cost was also found to predict change in SDMT. Although most participants displayed dual task walking cost, as opposed to dual task counting cost, it appears that, where there is a dual task counting cost that this is predictive of cognitive change. This can be seen both globally, as captured by the MMSE, and in processing speed as captured by the SDMT; which has been shown as a valid and reliable measure of cognitive function (Sheridan et al, 2006).

Limitations

Potential limitations of the study included a modest sample size, which could have left the study underpowered. While ideally studies would include much larger samples, the complexity and associated challenges of recruiting those with HI to long-term follow up prohibits this. Therefore, it is important to strive to explore this within small samples, but interpret any findings with appropriate caution.

As mentioned previously, too few participants showing cognitive change or too small a change within the sample also limits the scope of interpretation. As there was limited cognitive change over time within the sample, it was not possible to definitively answer the research questions. With little previous research in the area, it had not been possible to predict what level of cognitive change would have been expected. Although we cannot be confident that there is no effect here, we can see that in future a larger sample will be required to answer these important questions. Data collection is ongoing to further explore the aims of this study as well as the wider aims, regarding genetics, of the larger longitudinal study.

Conclusions

Overall this study utilised a unique sample to explore an area of increasing interest; the importance of walking and cognition. Although the overall cognitive stability of the sample limited interpretation of the results, it can be seen that the dual task measure- incorporating both a walking and counting component- has the potential to provide important information about ongoing cognitive functioning. Future research should include a longer time between baseline and follow up or a larger sample, where more cognitive decline would be expected to occur. With those who have experienced a HI being at increased risk of cognitive decline, it is important that the potential of this is fully explored. Any tools which have the potential to screen for later difficulties could help ensure people receive the appropriate intervention as early as possible.

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Appendix 1.1. Instructions for authors for submission to 'Gait and Posture' journal.

Gait & Posture is a vehicle for the publication of up-to-date basic and clinical research on all aspects of locomotion and balance.

Peer review
This journal operates a single blind review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

Introduction
State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

1. Article types accepted are: Original Article (Full paper or Short Communication), Review Article, Book Review. Word limits are as follows: Full paper 3,000 words plus no more than 6 figures/tables in total; Short Communication 1,200 words plus no more than 3 figures/tables in total. The word limits are non-inclusive of figures, tables, references, and abstracts. If the Editor feels that a paper submitted as a Full Paper would be more appropriate for the Short Communications section, then a shortened version will be requested. References should be limited to 30 for Full Papers and Reviews and 15 for Short Papers. A structured abstract of no more than 300 words should appear at the beginning of each Article. The recommended word limit for Review Papers is 6,000 words. Authors must state the number of words when submitting.

2. All publications will be in English. Authors whose 'first' language is not English should arrange for their manuscripts to be written in idiomatic English **before** submission. A concise style avoiding jargon is preferred.

3. Authors should supply up to five keywords that may be modified by the Editors.

4. Authors should include a structured abstract of no more than 300 words including the following headings: Background, Research question, Methods, Results and Significance. The scientific and clinical background should be explained in 1-2 sentences. One clear scientifically relevant question should be derived from the background which represents the principle research question of the paper. The Methods section should summarise the core study methodology including the type of study (prospective/retrospective, intervention etc), procedures, number of participants and statistical methods. The Results section should summarise the study's main findings. The Significance section should place the results into context. Furthermore this section should highlight the clinical and/or scientific importance of the work, answering the question "so what?" This section should not simply repeat the study results or conclusions.

5. Acknowledgements should be included in the title page. Include external sources of support.

6. The text should be ready for setting in type and should be carefully checked for errors. Scripts should be typed double-spaced on one side of the paper only. Please do not underline anything, leave wide margins and number every sheet.

7. All illustrations should accompany the typescript, but not be inserted in the text. Refer to photographs, charts, and diagrams as 'figures' and number consecutively in order of appearance in the text. Substantive captions for each figure explaining the major point or points should be typed on a separate sheet.

8. Tables should be presented on separate sheets of paper and labelled consecutively but the captions should accompany the table.

9. Authors should also note that files containing text, figures, tables or multimedia data can be placed in a supplementary data file which will be accessible via ScienceDirect (see later section for further details).

10. When submitting your paper please ensure that you separate any identifying author or institution of origin names and details and place them in the title page (with authors and addresses). Submissions including identifying details in the manuscript text will be returned to the author.

Essential title page information

• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.

• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.

• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**

• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Highlights

Highlights are mandatory for this journal. They consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and make sure to strictly adhere to the following specifications: include 3 to 5 bullet points (maximum 85 characters (not words), including spaces, per bullet point).
See http://www.elsevier.com/highlights for examples.

Keywords
Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

References
Indicate references to the literature in the text by superior Arabic numerals that run consecutively through the paper in order of their appearance. Where you cite a reference more than once in the text, use the same number each time. References should take the following form:
1. Amis AA, Dawkins GPC. Functional anatomy of the anterior cruciate ligament. J Bone Joint Surg [Br] 1991; 73B: 260-267
2. Insall JN. Surgery of the Knee. New York: Churchill Livingstone; 1984
3. Shumway-Cook A, Woollacott M. Motor Control: Theory and Practical Applications. Baltimore: Williams and Wilkins; 1995.

Please ensure that references are complete, i.e. that they include, where relevant, author's name, article or book title, volume and issue number, publisher, year and page reference *and* comply with the reference style of *Gait Posture*. Only salient and significant references should be included.

Appendix 1.2 Data extraction form

ID_____

Participants (sample size, age range and mean, gender, ABI profile)

Exposures (measurement of walking speed and cognition)

Comparisons (use of control group, follow up)

Outcomes (relationship between walking speed and cognition)

Study design

Appendix 1.3. Risk of bias rating form

ID_____

1. Methods for selecting study participants (inclusion and exclusion criteria are clear, adequate assurance they meet criteria of having experienced an ABI. The sample is representative of the ABI group is includes.) HIGH/LOW

2. Methods for measuring exposure and outcome variables (use of standardised measures) Walking speed HIGH/LOW Cognition HIGH/LOW

3. Design specific sources of bias (appropriate methods outlined to deal with any design specific issues such as biased loss to follow or blinding) HIGH/LOW

4. Methods to control confounding (appropriate consideration of potential confounders on the relationship between walking speed and cognition) HIGH/LOW

5. Statistical methods (appropriate use of statistical analysis) HIGH/LOW

6. Conflict of interest (declarations of conflict of interest **or** identification of funding sources) HIGH/LOW

Appendix 2.1 Major Research Project Protocol

DOCTORATE IN CLINICAL PSYCHOLOGY

SUBMISSION FRONT PAGE

Name: Rachel Pritchett

Matriculation Number: 0404077

Name of Assessment: MRP proposal

Title of Project: Does walking speed predict change in cognitive function late after head injury?

Academic Supervisors: Professor Tom McMillan and Dr Lin Maclean

Submission Date to Supervisor: 17.7.17

Version Number: 2

Word Count: 3240

For Office Use Only

Date Received:

Abstract

Background

Late after severe head injury there can be change in disability for better or worse including increased risk of neurodegeneration. Neuropsychological assessment to detect change in function after head injury (HI) can be time consuming, difficult to access and expensive and a simple assessment that might be carried out in primary care would facilitate triage. Walking speed is a predictor of cognitive function following a stroke and in those with dementia. Although those with severe HI are at increased risk of cognitive decline, it is not known whether walking speed predicts cognitive decline in this at risk group.

Aim

To determine whether walking speed identifies cognitive change late after severe head injury.

Methods

This study will follow up to 100 participants who experienced a severe head injury on average 25 years previously and who took part in a study on walking speed and cognitive ability 2 years before the present study. At follow-up cognitive ability, walking speed and measures of physical and mental health will be repeated.

Analysis: Regression will be used to explore whether walking speed at baseline predicts cognitive change at follow up.

Introduction

It has been argued that severe head injury (HI) is a risk factor for neurodegeneration late after injury (Gupta, 2016). Dunning et al (2016) conducted a meta-analysis of 21 studies, in HI survivors. When compared to controls, those with a HI had significant deficits in memory and visuospatial skills. The impact of HI may be long lasting and may put people at higher risk of cognitive decline later in life (Ozen et al 2015). Wang et al (2012) conducted a retrospective cohort study on 269,550 people; at five year follow up an increased risk of dementia was found in individuals with HI. This enhanced risk can cause ongoing concern to the individual and their loved ones.

Research into predictors of cognitive decline has explored the importance of gait. Gait incorporates motor, perceptual and cognitive processes and encompasses the phases which make up the walking cycle (Ayyappa, 1997). Some studies look at gait speed alone while others utilise it as part of a dual task whereby participants are asked to walk while doing another cognitively demanding task, for example, talking. Of the following six studies, two utilised a dual task procedure (Doi et al and Assayag et al), whereas four looked at gait speed alone. Miekle et al (2012) conducted a large population based study (n=1478) on walking speed as a predictor of cognitive decline. They found that faster walking speed was associated with better performance in memory, executive function and global cognition when followed for 20 years. This is in line with findings from a number of studies showing an association between walking and cognition (Callisaya et al, 2015 & Buracchio et al, 2010). This association has been shown in several diagnostic groups including those with mild cognitive impairment (Doi et al, 2014), stroke (Assayag et al, 2015) and dementia (Verghese et al, 2016). Three of these studies (Doi et al, Buracchio et al & Assayag et al) looked at an association between gait and a measure of cognitive function. The other three studies (Callisaya et al, Verghese et al, & Miekle et al) looked longitudinally at how gait was associated with cognitive decline over time.

It is not known whether the association between gait and cognitive change is evident in people who have a severe HI. Walking speed offers the potential of a quick, easy and naturalistic method of detecting risk for cognitive change. It is known that those with severe HI are at increased risk of cognitive change over time (Millar et al, 2003; Whitnall et al 2006); hence exploring the potential role of walking speed in predicting this risk has important clinical and research implications. If it was established that walking speed predicts cognitive change in this at risk group, then it could be used as a tool to triage

patients presenting in primary care to further screening of neuropsychological assessment. This would help ensure they received an appropriate intervention as quickly as possible.

2. Aims and hypotheses

2.1 Aim

The aim is to explore walking speed as an assessment for cognitive change late after severe head injury. If an association between walking speed and cognitive change is found, then an additional aim will be to investigate whether a walking speed cut off can be established to capture those with cognitive decline (i.e. with good sensitivity and moderate/ good specificity).

2.2 Hypothesis

Primary: Walking speed at baseline (as measured by a dual task) is associated with cognitive change (as measured by the difference in cognitive scores between baseline and 2-year follow up).

Secondary: A reduction in walking speed between assessment and reassessment will be associated with a greater decline in cognitive test performance.

3. Plan of Investigation

3.1 Participants

Participants will be recruited from two historical research cohorts that recruited people with a severe HI (Millar et al, 2003; Teasdale et al, 2005) of whom 190 were further assessed between 2015 and 2017. This project will form part of a larger follow up study of these 190 participants, at two year follow up, 2017-2019.

3.2 Inclusion and exclusion criteria

Participants will be included if they took part in the baseline gait assessment in 2015-17. All will have a history of severe HI and baseline data on their cognitive ability and walking speed as assessed in 2015-2017. All participants must be considered capable of giving informed consent.

Participants will be excluded if they have suffered a serious neurological event since the baseline assessment (e.g. a stroke or further HI), a physical injury affecting walking or are not capable of being assessed.

3.3 Recruitment procedures

All participants recruited to the first phase of this study will be asked to take part in a follow up assessment, approximately two years after their last ('baseline') assessment. Although all 190 participants will be contacted as part of the larger study, data collection for this MRP will only include those eligible for follow up between June 2017 and April 2018. This will include up to 100 participants. The follow-ups will be carried out by RP from August/September 2017 and by a research worker who was involved in the baseline study.

3.4 Measures

Background questionnaire -This includes basic demographic data, including the participant's age, gender and occupation. In addition, it will explore whether the person has experienced any significant life events since their previous assessment.

Walking measure

Dual task: A dual task (DT) procedure requires an individual to perform two tasks simultaneously, and can be compared to performance in single task (ST) conditions (McCulloch, 2007), allowing by subtraction, a response cost to be calculated. In this instance, participants will first be timed to walk 6 metres (ST) and then to walk and count backwards from 100 in 3s for 30 seconds. In addition to completing these tasks singly, participants will also complete them simultaneously (i.e. walking and counting at the same time). This is the DT, and considers factors that may affect speed in the single task condition. In the DT condition, there are a number of different outcomes. Walking may be slower or less stable, or counting may be slower or less accurate. Poorer performance in either walking and/or counting could occur. Reduced performance in the DT condition is described as dual task cost (calculated as DT-ST/ST). Dual task cost may represent impaired capacity to share cognitive resources between walking and an attention demanding task. Both dual task walking speed and dual task cost will be included in analyses.

Disability Assessment

Glasgow Outcome Scale Extended (GOSE, Jennett & Bond, 1975)-A global scale for functional outcome that uses a structured interview to rate patient status into one of eight categories; ranging from dead to good recovery.

Cognitive measures

*Mini Mental State Examination (*MMSE, Folstein et al, 1975)- A screening tool to assess general cognitive function. It includes items of orientation, registration, short term memory and language functioning.

Verbal paired associates test (WMS-R)-A subtest within the WMS-R which assess episodic memory. Participants are given a list of two linked words and asked to remember which word is associated with which.

STROOP test-A measure of executive function where the participant is asked to name the colour a word is printed in when the word itself is the name of another colour. The score is a measure of time.

Symbol digit modalities test -A screening tool for cognitive impairment, the participant is asked to use a reference key to pair specific numbers with given geometric figures. The score is a measure of time.

Wellbeing measures

Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983) - A fourteen item questionnaire which includes 7 items relating to anxiety and 7 items relating to depression.

General Health Questionnaire-28 (Goldberg, 1978) -A measure of emotional distress in medical settings. This present study will include items one and two from the questionnaire, which ask the participant to report on their current health, and health over the past 12 months using multiple choice responses.

Alcohol Use Disorders Identification Test (Bohn et al, 1995) -A ten question checklist to determine if a person may be at risk for alcohol abuse problems.

3.5 Design

The study is a longitudinal within group study. Walking speed at baseline will be explored as a predictor of risk of cognitive change at 2 year follow up.

3.6 Research procedures

All potential participants (n=100) will be contacted by letter from Professor McMillan with the study information, 2 years following their baseline assessment (2017-2018). They will be asked to read the information and return the enclosed consent form in a prepaid envelope should they wish to participate. They will then be contacted by phone to ensure they meet the inclusion criteria and to schedule the assessment. The participant will complete the measures when they attend. They will be provided with travel expenses and supermarket vouchers to the value of £15 to compensate them for their time. The data will be stored securely in line with the Data Protection Act.

3.7 Data analysis

The primary research question is to explore whether walking speed during DT predicts cognitive change late after HI. Cognitive change is the primary outcome variable. A composite score for cognitive ability will be created by creating and combining Z scores for the participant's performance on the verbal paired associates, Stroop and symbol digit modalities tasks. These will be created initially using the means and standard deviations of the whole sample at baseline. Change in (i) this composite score, and (ii) change in MMSE score are the primary outcome variables measuring cognitive change. Regression analysis will then be conducted to explore the relationship between walking speed at baseline and cognitive change. Age at baseline and number of years in education will be included in the model at baseline. If an association is found, sensitivity and specificity analysis will then be conducted to explore whether a clinically effective cut off score can be established to capture those showing cognitive decline.

If walking speed predicts change over time, then it is also of interest to explore change in health over time. Disability (GOSE), perceived health (GHQ-28) and mental health (HADS) will therefore also be explored as outcome variables. Change in a participant's alcohol use (AUDIT) will be explored as a potential confounder and controlled for if necessary.

A secondary RQ is that change in walking speed between baseline and follow-up will be associated with change in cognitive function. There would be an expectation that if there is

general decline as indicated by cognitive function then this would also be reflected in the predictor variable (i.e. that DT walking speed should also decrease).

3.8 Justification of sample size

The key analysis on this study is determination of the association between gait measures at baseline and change in cognition/outcome at time 2. There has not been research on gait and HI that is relevant to estimating sample size required for this study. Existing studies on gait and cognitive decline have largely used healthy adults or older adults at relatively high risk of cognitive decline, with gait as an outcome measure. There is also limited research on change in function over time after HI in the same participants, and this has been at different time points after injury. For example, Millar et al (2003), reported deterioration on the GOSE between 6 months and on average 18 years after injury in almost a third of 396 severe HI patients. Whitnall et al (2006) reported improvement or deterioration on the GOSE between 1 and 5-7 year follow-ups 54% of HI participants.

G Power indicates that with alpha set at 0.05, power at 0.8, and a medium effect size (*f*) of 0.30 that 82 participants are needed (Faul et al, 2009). In the absence of published literature relevant to this study's aims, Ferguson (2009) suggests that the minimum effect size needed for practical significance in social science research is 0.2; with an approximate n of 102 proposed here, an effect of 0.27 could be detected. If an effect size of 0.3 was achieved with a sample size of 100 then this study would have 0.88 power.

3.9 Settings and equipment

Research assessments will take place in the Clinical Research Facility within Glasgow Royal Infirmary. Questionnaire measures will be collected on paper. In addition, a marked out 6 metre length and stopwatch, will be required to complete the dual task.

4. Health and Safety Issues

4.1 Researcher safety issues

There are no known researcher safety issues. Data will be collected in NHS buildings where standard safety protocols will be adhered to. All participants have already been assessed by the research team in the past 2 years.

4.2 Participant safety issues

There are no known participant safety issues. All participants will have undergone a similar assessment 2 years prior. There is a short task where they are asked to walk a

short distance, however the exclusion criteria excluding anyone with walking difficulties should minimise any potential risk in this task.

5. Ethical Issues

The study has ethical approval from the West of Scotland NHS Research Ethics committee (ref 14/WS/1145). The participants will all be previous research participants, who have given their consent to be contacted again for future studies. Furthermore, the procedure will be similar to one which they have already undertaken. Written consent will be obtained. Participants will be free to withdraw from the research at any time.

A potential ethical issue may arise if someone shows significant cognitive decline. Any cognitive change will be primarily explored using the MMSE, an established screening tool. If someone presents with significant decline, as assessed using age and education normed clinical cut offs (Lezak, 2004), they will be asked to consent for their results being shared with their GP.

As ethics approval has already been obtained, I will complete an IRAS form to be checked and approved by my supervisors in relation to achieving this research competency.

6. Financial Issues

The main costs for this study are measures, participant travel expenses and honorarium, printing and postage costs. A full breakdown is included in the attached equipment form. Participant costs will be covered by the main research project.

7. Timetable

The proposal for study will be finalised by July 2017. The aim will be to commence data collection in August/September 2017 until April 2018. The data will then be analysed and results written up in preparation to submit in July 2018.

8. Practical Applications

It is hoped that the results will help in identifying assessment a simple test that can predict risk of cognitive change late after severe HI. Being able to predict cognitive change in an 'at risk' group provides an opportunity for early intervention. Individuals and their families can be offered support earlier and it may provide more opportunities for better treatment outcomes.

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Appendix 2.2 Ethical approval

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 5
West of Scotland Research Ethics Service
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SW

Professor Thomas McMillan
Professor of Clinical Neuropsychology
University of Glasgow
1st Floor, Mental Health and Wellbeing
Admin building, Gartnavel Royal Hospital
1055 Great Western Road, Glasgow
G12 0XH

Date 05 April 2017

Direct line 0141 232 1809
E-mail WoSREC5@ggc.scot.nhs.uk

Dear Professor McMillan

Study title: **An investigation of heterogeneity of outcome late after head injury**
REC reference: **14/WS/1145**
Amendment number: **3**
Amendment date: **23 March 2017**
IRAS project ID: **159844**

Summary of amendment: *Researchers wish to follow up participants who took part in the study and agreed to be contacted about further research participation, this will be a 2 year follow-up.*

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
GP/consultant information sheets or letters	1	21 March 2017
Letters of invitation to participant	1	21 March 2017
Non-validated questionnaire [General Questionnaire Update]	2	21 March 2017
Notice of Substantial Amendment (non-CTIMP) [REC ref AM05]	3	23 March 2017
Other [Participant Final letter]	1	21 March 2017
Participant consent form	3	21 March 2017
Participant information sheet (PIS)	3	21 March 2017
Research protocol or project proposal	8	21 March 2017
Validated questionnaire [General Outcome Scale Extended Postal Version]	1a	23 October 2008

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

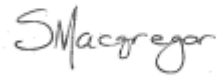
Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/WS/1145:	**Please quote this number on all correspondence**

Yours sincerely



for
Dr Stewart Campbell
Chair

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms Joanne McGarry, NHS Greater Glasgow and Clyde
Ms Emma-Jane Gault, University of Glasgow

Appendix 2.3 Participant Information Sheet

PARTICIPANT INFORMATION SHEET

TEAFOL 17

An Investigation of Heterogeneity of Outcome Late after Severe Head Injury

You recently helped us in a research study on head injury and we would like you to help us once more. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
We are carrying out studies on head injury to investigate why outcome can be different in different people and why, in some, disabilities can change over time.

Why have I been chosen?
You have been chosen because you took part in a study with us before on head injury about two years ago and seeing you again will help us to understand whether there has been any change in your health or abilities since we saw you last.

Do I have to take part?
It is up to you to decide whether or not to take part. You will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?
You will be invited to attend for a single assessment lasting about 60 minutes. This is much the same as the last assessment but a bit shorter. It will involve:
(i) a brief interview about recent health and history of head injury (ii) questionnaires about psychological wellbeing; (iii) tests of cognition such as concentration and memory; (iv) basic physical measurements such as lung capacity; (v) a 10ml blood sample (about two teaspoons) which we will use to check for markers we think may be relevant to outcome after a head injury. You will be offered vouchers for £20 that you can use in Tesco, Asda, Sainsburys or Boots to compensate you for your time.

Where will the assessment take place?
The assessment will take place in Glasgow. If you are unable to attend we can obtain some information by telephone.

What do I have to do?
You just have to attend for the assessment and not have consumed alcohol on that day.

What are the possible disadvantages and risks of taking part?
There are no particular disadvantages to taking part. There can be temporary bruising at the needle site, but only occasionally do some people feel faint when a blood sample is being taken.

What are the possible benefits of taking part?
You will receive no direct benefit from taking part. The information collected in the study will give us a better understanding of any long term effects of head injury and may allow us to make recommendations for health service improvements.

Will my taking part in this study be kept confidential?
All information collected about you during the research will be kept strictly confidential. You will be identified by an identity number, and any information about you will have your name and address removed so that you cannot be recognised from it. Scientific publications arising from the research will not identify any individual.

What will happen to the results of the research study?
When the project is completed, the findings will be submitted for publication in peer reviewed international journals.

Who is organising and funding the research?
The research is organised by the University of Glasgow. The research is funded by the University of Glasgow, the Chief Scientist Office and by the Sackler Foundation.

Who has reviewed the study?
The project has been reviewed by the University of Glasgow College of Medical Veterinary and Life Sciences and by the West of Scotland NHS Ethics Committee.

Contact for Further Information
You can contact Claire McLeod or Dr Lin Maclean who will be arranging and carrying out the assessments: 0141 211 3901; claire.mcleod@glasgow.ac.uk; linda.maclean@glasgow.ac.uk or Professor Tom McMillan thomas.mcmillan@glasgow.ac.uk (0141 211 0354) who is organising the research.

Thank you for considering this request to take part in the study.

Appendix 2.4 Consent form

Participant ID Number: _____

TEAFOL 17

CONSENT FORM

Title: An Investigation of Heterogeneity of Outcome Late after Severe Head Injury

Please initial box

1) I confirm that I have read and understand the information sheet dated March 2017 (Version 3) for the above study and have had the opportunity to ask questions. ☐

2) I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected. ☐

3) I agree to take part in the above study. ☐

4) I agree that the researchers can obtain NHS records pertaining to any hospital admission that I have had. ☐

5) I understand that anonymous data collected during the study, may be looked at by individuals from University of Glasgow, from regulatory authorities or from the NHS Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

6) I agree to my data being retained for 10 years, including following loss of capacity. I understand this is for the purpose of future research ad that all data will be destroyed confidentially after this period. ☐

7) I agree that I can be contacted about future studies on head injury. ☐

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix 2.5 Regression assumptions

Prior to conducting the regression, it was important, firstly, to investigate whether the model fits the observed data well or whether instead it is being influenced by a small number of cases, and secondly to see if the model can be generalised to other samples. The process which was worked through is outlined in Field (2009).

Firstly, an investigation was carried out into how accurate the regression model was. This was firstly done by looking for outliers and residuals. It would be expected that 95% of cases to have standardised residuals within ±2, with approximately 5% outside of these limits. In a sample of 48, there were 2 cases (4.17%) lying outside these limits in the MMSE regression and 1 case (2.08%) in the Z score regression, therefore the sample appeared to conform to what would be expected for a fairly accurate model. There were no cases with a standardised residual greater than 3, so none which raise concerns. In addition, there was an investigation into whether certain cases were having a large effect on the model using Cook's distance, where values greater than 1 give cause for concern. The highest Cook's value within the sample was 0.331, so this does not appear to be a problem.

Secondly it was important to investigate whether the model could be generalised to other samples, so that it could be assumed that any findings would be true for a wider population. For a regression model to generalised, it is necessary to make sure that underlying assumptions have been met, again as outlined in Field (2009):

Variable types: The variables are all measures at the interval level;

Non-zero variance: The predictors all have some variation in value;

No perfect multicollinearity: The independent variables to not correlate too highly with each other, with none have correlations >0.9. In addition, there are no variance inflation factors (VIF) greater than 10 or below 0.2, therefore no multicollinearity in the sample could be assumed;

Predictors are uncorrelated with 'external variables': There are no known variables which have not been included in the regression model but which correlate with the predictors and influence the outcome variable;

Homoscedasticity: scatter plots show that the residuals at each level of the predictors have similar levels of variance;

Independent errors: for any 2 observations, the residual terms are uncorrelated, as tested by the Durbin-Watson test, where a value of 2 means the residuals are uncorrelated; the values for this analysis were 1.915 (z score regression) and 2.019 (MMSE regression) which gave no cause for concern.

Normally distributed errors: the residuals in the model are random, showing normally distributed variables with a mean of 0;

Independence: all the values of the outcome variable are independent;

Linearity: the mean value of the outcome variable for each increment of the predictor lies along a straight line.

Overall, the assumptions for conducting regression with this sample were met: it could be seen that the model was a good fit for the data and should be generalised to other samples. It was therefore possible to analyse the data as planned.

Appendix 2.6 Additional analysis

Dual task and STMBT. Univariate regression analysis

	Variable	B	SE B	Significance
Dual task walking	Shape Memory	-0.00	0.00	0.27
	Memory binding	0.00	0.00	0.57
	Memory binding cost	-0.00	0.01	0.89
Dual task walking cost	Shape Memory	-0.02	0.03	0.46
	Memory binding	0.05	0.05	0.33
	Memory binding cost	-0.04	0.05	0.48
Dual task counting	Shape Memory	0.06	0.03	0.07
	Memory binding	-0.07	0.07	0.32
	Memory binding cost	0.06	0.06	0.33
Dual task counting cost	Shape Memory	0.01	0.02	0.77
	Memory binding	-0.02	0.03	0.54
	Memory binding cost	0.01	0.03	0.77