Virtual Reality-Based Smartphone Applications for the Assessment of Post-Stroke Unilateral Spatial Neglect

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Declaration

I, Charif Sada, hereby declare that this thesis and the work presented in it is entirely my own.

Where I have consulted the work of others, this is always clearly stated.

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Abstract

Unilateral spatial neglect (USN) is a post-stroke defect in one's ability to detect, respond or orient to stimuli presented on the contralesional side. Due to USN's heterogeneity, current assessment tools have been limited to pencil and paper or behavioural tasks. However, these assessments suffer from low detection sensitivity of mild to moderate forms of USN and lack ecological validity.

Virtual reality (VR) is a novel technology that has been used increasingly in various medical fields, including cognitive assessment and rehabilitation, due to its superior features in mimicking real-life scenarios and providing a higher degree of ecological validity to conventional assessments.

Armed with passion to develop virtual systems for the future, we created three fully immersive VR prototypes for the assessment of USN. Two applications developed were VR street-crossing systems - one utilising physical commands with Microsoft Kinect Motion Sensor, and the second utilising verbal commands through Microsoft Cortana Voice Assistant. The third VR application – objection detection and collection, used Leap Motion Controller to detect hand gestures in a virtual environment. Following prototype evaluation across different settings, protype two - USN-VR street-crossing using Microsoft Cortona, was deemed fully operational and performed satisfactorily, and was thus piloted to assess its feasibility and accuracy for the assessment of USN.

In the first two chapters, the USN disorder and VR technology are discussed. Chapter three presents the aims, objectives, and hypotheses of this project. Chapter four is a systematic review of USN assessments, including VR, whereas Chapter five is a review of USN interventions reported in the literature.

Chapter six focuses on the technical aspects of prototype development and summarises the evaluation process conducted to assess the prototypes developed.

In Chapter 7, findings of a pilot study are presented. The pilot study aimed to compare the ability of the VR street crossing task to detect USN with that of two widely used paper. Chapter 8 is a thematic analysis of qualitative interviews conducted with stroke patients to assess the acceptance and usability of the VR task developed.

The final chapter summarises findings of this thesis and provides reflections, lessons learned and recommendations for future studies.

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Chapter 1

Post-Stroke Unilateral Spatial Neglect: A General Introduction

History of the Term "Stroke"

From ancient times to the present day, humankind has continually had to deal with strokes and their ramifications (Resende et al. 2008; Starostka-Tatar et al. 2017). Apoplexy [from ancient Greek ἀποπληξία (apoplexia) meaning 'a striking away'] – was a term used by the Greeks, and is still employed today, to describe an illness where patients would suddenly fall to the ground, struggle to make voluntary movements and lose their senses (Engelhardt 2017). The effects of this disease are extremely rapid in nature such that persons appear to have been "struck by lightning" (Clarke 1963; Cooke 1820; Storey and Pols 2009). The word 'stroke' first appeared in English literature in the late 16th century (Algeo, Barnhart, and Steinmetz 1989). For centuries, the word 'stroke' was primarily used as a lay term to convey an "act of striking" whereby a blow is given or received (Pound, Bury, and Ebrahim 1997). However, historical records reveal that physicians favoured the term 'apoplexy' from the era of Hippocrates (c. 460 BC – c. 370 BC) up until the mid-twentieth century to describe the medical condition commonly known today as 'stroke' or 'cerebrovascular accident' (Caplan 1990; Nilsen 2010; Pappert and Goetz 1995). In 1962, the UK-based Chest and Heart Association published a booklet titled "Modern Views on 'Stroke' Illness" which laid the foundations for the development of a new system of management for 'stroke illness' (London 1962). The Association booklet stated that while 'stroke illness' is more of a lay term, the word 'stroke' alone represents a more "convenient expression". The publication of the above-mentioned booklet led to the adoption of the term 'stroke' by a wide range of healthcare professionals, and from this point onwards the term 'apoplexy' started to gradually disappear from modern medical literature (Pound et al. 1997).

Pound et al (1997) argued that the adoption of the word 'stroke' signified a shift – not only in the terminology but also in doctors' understanding and treatment of this illness – that is, opting

for a lay word over a medical term denotes the return to the centrality of the individual rather than the case, where particular emphasis is placed on the subjective experience of the condition.

Stroke

Stroke [also known as cerebrovascular accident (CVA)] is defined by the World Health Organisation as "rapidly developing clinical signs of focal disturbance of cerebral function lasting more than 24 hours, or leading to death, with no apparent cause other than that of vascular origin" (WHO 1988). There are two main types of stroke: one caused by a clot which interrupts the blood supply to the brain [ischemic stroke] and accounts for approximately 80% of all cases, the other caused by the rupture of a blood vessel in the brain [haemorrhagic stroke] and accounts for about 20% of all stroke patients (Krafft et al. 2012; Warlow 1998).

Stroke is the fourth largest cause of death in the UK (Wafa et al. 2020; Wang 2020). Although the significant medical advances made in the diagnostic and treatment strategies of stroke have decreased the mortality rate, a recent report by the Stroke Association stated that over 1.2 million stroke survivors reside in the UK – the cost of care for whom is an estimated £26 billion per year. According to the same report, a stroke occurs every five minutes in the UK, amounting to more than 100,000 stroke events every year. Nearly two-thirds of stroke survivors are reported to have a stroke-related disability upon discharge from hospital. The incidence of stroke in the UK is expected to rise to just under 200,000 events per year by 2035, when the population of stroke survivors is projected to reach over 2 million (Stroke Association 2018).

Several studies have reported that the early discharge of stroke survivors, due to increasing pressure on hospitals, leave many patients struggling to independently perform simple daily activities (Kjærhauge Christiansen et al. 2020; Wray and Clarke 2017). This may increase the risk of accidents and injuries as well as the frequency of return to rehabilitation centres (Brewer and Williams 2010; Langhorne et al. 2005; Mas and Inzitari 2015). Thus, understanding stroke patients' functional abilities prior to discharge to independent living is key to reducing the risk

of accidents and frequency of visits to rehabilitation clinics. Among the various PSCIs, unilateral spatial neglect (USN) is often associated with poor functional ability (Caggiano and Jehkonen 2018; Jehkonen, Laihosalo, and Kettunen 2006).

Unilateral Spatial Neglect (USN)

USN is a common post-stroke cognitive impairment, affecting approximately 30% of all stroke survivors. (Hammerbeck et al. 2019) Whilst both left and right hemisphere lesions may cause USN, right-sided lesions are far more likely to lead to more frequent and severe forms of USN (Bartolomeo, Thiebaut de Schotten, and Chica 2012; Kerkhoff 2001; Vuilleumier 2013). USN affects two-thirds of patients with right hemisphere lesions in the acute stage (Parton, Malhotra, and Husain 2004a), whereas chronic USN affects about 15% of stroke patients (Chen et al. 2015; Karnath et al. 2011a). USN is defined as the failure to process and respond to stimuli presented on the contralesional side of brain damage (i.e. the right side for patients with left hemisphere lesions and vice versa) (Adair and Barrett 2008; Heilman KM, Watson RT 1993). Lesions in the right hemisphere are far more likely to lead to severe and enduring neglect than those in the left hemisphere (Verdon et al. 2010). This may be because one of the dominant functions of the left hemisphere is language processing (in right-handed people) (Suchan and Karnath 2011). Therefore, it is less involved with visuo-perceptual function, and damage results in dysphasia which allows earlier self-detection and treatment (Ihori, Kashiwagi, and Kashiwagi 2015). However, a number of other factors are probably involved in hemispheric differences in USN (Li and Malhotra 2015).

USN impairs the ability to explore and navigate the environment, and to detect and locate objects (Halligan et al. 2003). USN symptoms are heterogeneous but can be categorised into three groups of impairment: i) spatial attention and orientation deficits, ii) spatial awareness deficits and iii) non-spatial attention deficits (Fordell et al. 2011a; Ogourtsova et al. 2017).

Studies report a hemispheric difference among USN patients, with significantly higher incidence rates observed with right hemisphere lesions (Kleinman et al. 2007; Luukkainen-Markkula et al. 2011). For example, Stone and colleagues assessed the incidence of USN in 171 patients with an acute hemispheric stroke (102 left hemisphere, 69 right), and reported USN frequencies of 82% and 69% for right and left hemisphere damage, respectively (Stone, Halligan, and Greenwood 1993). Estimates of right spatial neglect, following a left hemisphere stroke, significantly vary from 0 to 76% across studies (Kinsella and Ford 1980; Stone et al. 1991). This may be due to speech impediments associated with left hemisphere damage (Beis et al. 2004). Heterogeneity also exists in studies assessing patients with right hemisphere damage. Some studies report USN frequencies at approximately 50% during the acute phase (Appelros et al. 2002; Buxbaum et al. 2004).

USN is frequently associated with lesions in the inferior parietal lobe and superior temporal cortex, and infrequently associated with lesions of the white matter tracts (Karnath, Ferber, and Himmelbach 2001; Mort et al. 2003). Rarely, USN may arise from lesions in the subcortical regions including the basal ganglia, thalamus and cingulate cortex. However, subcortical lesions are associated with more severe forms of USN (Fruhmann Berger, Johannsen, and Karnath 2009; Parton et al. 2004a). The right hemisphere dominance of USN stems from the anatomy of a partially lateralised attention function of the right hemisphere's ventral pathways (Corbetta and Shulman 2011; Vuilleumier 2013).

USN is often described as a heterogeneous disorder that manifests differently among stroke survivors (Karnath and Rorden 2012). USN can be sensory (visual and/or auditory), motor (decreased or absent ability to move one limb despite having little or no weakness), or both (Li and Malhotra 2015). USN is therefore a challenging condition to understand, assess and thus rehabilitate as some patients present with more than one type of USN at once – making it difficult for clinicians and researchers to develop a gold-standard assessment that can

accurately detect various forms of USN, not to mention that the above-mentioned USN categories are further subdivided into subcategories requiring multiple assessments that are costly, time-consuming and often exhausting for patients (Azouvi 2017; Ten Brink, Visser-Meily, and Nijboer 2018; Rengachary et al. 2009).

Patients with visual neglect usually fail to detect objects in one or more of the following spatial frames: personal space (related to one's body parts), peri-personal (sometimes referred to as near extra-personal space or within one's reach), and far extra-personal space (beyond one's physical reach) (**Figure 1.1**) (Kerkhoff 2001).

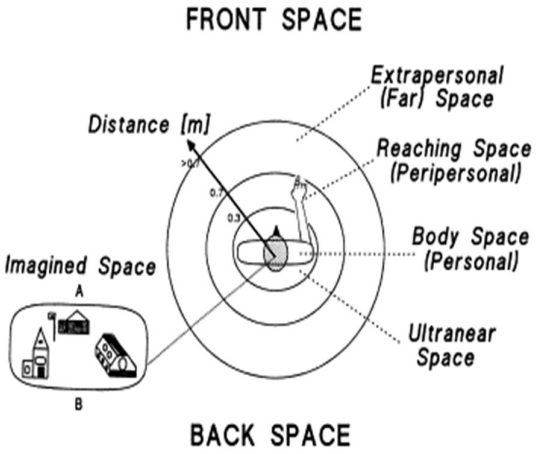


Figure 1. 1 Most commonly affected spatial ranges in USN (Kerkhoff 2001).

Additionally, some patients are unable to detect both visual and auditory stimuli presented on the neglected side (Smith et al. 2010). Furthermore, some USN patients may present with auditory neglect which is harder to diagnose than visual neglect. Auditory neglect is defined as the inattention to stimuli presented on the left hemispace of patients with right-hemisphere lesions (Bellmann, Meuli, and Clarke 2001).

The second main category of USN is motor neglect, which is defined as the failure to use the limbs contralateral to brain damage despite having little or no weakness in the contralesional limbs (Laplane and Degost 1983). Some patients, however, may use their contralesional limbs but only when they are strongly and repeatedly encouraged to do so (Punt and Riddoch 2006). In addition to the above-mentioned types of USN, numerous USN subtypes are well-documented in the literature including:

i. Personal USN (anosognosia) – this is particularly common in the acute stage. In extreme cases, USN patients may fail to recognise their own body parts (Caggiano and Jehkonen 2018).

ii. Egocentric USN – neglect from the patient's perspective (self-to-object). In this case, USN patients with right hemisphere lesions completely miss the left (contralesional) side of space (Chechlacz et al. 2012).

iii. Allocentric USN – neglect from the standpoint of the object that the patient neglects. Here, USN patients miss the left side of an object irrespective of where the object is placed in space (Jang and Jang 2018).

Studies have reported that the different locations of brain lesions, as well as the extent of brain damage, are the main contributors to USN heterogeneity and, thus, the various manifestations of the disorder seen among stroke survivors (Buxbaum et al. 2004; Molenberghs, Sale, and Mattingley 2012).

Several studies have compared stroke patients with and without USN, and found that the presence of USN is strongly associated with poorer functional outcomes as well as longer hospital stays - not to mention that USN patients were found to be more dependent on carers and required more assistance (Gerafi et al. 2017; Di Monaco et al. 2011; Stein, Kilbride, and Reynolds 2016).

For example, Di Monaco and colleagues investigated the correlation between severity of USN and functional recovery in ADLs in 107 patients with right hemisphere stroke in a rehabilitation hospital in Italy. All patients underwent the same rehabilitation protocol which included assessments such as the Functional Independence Measure (FIM) – an assessment that examines the disability level of patients through their need for assistance or aids while performing ADLs.

Further, all patients performed three USN assessments during the first three days of their rehabilitation stay. The three USN assessments were:

- The conventional Behavioural Intention Test (BIT) consisting of six subtests
- The nonconventional BIT which is a longer version than the conventional test (it consists of nine subtests)
- and Diller's test which is a double letter cancellation test

According to Di Monaco et al, 54 patients (50.5% of the total sample) had USN. Further, there was a significant correlation between the conventional and nonconventional BIT scores and the FIM scores of USN patients assessed at discharge from rehabilitation (ρ values were .385 (P=.004) and .396 (P=.003), respectively) (Di Monaco et al. 2011).

It has been reported that the prevalence of USN tends to decrease with time, with most recovery occurring within the first few weeks following a stroke – after which most patients reach a plateau (Nijboer, Kollen, and Kwakkel 2013; Stone et al. 1993).

Whilst the majority of stroke survivors with USN tend to recover rapidly, some with more persistent symptoms experience various difficulties, and thus fail to perform simple everyday tasks such as eating, dressing, and crossing the road (Grech et al. 2017). Failure to carry out such tasks has been reported to increase the patient's risk of accident and injury (Czernuszenko and Czlonkowska 2009). For example, patients with left-side USN may not look to the left when crossing the road and fail to detect objects on the neglected side, which may lead to dangerous accidents and make it virtually impossible to live safely and independently. Thus, USN patients with persistent symptoms require assistance with everyday activities which in turn places an emotional and financial burden on the families of patients (Buxbaum et al. 2004).

Attention Networks of the Human Brain

The complex interaction between human and environment yields a tremendous amount of sensory information (Bassett and Bullmore 2009; Macaluso and Doricchi 2013; Ptak and Schnider 2011). Given that processing such a vast quantity of input at once is beyond the capacity of the human brain, sensory information cannot be treated equally (Chica and Bartolomeo 2012). The attention system operates in a manner that determines which information to prioritise when and why, to ensure appropriate responses are produced in different situations (Lu et al. 2012; Posner 2012). For example, we may not notice misplaced house keys when we are preparing dinner after work, but we can easily locate them when we are about to leave for work the next morning. Therefore, *attention* is, generally, a mechanism through which we can determine what information to prioritise when, using a selective filtering process that allows us to respond to or ignore stimuli depending on the degree of relevancy of the stimulus at a given point of time. However, the distribution of the attention ability across an environment is often referred to as *spatial attention* (Carrasco 2011; Vecera and Rizzo 2003).

To try and establish an understanding of the attention deficits experienced in USN, one must study the attention system of the human brain. Over the past few decades, significant advances in neuroimaging techniques have made it possible for researchers to establish with increasing accuracy the various brain regions involved in the system of attention (Pessoa and Ungerleider 2004; Posner and Fan 2008; Vossel, Geng, and Fink 2014).

The attention system of the human brain can be divided into three main networks, each involved in a specific function of attention. These networks are:

I. **The Alerting Network** - the role of this network is to attain and maintain an optimal vigilant state. The brain regions involved in the alerting network include the locus coeruleus located in the pons of the brainstem, as well as the frontal and parietal cortex.

Conditions associated with a dysfunctional alerting network include attention-deficit/hyperactivity disorder (ADHD) and disorders related to ageing as a primary risk factor, such as Alzheimer's disease (Aston-Jones 2005; Posner, Rothbart, and Ghassemzadeh 2019) .

II. **The Orienting Network** – as our senses are constantly bombarded with a wide range of, and often competing, environmental sensory stimuli, the role of the orienting network is to ensure that certain sensory inputs are prioritised and responded to with the appropriate modality. Brain regions involved in the orienting network include cortical (ventral and dorsal frontal and parietal regions) and subcortical (e.g. pulvinar) areas. Disorders associated with an impaired orienting network comprise post-traumatic stress disorder (PTSD), autism and *unilateral spatial neglect (USN)* (Corbetta and Shulman 2002; Petersen and Posner 2012; Posner and Petersen 1990) .

III. **The Executive Network** – this network is focused on executive attention, meaning that it acts as a control panel that governs 'target detection' and produces voluntary responses to stimuli. One of the limitations of the attention system is that while it is feasible to scan for many targets using various processing streams, target detection - which is often referred to as focal attention - works in a manner that slows down the detection, and therefore the awareness, of one target in favour of another, particularly in situations where conflicting stimuli, and thus responses, are likely. Brain structures involved in this network include the anterior cingulate, anterior insula and basal ganglia. Studies have reported a number of psychological disorders associated with a dysfunctional executive network including anxiety, depression and obsessive-

compulsive disorder (OCD) (Corbetta and Shulman 2002; Posner and Petersen 1990; Posner et al. 2019).

Major Theoretical Accounts of USN

Over the past three decades, it has been well established that the right posterior parietal cortex (PPC) plays a primary role in the process of visuospatial attention. Such is the dominance of the right PPC that lesions in the right hemisphere lead to significantly stronger USN symptoms compared to the left hemisphere (Andersen and Buneo 2002; Behrmann, Geng, and Shomstein 2004; Vuilleumier 2013).

A number of models have been proposed to account for the mechanisms of USN. Prominent among them is the 'interhemispheric competition' model by Kinsbourne, which was first published in 1970, and was later updated and expanded (1970; 1987; 1994). Here, Kinsbourne affirmed that while in healthy subjects both hemispheres have an equal tendency to direct attention to the contralateral side of space, the right hemisphere tends to exercise stronger effects compared to the left hemisphere. Kinsbourne noted that to ensure an optimal gradient of neural activity is maintained, there is a sort of competition between the two hemispheres and each hemisphere can reciprocally inhibit the activity of the other (Kinsbourne 1970, 1987, 1994).

More importantly, following a brain injury in either hemisphere as a result of stroke, the other damage-free hemisphere goes into "hyperactivity mode" to compensate for the damaged hemisphere. According to this model, left unilateral neglect patients appear hyperattentive to the ipsilateral side of space – that is, the right side for stroke patients with right-hemisphere lesions, as a result of the left-hemisphere's hyperexcitability which is apparently caused by the lack of activity in the right hemisphere. Several imaging studies have provided evidence to

confirm the hyperexcitability theory of the damage-free hemisphere which leads to hyperattention on the ipsilateral visual fields (Kinsbourne 1970, 1987, 1994).

Heilman and Van Den Abell (1980) proposed the 'hemifield' model in an attempt to explain post-stroke attentional asymmetries. The authors proposed that the left hemisphere can only direct attention to the contralateral side of space, whereas the right hemisphere is able to attend to stimuli on both the ipsilateral and contralateral hemispaces; the right hemisphere can therefore compensate for left hemisphere damage, but the left cannot compensate for right-sided damage. Indeed, the authors argued that this theory may explain why right hemisphere damage yields far more persistent neglect symptoms compared to left-hemisphere damage (Heilman and Van Den Abell 1980).

Another prominent account for the mechanism of USN is one proposed by Posner and colleagues which, to a certain extent, resembles the Kinsbournse's model. Posner et al designed and administered a series of tasks known as the "Posner Cueing Task" or "Posner Paradigm" that has become a widely accepted method of measuring attention. Although the original task was proposed by Posner and colleagues in the 1970s, investigators have opted for different variations of the original task over the past four decades. The typical order of events in this test, however, remains unchanged (Hayward and Ristic 2013; Perchet et al. 2001; Posner et al. 1987; Posner and Boies 1971).

The original Posner task, which consists of 100 trials, requires participants to be seated in front of a computer screen or monitor positioned at eye level. On the monitor, a point of fixation in the form of a dot or cross, and two boxes - situated at an equal distance of the right and left side of the fixation point - are presented. For a very brief interval, a visual cue (for example, a flashing light) points to, or is presented in, one of the boxes on either side of the fixation point – the cue is then rapidly removed and is followed by a stimulus (letter, word or shape etc…). The participant is required to indicate the location of the stimulus as quickly as possible,

typically using a response mechanism that normally involves a keyboard with two pre-specified keys for right and left targets. This response mechanism is used to measure the participant's reaction time (RT). The visual cue can be valid or invalid. In the valid trial, the cue appears at or indicates the correct location of the stimulus, whereas the invalid cue appears at or points to the incorrect location of the stimulus that swiftly appears following the removal of the cue. The number of trials, type of visual cue and number of valid and invalid cues can be adjusted by the investigator (Posner 1980; Posner and Cohen 1984).

Posner and colleagues carried out a series of experiments on healthy and stroke subjects in which they attempted to induce bias in attention using visual cues as indicators of where the stimulus is likely to appear. Posner et al reported that some of the normal and stroke subjects, who showed a tendency to neglect one side of space, managed to detect the stimulus more rapidly when a valid cue was provided. Yet in trials where an invalid cue was presented (the aim of which is to mislead the participant to believe that the target stimulus will appear on the normal side but instead it appears on the neglected side of space), stroke subjects showed disproportionate impairment. The authors maintained that a difficulty in voluntarily disengaging attentional "spotlight" from the normal (where the invalid cue appears), to the neglected (where the target stimulus appears) side, has led to the observed effect of an invalid cue, and that it is possible to overcome the visual deficit by cuing subjects to shift the "spotlight" to the neglected side of space (Posner 1980; Posner et al. 1987; Posner and Fan 2008).

The most influential model of explaining the mechanism of USN was presented in the early 2000s, when Corbetta & Shulman (2002; 2011) published a widely studied review in which they proposed a model that involves two somewhat separable attention networks in the brain both of which are located in the parietal lobe (Corbetta and Shulman 2002, 2011). These networks are:

I. The dorsal frontoparietal attention network (DFAN)

II. The ventral frontoparietal attention network (VFAN)

While the DFAN shows bilateral representation across both hemispheres, the VFAN displays asymmetrical representation as it has been shown to be more lateralised to the right hemisphere in healthy subjects. In Corbetta & Shulman's model, the DFAN was generally presumed to control the internally and voluntary guided direction of attention also referred to as "top-down, memory dependent" attention, whereas the VFAN was proposed to dictate the "bottom-up, memory-free" allocation of attention, that is, attentional guidance triggered by external and unanticipated salient stimuli; hence, the response to which is reactive in nature (Corbetta and Shulman 2011).

One of the major features of USN is the failure to voluntarily allocate attention to the contralateral side of space. This deficit indicates an impaired DFAN which, in healthy individuals, governs the internal voluntary guidance of attention. However, a large body of literature has frequently associated USN with a damaged ventral pathway which is responsible for the bottom-up deployment of attention to unexpected but relevant external stimuli. Corbetta & Shulman proposed that the two networks dynamically interact with one another depending on the demands of the task at hand. The authors concluded that a disruption across both networks is the likely causality of USN and may offer a better explanation of this syndrome and placed particular emphasis on further understanding the complex interplay between these networks, especially in the context of hemispheric specialisation and nature of interaction (Corbetta and Shulman 2002, 2011).

International Classification of Functioning, Disability and Health

Published in 2001 by the World Health Organisation (WHO), the International Classification of Functioning, Disability and Health (ICF) is a comprehensive framework for the

classification, management and documentation of information related to functioning and disability (WHO 2001). The ICF encompasses major models of disability, namely the medical model and social model, thereby integrating both into a "biopsychosocial model" (Stucki, Cieza, and Melvin 2007). The ICF model does not only consider health conditions, functioning and disability - but also recognises the role of environmental factors in the causation and exacerbation of disability. In other words, the ICF gestates functioning as a "dynamic interplay" between several factors, including a person's health conditions, environmental and personal factors (Dahl 2002).

Further, the ICF set forth a standard language to define, describe and measure disability. This language is supplemented with classifications and codes (Kostanjsek 2011). According to the ICF, functioning and disability are blanket terms indicating the positive and negative features of functioning via a multi-dimensional, biopsychosocial lens which encompasses biological, individual, and social factors (WHO 2001). The ICF's definitions and classifications are expressed using neutral terminology. This neutral language allows the classification to be used in a manner that documents various characteristics of functioning; that is, both the positive and the negative aspects, rather than one or the other only (Badley 2008).

The ICF's multidimensional model is aetiology-neutral, meaning that aetiology does not determine the classification of disability (Stucki et al. 2007). In the process of classifying functioning and disability, the ICF makes no implicit or explicit differentiation between different health conditions [i.e., disability is not classified according to aetiology]. The ICF emphasises that medical diagnosis alone cannot determine the level of participation in everyday life (Vargus-Adams and Majnemer 2014). For example, if a person cannot perform simple everyday activities such as walking and going to work, this inability could be related to any one of several health conditions. In this sense, the ICF shifts the focus from health condition to functions, thereby treating all health conditions in an equal manner. The equal footing placed

on all health conditions in the ICF allows them to be compared on the basis of their related functioning, via a universal framework (Jette 2006). The ICF is designed to cover the entire life span of an individual (Björck-Åkesson et al. 2010). The WHO is tasked with updating and modifying the ICF in accordance with scientific advancement to enhance its relevance for all age groups (Vargus-Adams and Majnemer 2014; WHO 2001).

In summary, the ICF model is an important international reference framework of terminology for health conditions and disability. The ICF offers clear definitions for health conditions, impairments, activity, participation, activity limitations, participation restrictions, personal and environmental factors. As for post-stroke USN and motor function, the two belong to the body functions component of the ICF, whereas the activity of daily life falls under the ICF category of activities. As discussed previously, post-stroke USN is associated with poor motor function recovery, which can lead to activity limitations and participation restrictions.

Diagnostics & Rehabilitation of USN

There are various screening tools available to assess USN among stroke survivors. However, the heterogeneity of the disorder means that there is no single gold standard assessment that can be used to evaluate all the probable USN-related deficits. Rather, a combination of different tools that involves behavioural and functional assessments are used to examine the presence and extent of USN (Azouvi 2017; Bodak et al. 2014; Di Monaco et al. 2011).

The early and accurate diagnosis of USN is key for the development of successful rehabilitation plans (Grech et al. 2017). Traditionally, conventional paper-and-pencil tests have been used to detect USN (Barrett et al. 2006). The most commonly used assessment is the Rivermead Behaviour Inattention Test (RBIT) which is comprised of several subtests including cancelling out static targets (letter/star cancellation), locating objects and/or copying figures (B Wilson, Cockburn, and Halligan 1987). Despite well-documented limitations (several studies report

low sensitivity, inability to mimic everyday tasks, failure to detect milder forms of USN – especially in the chronic stage) paper-and-pencil assessments are the most commonly used method of assessment for USN (Buxbaum et al. 2004; Grech et al. 2017; Rengachary et al. 2009).

Severe USN in the acute stage can be easily observed by monitoring stroke patients' behaviour. However, subtle USN deficits may go unnoticed in the stroke ward (Swan 2001). In emergency settings, screening for USN is considered part of the standard procedure recommended in stroke guidelines. The Visual (No 3) and Extinction and Inattention (No 11) items on the NIH-Stoke-Scale (NIH-SS) are the standard screening tools for USN in a stroke ward (Riestra and Barrett 2013). The two items are quick and easy to administer and score (Tulsky, Carlozzi, and Cella 2011). However, a study by Halligan et al. (1989) reported that the two neglect items on the NIH-SS detected USN in 43% of stroke patients with acute right-hemisphere lesions compared to 85% assessed on conventional paper-and-pencil assessments such as star and/or letter cancellation tests. The study concluded that conventional assessments have a higher sensitivity for the detection of USN than the two NIH-SS neglect items (Halligan, Marshall, and Wade 1989).

The Rivermead Behavioural Inattention Test (RBIT) comprises 15 subtests and is the most widely used tool for USN detection. The RBIT is divided into two categories: conventional (six subtests including line bisection, line cancellation, star/bells cancellation, letter cancellation, figure and shape copying, and representational drawing) and behavioural (nine subtests including picture scanning, telephone dialling, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation and card sorting) (B Wilson et al. 1987). Although the RBIT is considered the standard assessment for USN, the various RBIT subtests take at least an hour to complete and an additional 30 minutes to score. Thus, the RBIT is deemed to be time-consuming for clinicians/therapists and only

suitable for patients who have a high functional level and are, therefore, able to concentrate for at least an hour. As an alternative, researchers tend to use one or a selection of RBIT subtests to assess USN for patients who are unable to concentrate for the length of time required to complete the full RBIT battery. However, the use of one or two subtests instead of the whole RBIT battery, particularly for chronic USN, increases the risk of missing subtle USN-deficits (Buxbaum et al. 2004; Vallat-Azouvi et al. 2017).

Additional tests focus on the functional ability of patients to assess the extent and severity of USN in the activities of daily living (ADLs) (Chen et al. 2012). A common functional ADLs assessment is the Catherine Bergego Scale (CBS) and the modified Kessler Foundation-NAP version of the CBS assessment (Azouvi, Olivier, de Montety, et al. 2003; Chen et al. 2015). These tests aim to detect and assess the extent of impairments in spatial attention among USN patients. The CBS and Kessler Foundation-NAP tests include a visual scanning task as well as tasks assessing the direction of gaze and response to auditory stimuli (Chen et al. 2012). Additional items assess patients' ability to self-care for their body parts on the opposite side of brain damage. This includes observing patients carrying out daily activities such as eating, dressing and grooming (Azouvi, Olivier, de Montety, et al. 2003).

Different treatment and rehabilitation strategies for USN including behavioural techniques [e.g. visuospatial training], specialised devices [e.g. neglect alerting device (NAD)] and pharmacological intervention [e.g. dopaminergic drugs] are currently used (Hartman-Maeir et al. 2007; Singh-Curry and Husain 2010), but the outcome tends to be varied (Bowen and N. Lincoln 2007), showing short-lasting functional improvement (Luauté et al. 2006). This point is particularly poignant in the chronic stage of USN which is associated with poor functional recovery (Rengachary et al. 2009).

In conclusion, conventional paper-and-pencil assessments may be sufficient for the assessment of USN in the acute stage of the disorder. However, they are deemed inadequate for the

assessment of milder forms of USN, particularly in the chronic stage. Currently, there is no single gold standard assessment battery for USN due to the complexity and heterogeneity of this phenomenon. Rather, a combination of different tests that assess various domains of USN and the functional abilities of patients is recommended. Recently, researchers have been exploring the use of computerised tests such as virtual reality tools as a new means of assessment of USN.

Chapter 2

Virtual Reality: History, Development and Applications in Healthcare

Abstract

This chapter aims to explain virtual reality technology – its past, present and future, the application domains and system/operational requirements of virtual reality systems. It also examines currently available VR systems and the latest advances made in the field of virtual reality and its applications in healthcare.

Introduction

A Brief History of Virtual Reality

Although virtual reality (VR) systems may seem like something from a science fiction book, VR technologies are based upon concepts that go back as far as the 19th century. In 1838, Sir Charles Wheatstone - an English scientist and inventor, designed the first known stereoscope: a device that uses twin mirrors to generate a single three-dimensional (3D) image. The stereoscope concept was the backbone of what eventually became known as the View-Master, which was patented in 1939 and continues to be produced to this day (Wade 2002; Wade and Ono 1985).

The term "virtual reality", however, was first coined in the mid-1980s by Jaron Lanier, an American computer scientist and founder of VPL Research, who laid the foundations for the modern VR technologies that we see in the market today (Cong, Li, and Jiang 2020). Lanier and his team developed several VR prototypes including VR goggles, data gloves and a data suit. Lanier described the above equipment as necessary gear to experience what he called "virtual reality" (Karaliotas 2011; Lasko-Harvill et al. 1988; Srivastava, Das, and Chaudhury 2014).

But prior to VPL's breakthrough, technologists were obsessively trying to develop simulated environments (Cipresso et al. 2018). Many attempts were made to create virtual environments that could take the users on a journey in a parallel world from the comfort of their seat via

immersion (Coyne et al. 2019; Markowitz et al. 2018). Chief among such attempts was the invention of the Sensorama in 1956 by prominent Hollywood cinematographer Morton Heilig, who wanted to offer users an immersive experience whereby they would feel like they were "in" the movie rather than being outside it (Cipresso et al. 2018; Jones and Dawkins 2018). Indeed, the Sensorama, which is a "movie box" machine, was truly revolutionary in the fuller sense of the concept (Branda 2015). The Sensorama simulated a "real city" environment in Brooklyn, whereby users would ride a motorcycle with multi-sensory stimulation in the form of 3D visual stimulation with wind blowing through the hair, the sound of engine rumblings, vibrations and smell of engine exhaust all whilst users stuck their heads into the movie box in an attempt to achieve full immersion in the "designed environment" (Branda 2015). In the early 1960s, Heilig had a working prototype of the Sensorama and had also managed to patent an early prototype of the head-mounted display (HMD) device (now known as virtual reality goggles or headset) termed at the time as the Telesphere Mask (Cipresso et al. 2018; Coburn, Freeman, and Salmon 2017). Heilig's ground-breaking work paved the way for future investors who built upon his ideas to take VR technology to a higher level (Jones and Dawkins 2018).

Another milestone in the evolution of VR technology was achieved in 1965 with the publication of a seminal paper titled "The Ultimate Display." The author, Ivan Sutherland - an American computer scientist and pioneer dubbed the "father of computer graphics" – presented the key concepts of what later became known as immersion in a computer-generated world with multi-sensory input and output. Sutherland suggested that his "Ultimate Display" – a head-mounted device (HMD) – would serve as a "window into the virtual world." His work continues to be the basis of current VR research. Sutherland summarised the challenge that technologists face to create a window through which users can be immersed into a virtual world. The challenge was, and still is, to create a virtual world that looks, feels, acts and sounds

real to ensure that users would have a fully immersive experience in a computer-simulated world (Cipresso et al. 2018; Sutherland and Sutherland 1965).

The 1970s and 1980s saw several landmark advances in the VR field which ran parallel to projects that focused on the invention of optical and haptic (touch) devices as well as other similar instruments that would enable users to move around and use their limbs in virtual environments. In the mid-1980s, NASA developed the Virtual Interface Environment Workstation (VIEW) system, which managed to combine an HMD with data gloves to offer users a virtual experience with haptic interactions (Cipresso et al. 2018; Fisher et al. 1987).

Throughout the 1990s, VR gradually made its way into science and medicine. Researchers and clinicians began to see the benefits of developing VR applications that can be used as an intervention delivery as well as diagnostic and rehabilitation tools. Since the advent of this technology to the world of healthcare, various VR-based interventions have been developed and studied. VR-based interventions cover a wide range of medical conditions including post-traumatic stress disorder (PTSD), eating disorders, phobias, chronic pain, depression, and anxiety (Cornick and Blascovich 2014; Ferrer-Garcia, Gutiérrez-Maldonado, and Riva 2013; Llobera et al. 2013; McCann et al. 2014; Rothbaum et al. 2000; Wiederhold 2006).

Several recent significant advances in the VR field have made this technology increasingly more accessible, affordable and portable – but, more importantly, so immersive and flexible that it can now accommodate all kinds of users (Slater and Sanchez-Vives 2016). From a younger tech-savvy audience to an older audience that growing up only read about this technology as a futuristic possibility in science fiction books (Coburn et al. 2017). Such advances mean that this technology can now be used in a variety of settings – non-clinical as well as clinical (Riener and Harders 2012b).

What is Virtual Reality?

Virtual reality refers to the interactions between a user and a computer-simulated environment which stimulates multi-sensory modalities including sensory (visual and auditory) and haptic (touch) involvements (Kaltenborn and Rienhoff 1993). The virtual reality experience is made possible by the use of HMD (also known as VR goggles or headset), as well as projectors and/or computers. Additionally, sensor-fitted gloves and touch-sensitive devices are used by technologists/gamers/researchers and clinicians to monitor and assess the user's degree of immersion and presence in the virtual environment (Ahmed et al. 2018). The technology can be used in a safe, reliable and repeatable way and can be easily manipulated to suit all levels of ability. The virtual environments can be a replication of a "real-world" scenario or totally invented scenarios that involve a target-specific task (Wiederhold 2006).

The main aim of VR technology is to create virtual environments that can offer a full sense of immersion (Rose, Nam, and Chen 2018). To achieve a fully immersive experience, a sense of presence must be generated within a virtual environment (Slater 2018). Whilst the terms immersion and presence are somewhat related and sometimes used interchangeably, each of these two concepts has its own definition. Immersion in a virtual environment often refers to the degree of ability of the computer-generated environment to create a sense of presence within a constructed virtual setting (Sanchez-Vives and Slater 2005). Thus, computer-generated immersion is related to the technical means used to construct a virtual environment, and the extent to which these means are able to trigger and engage the senses of the user to achieve a high degree of presence (Smith 2013). The technical considerations that determine the level of immersion include the type of imagery and auditory stimuli used, field of view, degree of display resolution, refresh rate and the extent of interaction within a virtual environment (Bowman and McMahan 2007). Presence, however, refers to the sense of actually being present within a virtual environment or, in layman's terms, a sense of 'being there' (Chan

et al. 2005; Coelho et al. 2012). The sense of presence is achieved through, among other aspects, the technical means of immersion mentioned above, which determine the degree of immersion, and therefore, presence (Riva and Mantovani 2012).

One of the biggest challenges VR researchers and developers face is developing systems that allow VR users to interact and communicate with the virtual world in the same manner that they interact with the real world (Nilsson et al. 2018). This would make the whole VR experience more natural and less unfamiliar to the average user, particularly older individuals (Cipresso et al. 2018).

Virtual Reality Components

To build VR systems, two main components are required: the hardware components and the software components. Each is further subdivided into various sub-components (Bamodu and Ye 2013).

Virtual Reality Hardware

The hardware components of VR can be divided into five categories (Bamodu and Ye 2013; Novák-Marcinčin 2010).These are:

1. Computer workstation
2. Sensory displays
3. Process acceleration cards
4. Tracking system
5. Input devices

Virtual Reality Software

The software components of VR can be divided into four categories (Bamodu and Ye 2013; Bierbaum and Just 1998). These are:

1. Three-dimensional modelling software
2. Two-dimensional graphics software
3. Digital sound editing software
4. Virtual reality simulation software

Types of Virtual Reality Systems

There are three main types of VR systems (Bamodu and Ye 2013; Saeed Alqahtani, Foaud Daghestani, and Fattouh Ibrahim 2017). They are:

1. Non-immersive virtual reality systems
2. Semi-immersive virtual reality systems
3. Immersive (also known as fully immersive) virtual reality systems

Sometimes people confuse the classification of VR systems with the methods used to develop said systems, which means that these methods are wrongly thought of as types of VR systems rather than a method of development. Methods of VR system development include simulation based systems, projector based systems, avatar-image based systems and desktop based systems (Bamodu and Ye 2013; Saeed Alqahtani et al. 2017; Yang, Cheng, and Yang 2018).

- **Non-immersive virtual reality systems**

  The non-immersive desktop system is the most widely used VR system. In non-immersive systems, VR is implemented on a desktop computer and, as the name suggests, is the simplest form of VR techniques (Cox 2003). This category is sometimes referred to as “Window on the World” (WoW). The desktop system acts as a medium through which the virtual environment is viewed via a portal or window (Mandal 2013). This is achieved by using a standard high-resolution monitor. In this system, interactions with the virtual environment are done through conventional devices such as a keyboard, mouse or trackers (Bamodu and Ye 2013)(Sala 2007).

- **Semi-immersive virtual reality systems**

The semi-immersive VR systems consist of a relatively sophisticated graphics computing system which is normally accompanied by a large screen monitor, a projection system and/or multiple television projection system (Mihelj, Novak, and Beguš 2014). A wide field of view is used in semi-immersive systems to enhance the user's experience and feeling of immersion and/or presence in the virtual environment. A type of shutter glass is used in this system to achieve stereographic imaging (Muhanna 2015; Yang et al. 2018).

- **Fully immersive virtual reality systems**

  Immersive systems are the most sophisticated of all VR systems and offer the most direct experience of virtual environments. This system requires a head-mounted display (HMD) or a Binocular Omni-Orientation Monitor (BOOM) (Bamodu and Ye 2013; Daghestani 2013). The user wears either of these goggles to view the virtual environments. Additional devices such as tracking sensors or haptic (touch) devices are also used in this system (Saeed Alqahtani et al. 2017; Yang et al. 2018).

The Science of Virtual Reality

Understanding how our brain functions in a virtual world would undoubtedly revolutionise our understanding of how the brain works in the real world (Slater and Sanchez-Vives 2016). Following the advent of VR technology, scientists have been trying to provide a scientific and logical justification for how VR can play with our senses to transport us from the real world to a virtual one (Kim, Jeon, and Kim 2017). Whilst several theories have been suggested to explain this phenomenon, certain questions – including the ability of VR environments to convince our brain to take us to "virtual worlds", and how our brain reacts to being in a virtual world – remain to be answered and fully comprehended (Cipresso et al. 2018; Lécuyer et al. 2008).

The brain normally uses past experiences to develop mechanisms or "rules", through which it interprets the world (Lisman 2015). Using the sky as a cue, we are able to tell which way is up and which way is down – similarly, shadows tell us where light is coming from and the relative size of certain objects tells us about their location, and which one is closer or further away (Peacock and Ekstrom 2019). These rulebooks allow the brain to function more effectively (Riva, Wiederhold, and Mantovani 2019).

When designing a VR tool, developers must take these rules into account to ensure that the brain receives and processes the information gathered in the virtual environment in the same manner it processes such input in the real world (Cipresso et al. 2018). The challenge for VR developers is to create VR environments that match the expectation of the human brain as the brain is far more complex than the most sophisticated of computers, and when a virtual environment does not match our brain's expectations VR users my start to feel disorientated or nauseated as a sign of disharmony (Gonzalez-Franco and Lanier 2017). For example, to ensure that the virtual cues are effective and sophisticated enough, any type of movement inside the virtual environment should match the brain's expectations of the laws of physics. Further, the shading and texture of the designed environment should enable users to determine depth and distance in a manner that obeys the brain's expectations (Slater et al. 2020). As VR environments involve the use of several virtual cues, scientists and VR developers continue to test and explore which cues are more important than others and which ones must be prioritised in VR environments (Jerdan et al. 2018).

VR technology has also been offering new insights into how our brain functions (Riva et al. 2019). As VR-supported videogames continue to grow in popularity, they have become more easily accessible, cheaper and more reliable (Li et al. 2017). This has allowed neuroscientists, physiologists as well as other researchers to utilise these invaluable tools to conduct research in various fields (Farra et al. 2019; Patel et al. 2020; Wang et al. 2018). Navigation studies are

one stream of VR-related research that is worth mentioning (Hung et al. 2014; Pan and A. F. de C. Hamilton 2018).

Navigation studies require complex experiments that can only be conducted in VR-specialised labs as, in the absence of VR labs, researchers would have to conduct field studies that are difficult to carry out, time-consuming and extremely costly (Cipresso et al. 2018). Researchers conducting navigation studies in VR labs have the advantage of creating flexible virtual environments that can be easily manipulated to answer a variety of research questions (Diersch and Wolbers 2019; Farra et al. 2019; Van Veen et al. 1998). The importance of navigation studies stems from the long and ever-growing interest in advancing our understanding of human memory in dementia (Levine et al. 2020; Lithfous, Dufour, and Després 2013; Ly et al. 2015). In 2014, John M. O'Keefe, May-Britt Moser, and Edvard I. Moser were awarded the Nobel Prize in "Physiology or Medicine" for their discoveries of specialised "navigation" nerve cells that allow us to have a sense of place and navigation of space (Burgess 2014; Noble Prize 2014). These navigation cells have been dubbed "the brain GPS" system by many journals and magazines (BBC 2014; The Scientist 2014; Underwood 2014; University of Cambridge 2019). One of the aforementioned winners, Edvard I. Moser, highlighted the importance of VR for research, clinical utility and the potential integration of VR into standard clinical practice (Bohil, Alicea, and Biocca 2011a; Minderer et al. 2016; Riva et al. 2011).

Following the advent of VR, the technology has been used in various fields including gaming (Meldrum et al. 2012; Zyda 2005), military training (Alexander, Westhoven, and Conradi 2017), architecture (Song et al. 2018), visualisation (Marks, Estevez, and Connor 2014), education (Englund, Olofsson, and Price 2017), social skills training (Gaggioli 2009; Yuan and Ip 2018), surgical procedures training (Gallagher et al. 2005) as well as rehabilitation and assistance to psychological treatments (Aravind and Lamontagne 2018; Levac et al. 2015; Riener and Harders 2012a; Saleh et al. 2017). The technology continues to find its way into

new fields as it evolves by the day. Studies indicate that virtual reality will soon become an integral part of the entertainment sector as well as travel, news and education – not to mention that the technology has already made significant breakthroughs in the field of medicine and healthcare (Ahn and Lee 2013; Cipresso et al. 2018; Radianti et al. 2020; Simões et al. 2018). Studies have reported that VR will soon become key in treating a host of different psychological disorders such as anxiety, schizophrenia, depression, and eating disorders (Ferrer-Garcia et al. 2013; Freeman 2007; Maples-Keller et al. 2017; McCann et al. 2014; Perpiñá, Botella, and Baños 2003; Zeng et al. 2018).

The key feature of VR that makes it very attractive is its ability to act as a stimulus in a safe environment (Schwebel and McClure 2010). VR allows researchers to recreate experiences with a high degree of realism in a controlled manner that otherwise would be almost impossible to replicate in the real world (Proffitt and Lange 2015). Hence, the technology has been increasingly used in research to find new and more effective delivery methods of psychological treatments of task-specific training. For example, virtual reality technology has become a key treatment method of phobias (fear of height, fear of flying, fear of spiders, etc.) (Botella et al. 2017). Additionally, the technology continues to dominate research into how to improve the traditional systems of motor rehabilitation following neurological injuries, with a particular focus on developing VR games that improve the efficacy of rehabilitation tasks (Borrego et al. 2016; Lloréns et al. 2015). VR is projected to become a key component of medical education and training due to its ability to offer powerful visualisation experiences that could possibly revolutionise education from early years up to university education (Fertleman et al. 2018; Maresky et al. 2019). Virtual Reality Exposure Therapy (VRET) has, thus far, shown positive results in terms of helping patients to gradually overcome their fear stimuli and/or stress-triggering situations in a safe environment where clinicians, therapists and researchers can be

in total control of all aspects of the virtual environment and thus, manipulate it according to each individual's condition and needs (Gujjar et al. 2018; Wald and Taylor 2000).

The question remains: how does VR play with our brain to, for example, help treat people with phobias?

As mentioned previously, the brain oversees creating its own reality based on past experiences and sensory information surrounding us, and this makes it susceptible to deception by optical cues which mimic reality (Carbon 2014). When one sees something that is familiar to them, they immediately predict what will happen next, regardless of whether the prediction is sensible or not. It is purely based on experiences lived in the past and sensory information gathered (Pan and A. F. d. C. Hamilton 2018; Pan and A. F. de C. Hamilton 2018). This means that our brain works tirelessly and constantly to predict the future, and the more it predicts the future, the more we feel a sense of presence and realism – and so, by the virtual environment and the objects within it behaving in the same manner as one would expect in the real world, a sense of presence is generated, and thus VR tricks the brain into perceiving something as real which is not (Gonzalez-Franco and Lanier 2017; Rubia Vila 2005).

Limitations of Virtual Reality Technology

Despite significant recent advances in the field of VR technology, several limitations and obstacles remain to be overcome. Chief among them is the difficulty to achieve a sense of presence and the lack of universal methods to measure the subjective experience of presence. Another major limitation of VR is cybersickness - which has been commonly referred to as motion sickness, although it was recently classified as a sub-type of motion sickness rather than a synonym of the latter (Boud et al. 1999; Minderer et al. 2016; Wilson, Foreman, and Stanton 1997).

Since the conception of VR technology, attaining a full sense of presence has been the single most important determinant of a successful VR experience (Flavián, Ibáñez-Sánchez, and Orús 2019; Marín-Morales et al. 2019). Several investigators argue that presence is correlated with the extent of interaction in a constructed VR world as well as the degree of realism of sensory input conveyed from the VR environment (Ijsselsteijn 2006; Mestre and Vercher 2011; Minsky 1980; Park and Regenbrecht 2019). It is worth noting that researchers have made a distinction between immersion (which, essentially, is a measure of the VR system's ability to shut-off the real world so that the user feels completely engrossed or immersed), and presence (Mandal 2013; Slater 2018). A subject may find a VR task extremely captivating and feel completely engrossed in it without attaining a sense of presence. Likewise, the VR system's ability to shut-out the real world (immersion) does not necessarily mean a sense of presence has been attained (Bowman and McMahan 2007; Mandal 2013; Mestre and Vercher 2011).

The challenge with presence has always been: how does one measure presence in a VR environment, given that our susceptibility to presence, whether in VR settings or otherwise, varies considerably (Schubert, Friedmann, and Regenbrecht 2008). Indeed, it is very difficult to design a universal method of measuring presence as subjective experience plays a defining role. Nonetheless, researchers have proposed several methods for obtaining subjective measures of VR experiences. These methods/scales include self-report scores collected while performing a VR task, verbal or written accounts of the degree of presence attained, and a wide range of questionnaires administered after VR exposure (for instance, the "Presence Questionnaire" or "Igroup Presence Questionnaire"). Each of these methods, however, has advantages and inadequacies, and even though a wide range of approaches exist, there is currently no consensus among researchers as to what would be the best method of obtaining subjective measures of presence during and/or post-VR exposure. Therefore, the issue of

attaining presence and its measurement remains an obstacle to be overcome (Igroup 2019; Igroup Project Consortium 2015).

The second major limitation of VR is cybersickness. Like presence, various definitions of cybersickness exist in the literature (Weech, Kenny, and Barnett-Cowan 2019a). Generally, however, cybersickness is defined as a collection of symptoms, marked by discomfort and sickness, resulting from exposure to VR (Kiryu and So 2007). Although the terms motion and cyber sickness are often used interchangeably, experts have proposed that cybersickness is rather a sub-type of motion sickness caused by visual stimuli conveyed from a VR environment, and unlike classic motion sickness, does not involve the vestibular system (LaViola 2000; Rebenitsch and Owen 2016). However, a recent study in 30 young adults reported that motion sickness and cybersickness are the same condition. This claim, which contradicts findings of several other studies, is the subject of much debate and calls for further research have been made (Gavgani et al. 2018).

While cybersickness is symptomatically akin to simulator sickness, which is another subcategory of motion sickness experienced during exposure to vehicle simulators, the two are somewhat different forms of motion sickness (Kemeny et al. 2017; Stanney, Kennedy, and Drexler 1997). Cybersickness is related to signs of disorientation, whereas simulator sickness is symptomatically characterised by oculomotor impairments. Indeed, some subjects appear more susceptible to VR cybersickness than others. A number of possible causations of cybersickness have been reported in the literature, including disparities between the expectations of the brain and sensory information observed, quality of visual display, conflicting information as to one's location in a VR environment, and individuals' level of gaming experience (Sevinc and Berkman 2020; Weech et al. 2019a).

Regarding the modes of measuring cybersickness during and post-VR exposure, several objective and subjective measures have been proposed. Like presence, subjective measures of

cybersickness are mainly obtained using questionnaires designed to assess and score different causal factors of cybersickness such as disorientation and discomfort (Gavgani et al. 2018; Rebenitsch and Owen 2016; Weech, Kenny, and Barnett-Cowan 2019b). Objective assessments, however, include measures of heart rate, respiration rate, sweat rate, skin conductance as well as competence of task performance and termination of task due to nausea. Indeed, subjective measures (by means of questionnaires) are by far the most widely used method of cybersickness assessment (Bruck and Watters 2011; Davis, Nesbitt, and Nalivaiko 2014; Sevinc and Berkman 2020).

Virtual Reality & Spatial Neglect

Virtual reality (VR) is a developing technology that has been increasingly used to assess USN among stroke survivors. VR is an artificial environment created through computer simulations of three-dimensional (3-D) images which involve interactions between a person and a computer using specialist VR equipment such as a VR headset and VR gloves. VR systems can be fully immersive (i.e. involve wearing VR goggles and being fully immersed in the environment) or non-immersive (e.g. computer games involving an interaction through an external screen). Users can experience a variety of dynamically changing VR environments through various visual and auditory means of interactions using a mouse, a joystick or other external sensors (Bohil et al. 2011a).

VR systems are relatively novel tools for the assessment and rehabilitation of cognitive impairments of patients following a stroke (Rose, Brooks, and Rizzo 2005). These systems have been developed to recreate individualised 3-D environments where patients are trained to perform specific tasks to achieve a goal. As an assessment tool, VR systems can register and objectively measure the performance of patients within the virtual world and their behavioural responses; furthermore, as a rehabilitation tool, they have been shown to significantly

accelerate the improvement of USN (Kim et al. 2011; Ogourtsova et al. 2017; Weiss, Naveh, and Katz 2003).

Recently, an increasing number of researchers have been exploring the use of VR-based tools for the assessment of USN. VR tools can be a promising alternative to conventional USN assessments as they are able to track and record eye, limb and head movements. Additionally, VR systems can create 3-D environments that mimic real-life scenarios in which stimuli can be constantly changing, thus requiring dynamic responses from the patients. This can be beneficial when assessing the behaviour and responses of USN patients. These features make VR tools superior to conventional USN assessments which use static 2-D objects (Ogourtsova et al. 2017; Rose et al. 2005; Weiss et al. 2003).

One of the major advantages of VR systems over traditional methods is that they enable neuropsychological practice to be more engaging and generalisable owing to their ability to assess behaviour in controlled environments (Broeren et al. 2007; Buxbaum, Dawson, and Linsley 2012; Rizzo, Schultheis, et al. 2004). VR systems provide an advanced human-computer interface that allows patients to be assessed and trained through simulations that mirror everyday life activities without the need to use real environments which are often not available in a hospital setting (Tsirlin et al. 2009). VR systems are also superior to traditional assessment methods as they are able to provide information on head-eye co-ordinated movements, postural deviations and limb kinematics, which is highly valuable in detecting subtle changes (Tsirlin et al. 2009). VR assessments for USN include tasks such as navigation, obstacle detection and avoidance, road crossing and visual scanning exercises (Ogourtsova et al. 2017).

Additionally, VR environments can be easily manipulated by researchers/clinicians to assess different forms of USN – a flexibility not possible in clinical settings. Several studies have been published on the use of VR for the assessment and rehabilitation of USN. Studies have

found that detection of USN is more prevalent on VR tools compared to conventional paper and pencil USN assessments (Broeren et al. 2007; Buxbaum et al. 2012; Fordell et al. 2011a). Although VR technologies have shown promising results thus far, multiple challenges remain to be addressed. Attaining a full sense of presence, overcoming cybersickness and developing VR technologies that are cost-effective, reliable and easily accessible are key for improving the assessment and rehabilitation of USN (Pedroli et al. 2015). Additionally, VR developers should focus on providing clinicians and specialist nurses with the necessary information and training to enable them to carry out VR assessment and rehabilitation tasks effectively. This can be achieved by designing infographics and providing training videos on how assessment and rehabilitation programs should be performed (Ogourtsova et al. 2017).

In conclusion, VR systems may offer a promising alternative to conventional paper and pencil USN assessments. To confirm this finding, we sought to conduct a meta-analysis on studies that used both VR and conventional tests to assess post-stroke USN (Chapter 4).

Chapter Three

Aims, Objectives and Hypotheses

Aims

- To develop a mobile phone application involving fully immersive virtual reality prototypes for the assessment of sensory and motor deficits associated with post-stroke unilateral spatial neglect (USN).
- To develop the mobile phone application for use in clinical and non-clinical settings using open-source software.

Objectives

- Data on the performance of USN and non-USN patients will be extracted using conventional paper-and-pencil assessments.
- Data on the performance of USN and non-USN patients in virtual street-crossing scenarios will be extracted from the mobile application.
- Performance of USN and non-USN patients on conventional will be compared to establish if correlation points exist between VR tasks and conventional paper-and-pencil assessments.

Hypotheses

- It was hypothesised that the VR street crossing ask can detect USN and distinguish between stroke patients with and without USN.
- The second hypothesis was that the VR street crossing task have good acceptance and usability among stroke patients.

Chapter 4

Virtual Reality Assessments for Post-Stroke Unilateral Spatial Neglect

Abstract

Background & Purpose

Unilateral Spatial Neglect (USN) is a common post-stroke visuo-perceptual defect. Virtual Reality (VR) based tools (whether immersive or non-immersive) are increasingly used as an alternative to conventional paper-and-pencil assessments; herein, we aim to evaluate and compare the detection rate of USN on conventional assessments and VR-based tools.

Methods

Searching Cochrane Library, PubMed and Google Scholar identified potential studies until October 2021 that included brain imaging of confirmed stroke in adults and compared incidence of USN detected on both conventional paper-and-pencil and VR-based assessments. Data was analysed using RevMan v5.3, with Odds Ratios (OR) and 95% confidence interval (CI) using a random effect model to estimate the detection of USN assessed by VR systems or conventional methods. A *p*-value of <0.05 was considered significant.

Results

Twelve studies (n = 414) were eligible for meta-analysis. Eleven (n = 284 cases) compared USN incidence on both conventional and VR-based assessments – the USN incidence rate being significantly higher using VR (57%), compared to 41% on conventional assessments [OR 0.48 (95% CI: 0.33-0.70); p = 0.001]. Six studies (n = 191) used non-immersive VR tools with a significantly higher yield of USN than conventional assessments [OR was 0.41 (95% CI: 0.23-0.73); p = 0.002]. Six (n = 95) used immersive VR tools – the USN incidence rate being significantly higher on immersive tasks compared to conventional assessments [OR 0.46 (95% CI: 0.24-0.86); p = 0.01].

Conclusion

Although VR tools reportedly detected a higher rate of USN compared to conventional assessments, it is not possible to draw any decisive conclusions on the superiority of VR to

traditional assessments due to the inability to carry out a receiver operating characterise (ROC) curve analysis. Methodological inconsistencies and the lack of gold standard assessment of USN across the studies included make it difficult to generalise the findings of this study. Most of the included studies focused on assessing one or two subtypes of USN. Future VR studies should focus on developing versatile systems that can assess both sensory and motor USN phenotypes. To address the lack of gold standard assessments, future studies could experiment with hybrid models of USN assessment by combining traditional tests and functional scales with novel VR technology, rather than using one only or comparing one with the other. This approach may offer a better understanding of this heterogenous disorder and more insights into USN-related deficits.

Introduction

Unilateral spatial neglect (USN) is a common post-stroke visuo-perceptual defect, characterised by reduced responsiveness where patients fail to detect, respond or orient to stimuli presented on the contralesional side of brain damage (Gillen, Tennen, and McKee 2005). USN may manifest in the visual, auditory and tactile channels, and can be caused by lesions affecting cortical and subcortical areas (Allegri 2000; Buxbaum et al. 2004).

While a third of stroke patients experience some degree of USN at stroke onset, chronic USN impacts approximately 15% of stroke sufferers (Karnath et al. 2011a; Kerkhoff and Schenk 2012). The majority of USN cases arise from right (50%) compared to left hemisphere brain damage (12-30%) (Allegri 2000; Chen et al. 2015). The incidence of USN amongst right hemisphere stroke survivors ranges from 13 - 82% (Bodak et al. 2014).

USN is a heterogeneous disorder and often associated with lesions of the inferior parietal lobe and superior temporal cortex, and infrequently with lesions of the white matter tracts (Karnath et al. 2001; Mort et al. 2003). However, subcortical lesions are associated with more severe forms of USN (Fruhmann Berger et al. 2009; Parton et al. 2004a). Typically, patients with USN may present with one or more of the following spatial deficits: personal space (relating to one's body), near extrapersonal space (within one's reach) and/or far extrapersonal space (beyond one's reach) (Halligan, Cockburn, and Wilson 1991). Because any combination of symptoms, lesions and impairments may occur at varying stages following a stroke, it can be challenging to assess the extent of brain damage and the resulting impairment of function.

The Behavioural Inattention Test (BIT), which has a "conventional" component and a "behavioural" component, has widely been used as standard screening tools for USN (B Wilson et al. 1987). However, the conventional tests of the BIT are limited by a number of problems, including limited ecological validity and high cost (e.g. the BIT costs approx. £430), as well as

lengthy administration [~60 mins] and scoring time [~30 mins] required. Few stroke survivors have a high enough functional level to enable them to concentrate for this long. Further, in clinical settings, the BIT and similar tests may depend on mechanisms requiring the voluntary allocation of attention (Olk, Hildebrandt, and Kingstone 2010). However, when performing activities in daily life the automatic orienting of attention is crucial (Atkinson, Simpson, and Cole 2017). Another limitation is that the BIT is language dependent (Buxbaum et al. 2004). Other more ecologically valid assessments of USN include the wheelchair obstacle test and the Catherine Bergego Scale (CBS) (Azouvi 2017).

The wheelchair test involves patients "driving" a wheelchair along a pre-specified route. The patients are asked to manoeuvre the wheelchair along the route while identifying specific targets and/or avoiding obstacles (Jacquin-Courtois et al. 2008). However, one limitation of the wheelchair test is the difficulty to recreate the same scenario/route in different settings. Therefore, it is difficult to standardise this test and its scoring across different environments (Azouvi 2017).

The CBS is a functional scale for the assessment of USN behaviours using a standardised approach developed by Azouvi and colleagues. The main aim of the scale is to provide a standardised checklist for the detection of USN and assessment of USN-related behaviours. The CBS is carried out by a trained therapist who observes and scores the patient's performance during different ADLs. A second aim of the CSB is to assess the patient's awareness and understanding of their own deficits and difficulties to complete simple ADLs (Azouvi et al. 2010; Azouvi, Olivier, De Montety, et al. 2003). The awareness level is assessed by comparing observation data with information obtained during interviews with patients. The CBS consists of 10 items related to simple everyday activities (e.g., grooming, dressing, eating etc). Each item is scored from 0 (normal/no USN) to 3 (severe USN). The overall score can range from 0 to 30. The CBS has three levels of severity based on the overall score:

- Mild USN: 1-10 out of 30
- Moderate USN: 11-20 out of 30
- Severe USN: 21 – 30

Studies suggest that the CBS is more ecologically valid and sensitive than any of conventional tests (e.g., line bisection, letter cancellation) alone (Luukkainen-Markkula et al. 2011; Pitteri et al. 2018). However, Chen and colleagues noted that the CBS does not provide specific instructions for clinicians administering the assessment, stating that the 10 items of the scale lack specific observational contexts (Chen et al. 2012). According to Chen et al, the absence of specific instructions may lead to significant variations in the administration of the CBS among clinicians. Further, the CBS does not clarify whether performance is assessed at a single time point or over several sessions. To address the limitations of the CBS, Chen et al collaborated with the Kessler Institute for Rehabilitation to develop a new method for administering the CBS, namely the Kessler Foundation Neglect Assessment Process (KF-NAP) (Chen et al. 2012).

The KF-NAP comprises two forms; the first form includes the scale, plus the instructions for calculating the score and level of USN severity, whereas the second offers specific instructions for making observations for each of the 10 items of the scale. The KF-NAP guidelines state that all observations must be completed in a single session, which may take 20 to 40 minutes depending on each patient's ability and level of fatigue (Chen et al. 2012).

While successful attempts have been made to develop more ecologically valid USN assessments, it is difficult to standardise physical environments. There is also a need for tasks that can safely assess the patients' automatic orienting of attention to stimuli in a manner that resembles real-life scenarios (e.g., crossing the road, navigating moving obstacles, avoiding dangerous items etc.). To address such needs and take advantage of technological advances, a number of new methods have emerged. One such method is virtual reality (VR) technology. VR allows for the standardisation of assessment environments, and may enable researchers to

safely assess both, the voluntary and automatic orienting of attention to goal-relevant stimuli (Tromp et al. 2020). For example, it might be difficult and potentially unsafe to assess a patient's ability to navigate dangerous obstacles or cross the road safely in real life. VR may offer an alternative that could help standardise assessment environments and create complex and challenging tasks, mimicking real-life scenarios, but in a safe and patient oriented manner (i.e., environments or level of difficulty can be adjusted in virtual environments, it is extremely difficult to adjust physical environments in hospitals or at home).

To this end, VR technology has been proposed as a potential, safe alternative to conventional and unstandardised ecological tests for the assessment of stroke and non-stroke patients. There are three main types of VR systems: non-immersive virtual reality systems, semi-immersive virtual reality systems and fully-immersive virtual reality systems (Saeed Alqahtani et al. 2017).

The non-immersive desktop system is the most widely used VR system. In non-immersive systems, virtual reality is implemented on a desktop computer and, as the name suggests, is the simplest form of virtual reality techniques (Cox 2003). This categor is sometimes referred to as "Window on the World" (WoW). The high resolution desktop system acts as a medium through which the virtual environment is viewed via a portal or window (Mandal 2013), whilst interactions with the virtual environment are achieved through conventional external devices such as a keyboard, mouse or trackers (Sala 2007).

The semi-immersive VR systems consist of a relatively sophisticated graphics computing system accompanied by a large screen monitor, a projector or multiple television projection system (Mihelj et al. 2014). A wide field of view is used in semi-immersive systems to enhance the user's experience and feeling of immersion and / or presence in the virtual environment. A type of shutter glass is used in this system to achieve stereographic imaging (Muhanna 2015).

Immersive systems are the most sophisticated of all virtual environments. This system requires a head-mounted display (HMD) or a Binocular Omni-Orientation Monitor (BOOM) (Bamodu and Ye 2013; Daghestani 2013). Additional technologies such as tracking sensors, or haptic (touch) devices may also be added.

A meta-analysis was performed to; (1) compare VR tasks and conventional PPTs' detection rate of post-stroke USN, (2) compare the detection rate of immersive vs. non-immersive VR types, and (3) compare the performance of stroke patients with non-stroke controls on VR tasks.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines (Liberati et al. 2009).

Data sources

A literature search was undertaken on multiple electronic medical databases, including Cochrane database, NCBI PubMed and Google Scholar up to October 2021.

Study selection

The search was limited to human studies in all languages. Search terms included: 'stroke' 'cerebrovascular accident' 'ischemic-stroke' 'haemorrhagic-stroke' 'unilateral spatial neglect' 'visuospatial neglect' 'hemispatial neglect' 'visual neglect' 'evaluation' 'assessment' 'intervention' 'virtual reality' 'technology' 'computer simulation' 'therapy computer assisted' with AND/OR used as Boolean operators. References of all primary papers used in the study were screened to identify additional studies which met our inclusion criteria (**Figure 4.1**).

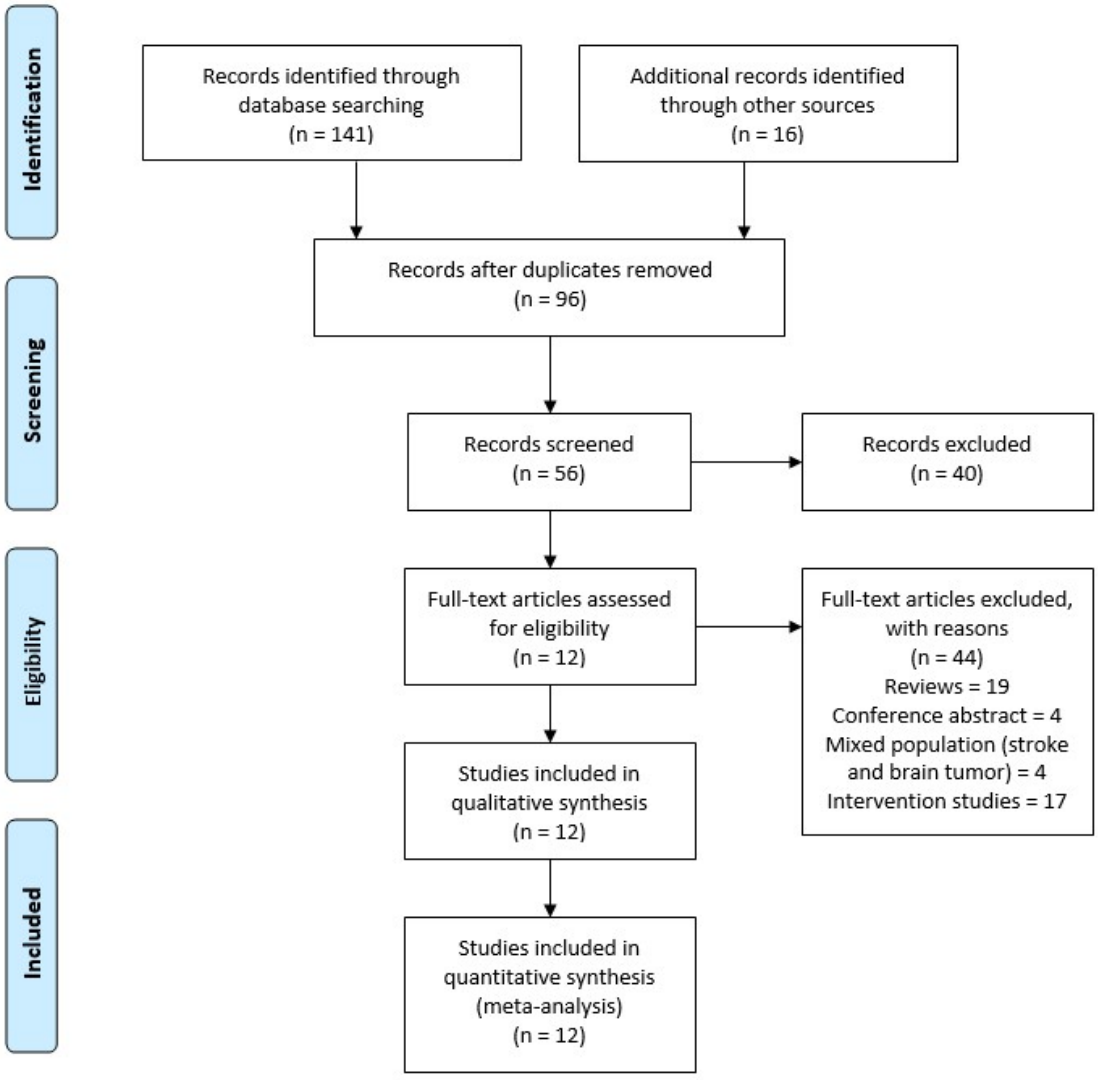


Figure 4. 6 Flow diagram showing process of study selection.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: 1) imaging-confirmed stroke (ischemic or haemorrhagic in either hemisphere); 2) patients ≥18 years of either gender; 3) comparison of performance of USN patients on both conventional paper-and-pencil assessments and VR tasks. Additionally, only case-controlled studies were included, with control subjects being either stroke patients without USN or healthy individuals. Published literature reviews,

feasibility or suitability studies, conference abstracts, brief reports, and letters to editors were excluded except as a search of their references for identifying additional manuscripts.

Data extraction and synthesis

Data was subdivided to record study characteristics (design, year, immersive vs. non-immersive VR), study population (sample size, participants, stroke characteristics) and intervention and assessment result. Incidence of visuospatial impairments in each study were noted along with the respective assessment (**Table 4.1).**

The relevant data was analysed as 1) USN cases (VR vs. conventional intervention), 2) USN cases for stroke patients vs. non-stroke controls, 3) stroke patients with USN vs. stroke patients without USN measured by VR tasks, and 4) comparison of the number of USN cases measured by immersive and non-immersive VR tasks.

Table 4. 2 VR-based USN assessments and tasks.

						Assessment Tools
Study	**USN+**	**USN-**	**HC**	**VR Type**	**VR Task**	**Conventional Pencil & Paper Assessments**
Spreij et al, 2020	33	28	22	Non-immersive	Simulated driving test	Shape cancellation, line bisection, letter cancellation
Knobel et al, 2020	10	5	35	Immersive	Virtual cancellation task	Paper -pencil cancellation task [Sensitive Neglect Test (SNT)]
Aravind et al, 2017	13	13	9	Immersive	Navigation / obstacle avoidance	Line cancellation test
Broeren et al, 2007	8	2		Immersive	Cancellation VR test	Star cancellation test, Baking Tray test
	9		4		Virtual wheelchair	Letter cancellation test, line bisection test, picture

Buxbaum et al, 2008				Non-immersive	navigation task	scanning subtest, menu reading subtest, dual task test, fluff test, far extrapersonal Line Bisection Test
Buxbaum et al, 2012	70		10	Non-immersive	VR Lateralised Attention Test (VRLAT)	Bells Test, Letter Cancellation Test, Line Bisection Test, Fluff Test
Dvorkin et al, 2012	8	9	9	Immersive	Virtual Environment for Spatial Neglect	Behavioural Inattention Test
Fordell et al, 2011	9	22		Immersive	VR Star Cancellation	Rivermead Behavioural Inattention Test
Gupta et al, 2000	2		4	Immersive	VR Eye system	N/A
Navarro et al, 2013	17	15	15	Non-immersive	VR street-crossing system Task	Behavioural Inattention Test
Peskine et al, 2011	7	2	9	Non-immersive	Virtual town navigation	Bells test, Catherine Bergego Scale
Ulm et al, 2013	10		10	Non-immersive	Circle Monitor (CM)	Star cancellation test, line bisection test, figure copying, clock drawing

USN+ = presence of unilateral spatial neglect; USN- = absence of unilateral spatial neglect; HC = healthy control; VR = virtual reality.

Statistical analysis

Data was analysed using RevMan v5.4 and presented as Odds Ratio (OR) and 95% confidence interval (CI) using a random effect model to estimate the detection rate of USN (dependent variable) assessed by VR systems or conventional methods (independent variables). The I^2

index was also used to calculate variation within each meta-analysis and funnel plots to assess publication bias. A *p*-value of <0.05 was considered significant.

Risk of bias of non-randomised controlled trials

Patient selection was assessed and found eight papers (Broeren et al. 2007; Buxbaum et al. 2008; Dvorkin et al. 2012; Gupta et al. 2000; Knobel et al. 2020; Navarro et al. 2013; Peskine et al. 2011; Ulm et al. 2013) to have a high risk. Overall, the studies had small sample sizes (e.g., n=2 for Gupta et al, 2000; n=9 for Buxbaum et al, 2008 and Peskine et al, 2011). These underpowered small studies may have resulted in precise meta-analysis estimates, leading to an increased risk of bias. Furthermore, Buxbaum et al (2008) did not report the inclusion and exclusion criteria for patient selection. Knobel et al administered the conventional assessment a day before the VR task. This may increase the flow and timing risk of bias as administering the conventional and VR assessments without randomising on different days may lead to a training effect. Speij et al recruited 70 patients for the study but excluded nine patients from the analysis because of missing data or the lack of statistical evidence. This could lead to exclusion bias. The trial by Gupta et al had an overall high risk of bias as it was not clear whether the thresholds were pre-specified for the index test and reference standard.

The remaining trial (Buxbaum et al, 2012) reported a detailed method for patient selection, had the largest sample size (n=70) of all the studies included in this meta-analysis, and provided sufficient information on the index test and reference standard used. Thus, it was deemed to have a low risk of bias.

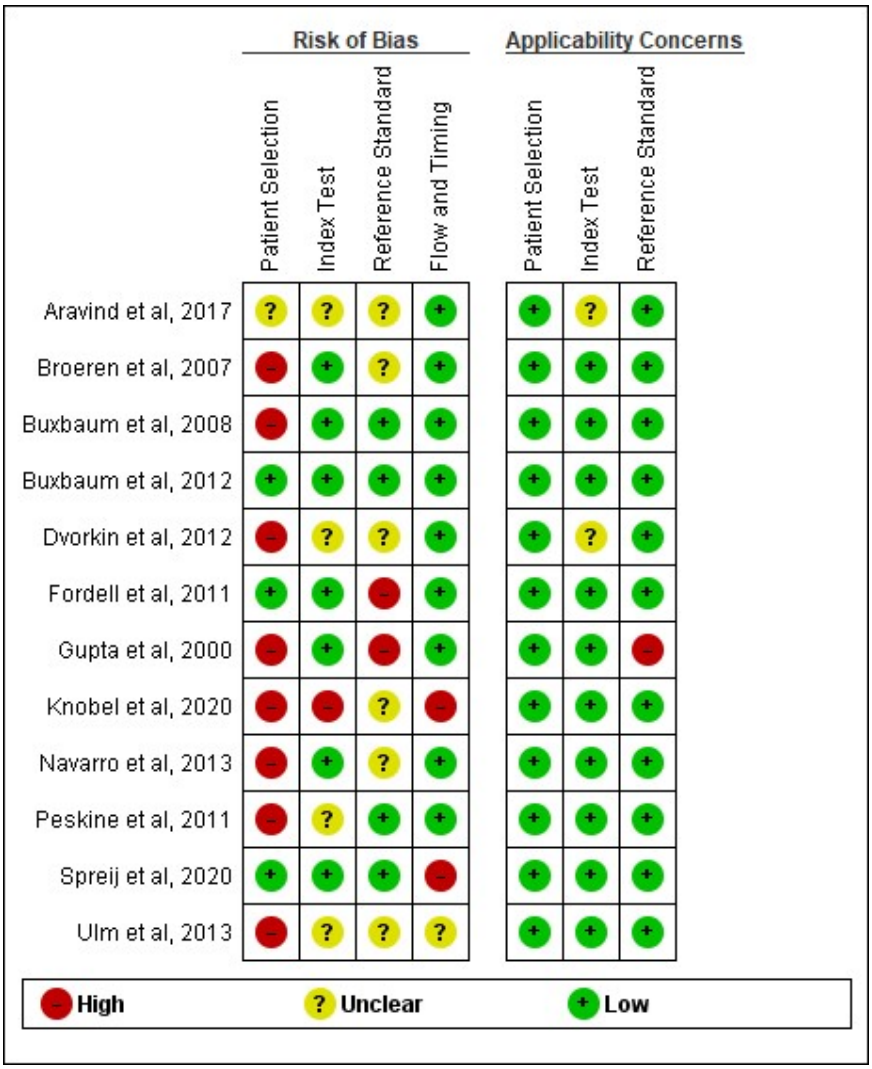


Figure 4.2 Risk of bias for meta-analysis studies.

Results

USN Rate in Stroke Patients [immersive and non-immersive VR (combined) vs. - conventional paper-and-pencil tests (PPTs)]

Eleven studies (Aravind and Lamontagne 2018; Broeren et al. 2007; Buxbaum et al. 2008, 2012; Dvorkin et al. 2012; Fordell et al. 2011a; Knobel et al. 2020; Navarro et al. 2013; Peskine et al. 2011; Spreij et al. 2020; Ulm et al. 2013) in 284 stroke subjects met our inclusion criteria and compared the incidence of neglect in stroke patients assessed by VR tasks (immersive and non-immersive combined) and conventional PPTs . The rate of USN detection was

significantly higher on VR tasks compared to the PPTs: OR 0.48 (95% CI: 0.33-0.70; p = 0.0001) (**Figure 4.3**). There was no significant heterogeneity (I^2=0%, p=0.48) or publication bias.

Whilst the PPTs indicated an incidence rate of USN in 41% of the patients, VR tasks (both immersive and non-immersive) showed that USN appeared in 57% of 284 stroke patients.

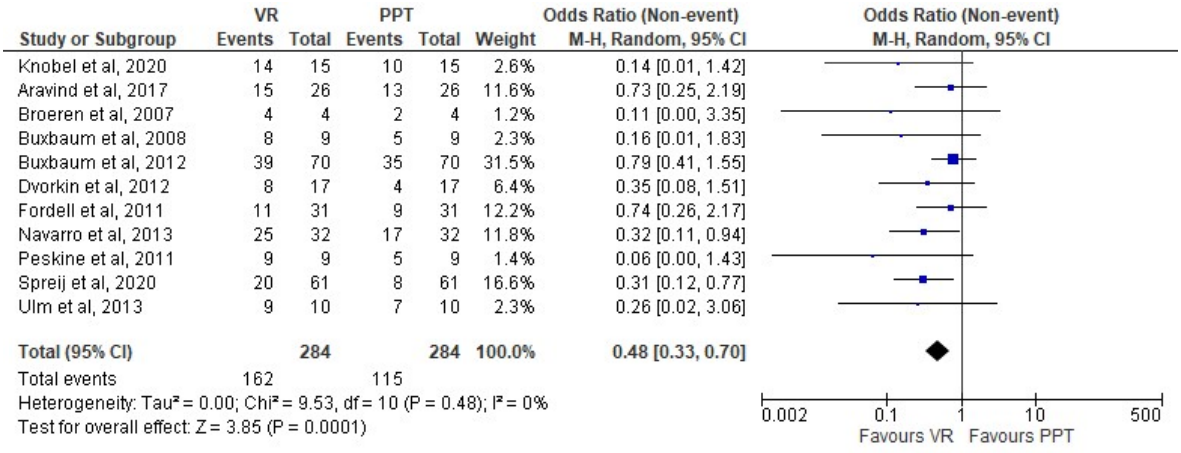


Figure 4. 7 VR tasks vs. conventional paper-and-pencil tests.

USN Rate - stroke patients vs. non-stroke controls Nine studies (Aravind and Lamontagne 2018; Buxbaum et al. 2012; Dvorkin et al. 2012; Gupta et al. 2000; Knobel et al. 2020; Navarro et al. 2013; Peskine et al. 2011; Spreij et al. 2020; Ulm et al. 2013) in 361subjects (242stroke cases and 119 healthy controls) assessed neglect using both immersive and non-immersive VR tasks. The rate of USN detection was significantly higher in stroke patients. Non-stroke controls performed significantly better on various VR assessments compared to stroke patients: OR 53.10(95% CI: 18.40-153.28); p = 0.00001) (**Figure 4.4**), with no evidence of heterogeneity (I^2 = 0%, P = 0.73) or publication bias.

The incidence of USN was 60% among stroke patients, whereas none of the non-stroke controls showed signs of USN on VR assessments.

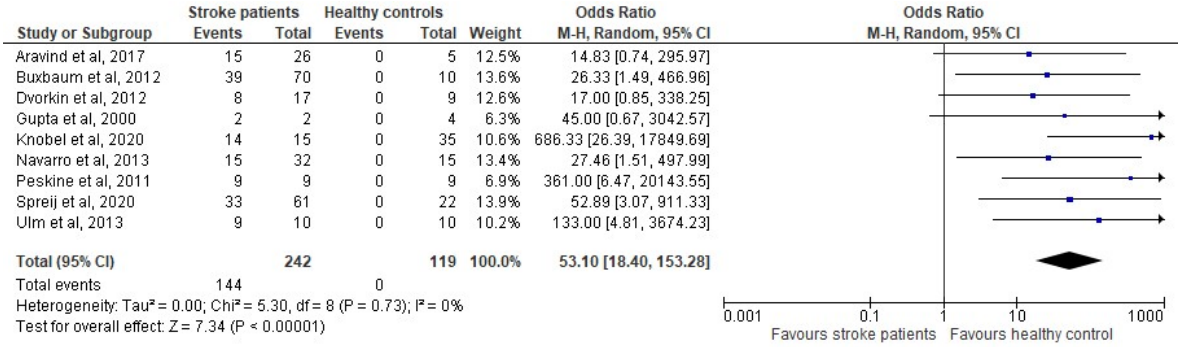


Figure 4. 8 Stroke vs. healthy controls measured by VR tasks.

USN Rate – Immersive & Non-Immersive VR vs. conventional paper-and-pencil tests (PPTs)

Six studies (Aravind and Lamontagne 2018; Broeren et al. 2007; Dvorkin et al. 2012; Fordell et al. 2011a; Gupta et al. 2000; Knobel et al. 2020) in 95 stroke patients assessed USN using immersive VR and PPTs . Immersive VR identified more USN cases (n = 56) than PPTs(n = 38), without significant evidence of heterogeneity (I^2 = 0%, P = 0.48) and with an overall OR of 0.46 (95% CI: 0.24-0.86; p = 0.01) (**Figure 4.5**). Similarly, six studies (Buxbaum et al. 2008, 2012; Navarro et al. 2013; Peskine et al. 2011; Spreij et al. 2020; Ulm et al. 2013) in 191 stroke subjects assessed USN using non-immersive VR and PPTs. There was a significant difference between non-immersive VR tasks and PPTs. Non-immersive VR detected more USN cases (n = 110) than PPTs (n= 77). The overall OR was 0.41 (95% CI: 0.23-0.73; p = 0.002) (**Figure 4.5**). No heterogeneity was identified between non-immersive VR studies (I^2 = 20%, P = 0.28) or between subgroups (P = 0.80). Overall, VR assessments (both immersive and non-immersive) identified more USN cases than conventional PPTs and the overall OR was 0.46 (95% CI: 0.32-0.66; p = 0.0001).

Whilst the incidence rate on immersive tasks was 59%, non-immersive tasks showed an incidence rate of 58%.

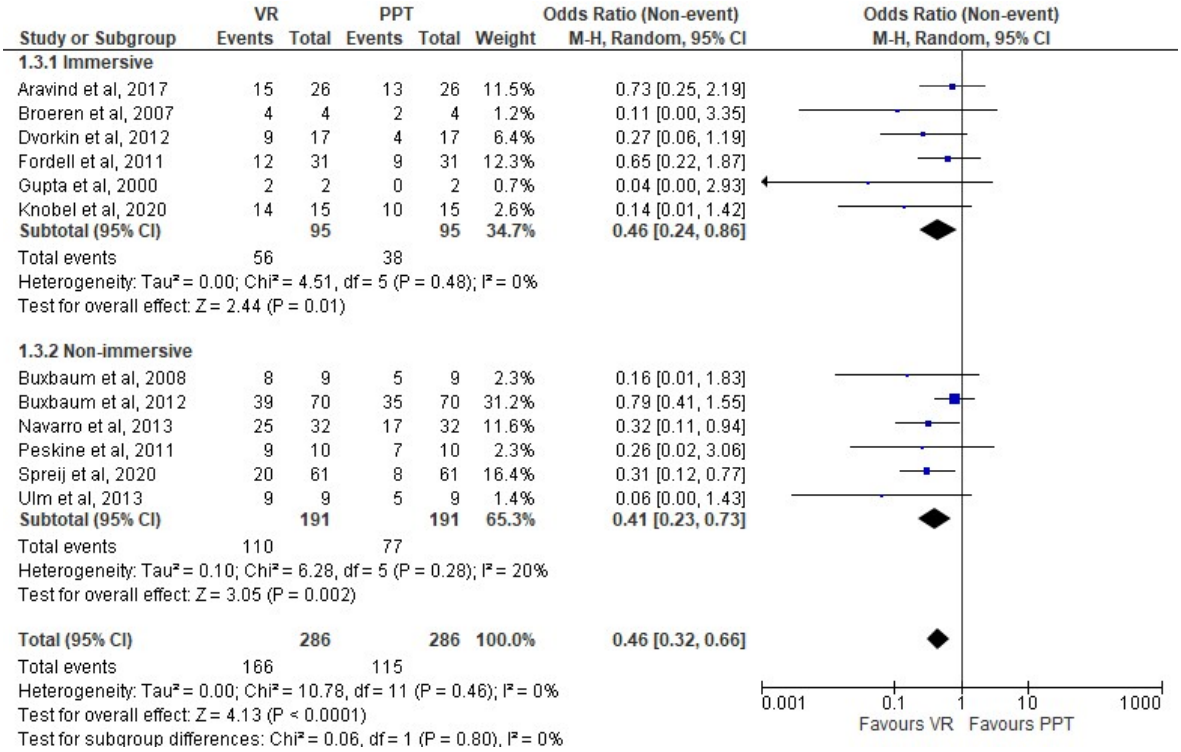


Figure 4. 9 Immersive & non-immersive VR vs. conventional paper-and-pencil tests (PPTs).

USN Rate – both immersive and non-immersive VR tests on stroke patients vs. non-stroke controls

Four studies (Aravind and Lamontagne 2018; Dvorkin et al. 2012; Gupta et al. 2000; Knobel et al. 2020) in 113 subjects (60 stroke patients and 53 controls) assessed USN in stroke patients and non-stroke controls using immersive VR tasks. Non-stroke controls performed significantly better on immersive VR assessments than stroke patients OR 48.97(95% CI: 8.01-299.44; $p = 0.0001$) (**Figure 4.6**). There was no evidence of heterogeneity ($I^2 = 17\%$, $P = 0.30$) or publication bias. Likewise, there was a significant difference between stroke patients and non-stroke controls when assessed by non-immersive VR tasks. Five studies (Buxbaum et al. 2008, 2012; Navarro et al. 2013; Peskine et al. 2011; Spreij et al. 2020) in 241subjects (181 stroke cases and 60 controls) assessed USN using non-immersive VR tasks. Stroke patients' performance was significantly worse than non-stroke controls: OR 39.18 (95% CI: 9.68-158.64; $p = 0.00001$) (**Figure 4.6**). There was no evidence of heterogeneity ($I^2 = 0\%$, $P = 0.82$)

or publication bias. Overall, non-stroke controls performed significantly better on both immersive and non-immersive VR tasks: OR 42.68 (95% CI: 14-123.54; p =0.00001).

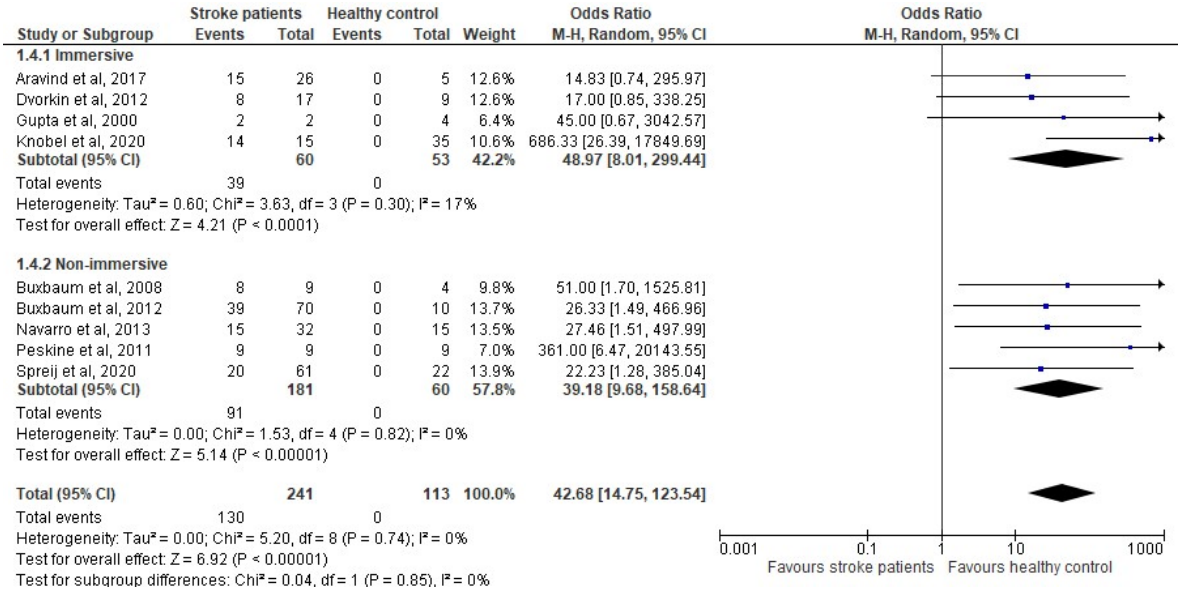


Figure 4. 10 Stroke patients vs. healthy controls measured by immersive & non-immersive VR tasks.

Discussion

Our findings suggest that VR may detect USN otherwise missed by conventional paper-and-pencil tests. Although VR tasks identified more USN cases than conventional tests, the lack of a comprehensive gold standard assessment for all USN types and subtypes across the included studies suggests that caution is needed when interpreting the results.

VR systems for assessment and rehabilitation of cognitive impairments of patients following a stroke (Rose et al. 2005) have been developed to recreate three dimensional (3D) environments where patients are trained to perform specific tasks to achieve a goal. As an assessment tool, VR systems can register and objectively measure the performance of patients within the virtual world and their behavioural responses; as a rehabilitation tool, they have been shown to significantly accelerate the improvement of USN (Weiss et al. 2003; Kim et al. 2011).

The major difference between VR tools and paper-and-pencil assessments lies in their three-dimensional (3-D) and two-dimensional (2-D) spatial information, respectively. Conventional tools employ static 2-D targets in the form of assessments that necessitate simple visual searches in the personal (relating to one's body) and peripersonal (within one's reach) spaces, neglecting USN-related deficits in the far extrapersonal space (beyond one's reach). By contrast, 3-D VR systems mimic real-life environments, in which stimuli can be constantly changing and require dynamic responses from patients. Unlike conventional tests, VR tasks have the potential to assess USN-related deficits in all three of the abovementioned spaces (Weiss et al. 2003; Rose et al. 2005; Kim et al. 2011; Aravind and Lamontagne 2017).

Beyond conventional paper-and-pencil assessments, there exists a number of ecologically valid tests such the CBS and KF-NAP (Azouvi, Olivier, De Montety, et al. 2003; Chen et al. 2012). However, standardising the physical assessment environment across different settings, as well as addressing the discrepancies that may arise during data collection pose several challenges (e.g., researchers and clinicians may score the same assessment differently, whereas automated data collection in a virtual environment will ensure standardisation). VR could offer the ability to assess several USN types and subtypes in a standardised and safe manner. Using VR, it may be possible to create and flexibly adjust the assessment environment to meet the specific needs of each patient, while also increasing the level of complexity and cognitive demands. This is not be possible with traditional assessments. Finally, VR could offer a cheaper alternative to traditional assessments such the BIT. For example, the BIT kits and support materials cost approximately £500. Although the novel VR technology is still relatively new and more studies are needed, it is not unreasonable to suggest that VR could offer a cheaper, ecologically valid alternative to assessments such as the BIT.

Some of the major advantages of VR systems over traditional methods are that they enable neuropsychological practice to be more engaging and generalisable owing to their ability to

assess behaviour in controlled environments (Broeren et al. 2007; Buxbaum et al. 2012; Rizzo, Schultheis, et al. 2004), provide an advanced human-computer interface that allows patients to be assessed and trained through simulations that mirror everyday life activities (Tsirlin et al. 2009) without the need to use real environments which are often not available in hospital settings, and are able to provide information on head-eye co-ordinated movements, postural deviations and limb kinematics – which is highly valuable in detecting subtle changes (Tsirlin et al. 2009).

The lack of gold-standard assessments for USN hampers researchers from carrying out sensitivity and specificity analyses to assess the diagnostic accuracy of VR tasks. Hence, obtaining data from non-stroke controls serves as an alternative method to calculate cut-off limits.

However, this alternative method does not address the issue of heterogeneity associated with USN and the need for a comprehensive gold standard assessment which will enable researchers to conduct sensitivity and specificity analyses. As such, there remains a need for further research to explore different options to develop a comprehensive gold standard assessment. For example, would combining novel technologies (e.g., VR and AR) with more conventional tests or ecological tools produce a better assessment battery than one or the other separately?

In this study, VR tasks (immersive and non-immersive tasks combined) showed that USN was more prevalent among stroke patients (57% of 284 patients) when compared to conventional assessments (47%). Additionally, the rate of USN detection on immersive tasks was 59%, whereas non-immersive tasks showed a detection rate of 58%. Studies using non-immersive VR tasks generally recruited more USN patients than those employing immersive VR tasks, which probably contributed to this finding. It is possible that elderly stroke patients might prefer non-immersive VR assessments that, unlike immersive VR systems, do not involve wearing an HMD (VR goggles), which elderly patients might be unfamiliar with and that may

have contributed to the discrepancy in the number of patients recruited across immersive and non-immersive studies.

VR offers the possibility of displaying ecological scenes that mimic realistic scenarios and activities that are otherwise difficult to perform in real life for stroke victims. Further, collection of data relevant to USN in a manner that is not possible using conventional assessments may be used to forward our understanding of management of USN. However, the technology requires identification of patient suitability and a certain level of technical expertise to administer, although future systems will likely be more user-friendly.

Although VR tasks may appear to detect more USN-related deficits, it is not possible to carry out sensitivity and specificity analysis due to the lack of a gold standard assessments. It is therefore not possible to draw any decisive conclusions on whether VR is truly superior to traditional assessments. A recent study by Spreij et al suggested that using a combination of assessments - both static (e.g., letter cancelation) and dynamic (e.g., VR), rather one or the other, might offer a better understanding of the heterogeneity of the disorder. Combining static and dynamic tests can potentially contribute to developing a comprehensive battery for the assessment of various USN types (sensory and motor) and phenotypes (near and far extra-personal USN). This may also contribute to resolving the issues associated with the lack of gold standard assessments (Spreij et al. 2020).

As with any meta-analysis, a number of limitations need to be noted. Only a small number of studies met the inclusion criteria for a meta-analysis. Most of the included studies had a small sample size. This represents a major limitation for the study as the results may not be representative of the full post-stroke USN-suffering population. Furthermore, only one study (Buxbaum et al. 2012) provided sufficient instruction on administering the VR task and time required to complete the assessment as well as the training required to administer the tasks. None of the 12 studies included provided any information on the cost of VR systems tested, or

the training required to administer those systems. Therefore, it was not possible to assess the utility of VR system in clinical and non-clinical settings.

In conclusion, VR technology may offer a more ecologically valid alternative to conventional paper-and-pencil tools for the assessment of post-stroke USN. However, this study could not draw any decisive conclusions on the superiority of VR over traditional assessments. The overall dataset analysed was relatively small, and no ROC curve analysis could be carried out due to the absence of gold standard assessments. Future studies should be focus on addressing the lack of gold standard assessments, the issues concerning standardisation of data collection and reporting, as well as the development of USN tests that can assess both motor and sensory USN types and phenotypes. Suggestions for future studies focusing on the use of VR for USN assessment purposes include the need for versatile systems that can account for the significant heterogeneity of this disorder. Future VR studies should also provide a detailed cost for development or purchasing the system as well as training materials for users. Further, to address the lack of gold standard assessments, future studies should perhaps experiment with hybrid models of USN assessment; that is, combining traditional paper-and-pencil tests and functional scales such as the CBS with novel technology.

Chapter 5

Virtual Reality Training for the Rehabilitation for Post-Stroke Unilateral Spatial Neglect: A Systematic Review

Abstract

Background & Purpose

Unilateral Spatial Neglect (USN) is a one of most common post-stroke visuo-perceptual impairments. Various interventions for the rehabilitation of USN currently exist and used to treat patients. Virtual reality (VR) is a novel technology that has recently been used to rehabilitate USN patients. This systematic review aims to appraise and compare VR training with conventional USN interventions.

Methods

Electronic databases including Google Scholar and PubMed were searched for relevant studies until October 2021. The search terms used included "virtual reality" AND "spatial neglect".

Results

Nine studies (four randomised controlled trials, one queasy-experimental, three pilot studies, and one preliminary trial) met the inclusion criteria and were included in this systematic review. Only one study reported moderate evidence of VR training being more effective than conventional interventions. Two studies reported limited evidence, whereas the remaining six studies presented conflicting evidence or completely lacked adequate evidence in favour of VR.

Conclusion

VR use for the rehabilitation of USN is still in its infancy. The evidence presented across the included studies is conflicting and inconclusive, making it difficult to draw any coherent conclusions. There is a need for more research on the effectiveness of VR training and whether it is truly better than conventional USN rehabilitation. Combining conventional USN assessments and interventions with VR is an understudied approach. Future studies could explore combining different interventions to help overcome the challenges posed by the

heterogeneity of USN symptoms and absence of consensus on the best diagnostic and rehabilitation methods.

Introduction

Unilateral spatial neglect (USN) is a common post-stroke cognitive disorder (Swan 2001). USN is characterised by reduced responsiveness and/or the inability to detect, react to, or orient toward stimuli or objects that are presented or located contralesionally (Bailey and Riddoch 1999). While estimates of the prevalence of USN vary from 40-70% (Bowen, McKenna, and Tallis 1999; Ten Brink et al. 2017; Paolucci et al. 2001), most studies report a USN occurrence rate of around 50% following right hemisphere damage (Buxbaum et al. 2004; Escalante et al. 2020; Schindler et al. 2002; Stone et al. 1992).

A recent review by Esposito et al. investigated the prevalence of USN in a sample of 6324 stroke patients, 3411 (54%) of whom had right hemisphere lesions, while 2913 (46%) had left hemisphere lesions. When time since stroke onset or type of USN assessment used were not considered, the study reported a prevalence of 38% and 18% after right and left hemisphere damage, respectively. The authors also compared the prevalence of USN using ecological (e.g., CBS) and non-ecological (e.g., letter cancellation) assessments. The comparison resulted in a higher prevalence of 53% in studies using ecological assessment (53%), compared to 24% using conventional, non-ecological assessments. Overall, the prevalence of USN among the total stroke population included was 29% (Esposito, Shekhtman, and Chen 2021).

USN is often described as a complex disorder of heterogenic nature (Li and Malhotra 2015). This means that USN patients can display a wide range of visuospatial (e.g., personal or peri personal) and functional spatial (e.g., colliding with objects while walking) impairments (Bowen and N. B. Lincoln 2007). There are two main types of USN: sensory and motor neglect (Kerkhoff 2001). Sensory USN is characterised by selective unawareness and/or reduced responsiveness to sensory stimuli (Parton, Malhotra, and Husain 2004b). Patients may neglect sensory (auditory, visual, tactile and olfactory) stimuli presented contralaterally to the side of brain damage (Rode et al. 2017). Motor USN is characterised by the reduced impromptu use

or a total disuse of contralesional extremities in the contralesional hemispace following a stroke, and in the absence of other motor deficits such as hemiplegia and hypertonia (Laplane and Degost 1983; Sampanis and Riddoch 2013). A third type - namely representational or imaginal USN, can occur in the absence of external stimuli and may affect the mental imagery of patients (Bartolomeo et al. 2005).

Given its complex and heterogenous nature, diagnosing and rehabilitating USN has proven to be a challenge (Bowen and N. B. Lincoln 2007; Luukkainen-Markkula et al. 2011). Several diagnostic methods, including conventional/nonecological tests, ecological, and technology-based (e.g., VR) assessments have been developed and tested (Azouvi, Olivier, De Montety, et al. 2003; Gammeri et al. 2020; Rorden and Karnath 2010). Yet no single gold standard assessment or battery has been agreed upon (Azouvi, Jacquin-Courtois, and Luauté 2017). Similarly, several USN rehabilitation methods have been developed and tested (Azouvi et al. 2017; Bowen and N. Lincoln 2007). However, there is still inadequate evidence to endorse or disprove their efficacy in terms of increasing functional independence and reducing the impact and severity of disability.

USN interventions and treatment

There currently exists many different pharmacological and non-pharmacological interventions for the rehabilitation of USN (Riestra and Barrett 2013). The aim of all interventions is to mitigate the negative effects of USN-related cognitive and motors deficits to improve the patient's ability to perform activities of daily living (ADLs), their quality of life and active social participation (Gammeri et al. 2020).

Types of interventions

USN interventions can be divided into two groups: pharmacological and non-pharmacological interventions. Generally, non-pharmacological interventions are used more frequently with

USN patients than pharmacological treatments, which were recently reviewed Luvizutto et al. (2015).

I. Pharmacological interventions:

Pharmacological treatment has been developed and applied to USN patients to improve their performance on conventional tests and assessments of ADLs (Arogyaswamy 2020). In Theory, there are various pharmacological drugs that can be used to treat USN. However, only a limited number of controlled studies addressed the specific effects of drug treatment for this disorder (Luvizutto et al. 2015). Pharmacological approaches for USN treatment are not often included in rehabilitation strategies, which tend to mostly employ non-pharmacological interventions (Riestra and Barrett 2013). Pharmacological interventions for USN include dopaminergic modulation (Mukand et al. 2001), combined modulation (dopaminergic and adrenergic modulation) (Malhotra et al. 2006), serotonergic modulation (Alex and Pehek 2007), and cholinergic modulation (Vossel et al. 2010).

Pharmacological drugs have been occasionally explored in both animals and humans, yet there is clinical uncertainty about the effectiveness of such drugs for USN treatment, perhaps because the literature remains scarce (Luvizutto et al. 2015; Malhotra et al. 2006). The best documented drug-based interventions to treat USN are those focusing on the dopaminergic system (Li et al. 2020). Corwin et al studied the effects of apomorphine - a dopamine receptor agonist, on USN which was induced by cortical damage in rats. The authors suggested that dopamine agonists can effectively treat and reduce USN (Corwin et al. 1986). Further, two human studies reported some improvement of USN-related symptoms following the administration of dopamine agonists (Fleet et al. 1987; Mukand et al. 2001).

However, both studies had limitations, mainly a very small sample size. Fleet et al. treated two USN patients with bromocriptine, while Mukland et al. administered carbidopa L-dopa to a small sample of four women with left-sided USN. Despite attempts to investigate pharmacological agents, there is currently no consensus on their effectiveness for USN treatment. Thus, further research is needed as no decisive conclusions can yet be drawn (van der Kemp et al. 2017).

II. Non-pharmacological interventions

Non-pharmacological rehabilitation strategies include a broad range of interventions that have been developed and administered to USN patients (Riestra and Barrett 2013). The goal of non-pharmacological interventions can vary depending on the type of intervention (Bowen and N. B. Lincoln 2007). For example, the goal can be to help patients to voluntarily compensate for their USN-related deficits through training and enhancing their awareness of the impairments, or it can be to alter the underlying elements such as the impaired spatial representation of the patient without necessarily requiring their awareness of the deficits (Barrett, Levy, and Rothi 2007; Proto et al. 2009). The non-pharmacological interventions for USN can be grouped into two categories: top-down approaches (e.g., visual scanning interventions, mental function therapy and sustained attention training), and bottom-up approaches (e.g., body/space awareness training, movement-based training, prism adaptation) (Luauté et al. 2006). The most commonly used non-pharmacological interventions for USN treatment are:

- **Visual scanning interventions**: These are among the earliest of USN interventions and continue to be used today in rehabilitation strategies (Husain 2008). These interventions include visual scanning exercises, often combined

with task-oriented activities, that aim to encourage the active and targeted exploration of spatial frames (e.g., peri-personal, and far extra-personal spaces) or the entire visual field (van Kessel et al. 2013). They also include interventions such as training of eye movement via static and/or dynamic stimuli (Walle et al. 2019). Another technique is eye-patching where the ipsilesional eye is patched to encourage visual exploration of the contralesional/neglected side of the visual field (Smania et al. 2013).

- **Body/space awareness training:** The aim of this method is to improve the patient's dynamic balance through awareness raising of the body and space. This training normally involves repetitive movements that also aim to achieve postural stability. Cueing awareness of the body and the neglected hemispace can be achieved through different methods, including verbal cues or sensory devices (Bang, Noh, and Cho 2015).
- **Prism adaptation therapy:** Although prism adaptation was known for decades prior to its adoption as an intervention for USN, it is now considered one of most promising and widely used treatments for this disorder (Chen et al. 2017; Harris 1963). This therapy requires patients to wear prism lenses which horizontally shift the visual field to the ipsilateral hemispace, and continually execute visuomotor tasks lasting for about 20 minutes. Following the removal of the lends, patients typically miss the visual target as they incorrectly reach toward the contralateral side of space (Goedert, Zhang, and Barrett 2015). The patients then compensate for their error by adjusting their movement to point correctly at the visual target – this is also known as adaptation (Saj et al. 2019). The post-therapy benefits can last for months and even years in some cases (Fortis et al. 2010; Panico, Rossetti, and Trojano 2020). Multiple therapy

sessions are normally recommended for USN patients. This is because prism adaption studies have reported that multi-session, rather a single session, therapy is more likely lead to positive effects on USN patients' visuospatial abilities (Rode, Rossetti, and Boisson 2001; Rossetti et al. 1998; Serino et al. 2006) as well as motor functional improvement (Goedert et al. 2014), postural stability (Nijboer et al. 2014), and ADLs (Champod et al. 2016). While the literature appears to support the use of prism adaptation for USN rehabilitation, Bowen et al. suggested that there may be publication bias resulting from the likelihood of studies publishing positive results regarding prism adaptation far more than studies that have negative findings (Bowen et al. 1999).

- **Movement-based therapy:** These are movement therapies that include physical therapy such as limb activation therapy, whole body training or balance-focused training. Some studies suggest that training the affected limb or whole body may indirectly contribute to reducing USN symptoms (Freeman 2001; Riley 2015).
- **Mental function therapy:** These include interventions that target mental processes such as thinking. This type of therapy may employ technology [e.g., virtual reality (VR) rehabilitation] (Morse et al. 2020), or more traditional approaches such as repetitive mental training (e.g., mental imagery) (Park and Lee 2015). The aim of this therapy is to ameliorate motor and visual scanning abilities without carrying out any physical activity (Kwon 2018).
- **Non-invasive brain stimulation:** This intervention uses methods such as repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS). The aim of these methods is to trigger changes to the sensory and motor functions of USN patients. These changes can be

achieved by altering the excitability of the motor cortex of USN patients (Müri et al. 2013).

- **Electrical stimulation:** This intervention includes therapies such as Transcutaneous electrical nerve stimulation (TENS), which involves the use of mild electrical currents to stimulate contralesional side of the body, most commonly the left neck muscles of right-brain-damaged USN patients (Pitzalis et al. 2013).

- **Virtual reality technology for the rehabilitation of USN**

Virtual reality (VR) is a novel technology that has been increasingly used in telerehabilitation (Laver et al. 2017; Rizzo, Strickland, and Bouchard 2004). While VR-based rehabilitation for USN is still in its infancy stage, the technology has the potential to offer alternative and/or complementary therapies to traditional interventions (Levin 2020). The potential of VR stems from its compatibility with mental functioning and its ability to recreate environments and scenarios that are multisensory, enjoyable, and flexible (Jack et al. 2001; Saposnik 2016). This flexibility enables the ongoing and future development of home-based/therapy after discharge from hospital, and allows for the remote monitoring of patients' performance and progress without the need for therapists (Sheehy et al. 2019; Stanica et al. 2020). The technology also offers the opportunity to create VR-based therapies that are complementary to, rather than competing with, conventional therapies, especially in terms of standardising assessment and rehabilitation environments (Montalbán and Arrogante 2020).

To date, a number of studies have investigated the use of VR for USN rehabilitation. These studies employed both immersive and non-immersive VR systems, and developed several scenarios including non-immersive street crossing virtual environments (Katz et al. 2005;

Kim et al. 2007), non-immersive visual scanning VR tasks (Kim et al. 2011), and wheelchair obstacle navigation tasks (Webster et al. 2001).

The importance of this study

VR is a relatively new technology, still in its early stages of development for USN rehabilitation. There have been studies into how VR can be used to rehabilitate USN patients, however, few of these have been randomised controlled trials. The purpose of this study was to summarise the material available regarding the use of VR to rehabilitate USN patients and offer an updated review of the literature. This updated review builds on previously published reviews (e.g., see systematic review by Pedroli et al. 2015) by identifying and reviewing VR papers published up to October 2021.

Objective

As VR-based tools for the rehabilitation of USN continue to be developed and tested, there is a continuous need to evaluate the effectiveness of this novel technology, especially as new tools emerge. Therefore, the aim of this review was to evaluate the effectiveness of VR rehabilitation for USN and compare it with conventional interventions. The continuous evaluation of recent and older VR tools is of great importance as this technology evolves. It will not only help understand the design and limitations of VR tools, but could also potentially inform the design of future VR studies/tools and help in standardising them.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines (Liberati et al. 2009).

Search Methods

Electronic search methods were used to find papers for the systematic review. Google Scholar and databases such as PubMed were used to search for published papers. The search was limited to human studies in all languages. Search terms included: ‘stroke’ ‘cerebrovascular

accident' 'ischemic-stroke' 'haemorrhagic-stroke' 'unilateral spatial neglect' 'visuospatial neglect' 'hemispatial neglect' 'visual neglect' 'evaluation' 'rehabilitation' 'training' 'intervention' 'virtual reality' 'technology' 'computer simulation' 'therapy computer assisted' with AND/OR used as Boolean operators. Studies included in the search were published up until 31st October 2021. References of all primary papers used in the study were screened to identify additional studies which met our inclusion criteria.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are outlined below:

- **Inclusion criteria:**
    a. Adults ≥ 18 years of either gender with confirmed stroke (ischemic or haemorrhagic)
    b. Included stroke patients with USN
    c. Included an intervention group that received VR training for USN rehabilitation
- **Exclusion criteria:**
    d. Did not include stroke patients with USN
    e. Patients with USN due to brain injury other than a stroke
    f. Children < 18 years of age
    g. Studies that did not include VR training as an intervention
    h. Single case studies

Levels of Evidence

The Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence was employed to assess the evidence level (EL) across included studies. Each of the included studies was assessed against the OCEBM EL criteria outlined below (**Table 4.1**). The criteria include a hierarchy of five levels of evidence, ranging from level one (highest EL) to level five (lowest EL) (Howick et al. 2011).

Table 5.1 OCEBM EL hierarchy, and criteria

Hierarchy		OCEBM EL Criteria
1	Highest	Systematic reviews of RCTs or *n*-of-1 trials +/– meta-analyses
2		RCTs
3		Non-randomised controlled cohort or follow-up studies
4		Case-series, case-control, or historically controlled studies
5	Lowest	Mechanism-based reasoning

Methodological quality assessment

We used the PEDro scale to assess the methodological quality (MQ) of the included studies in this systematic review (PEDro 1999). Since it was last amended in June 1999, the PEDro scale has been widely used as a method of MQ assessment of clinical trials (Matos and Pegorari 2020). While different versions of the scale (e.g., a three-item, a six-item scale, an eleven-item scale) exist in the literature, the most commonly used version is the scale with 10 criteria (de Morton 2009). The aim of scale is to gauge internal validity and assess the statistical information provided in clinical trials. When scoring the items of the scale each criterion is scored as either yes (present = 1 point) or no (absent = 0), and the overall sum of the 10 items is then calculated to provide a total MQ score for each study. The maximum score is 10, whereas the minimum score is 0 (Maher et al. 2003; de Morton 2009; PEDro 1999). The 10 criteria of the scale are presented in **Table 5.2** below.

Table 5.2 PEDro scale criteria for MQ assessment

Item	MQ criteria	Scoring
1	Random allocation of subjects to groups	Yes (1) OR No (0)
2	Concealed allocation of subjects	
3	Similarity of groups at baseline	
4	Blinding of all subjects	
5	Blinding of all therapists	
6	Blinding of all assessors	
7	At least one key outcome measure obtained from > 85% of all subjects	
8	Intention to treat analysis	
9	Between-group statistical comparison reported for at least one key outcome	
10	Point and variability measures reported for at least one key outcome	

Results

Using the search terms outlined above, the initial search of electronic databases such as Google Scholar and PubMed returned 32,597 results. These results were inspected and filtered out. Duplicates and ineligible studies were removed using Mendeley software, title, and abstract screening. Following the second round of scanning, 26 articles were eligible for full review. From these 26 articles, 17 did not meet the inclusion criteria. Nine studies met the inclusion criteria and were included in the systemic review. A flow diagram can be seen in **Figure 5.1** below.

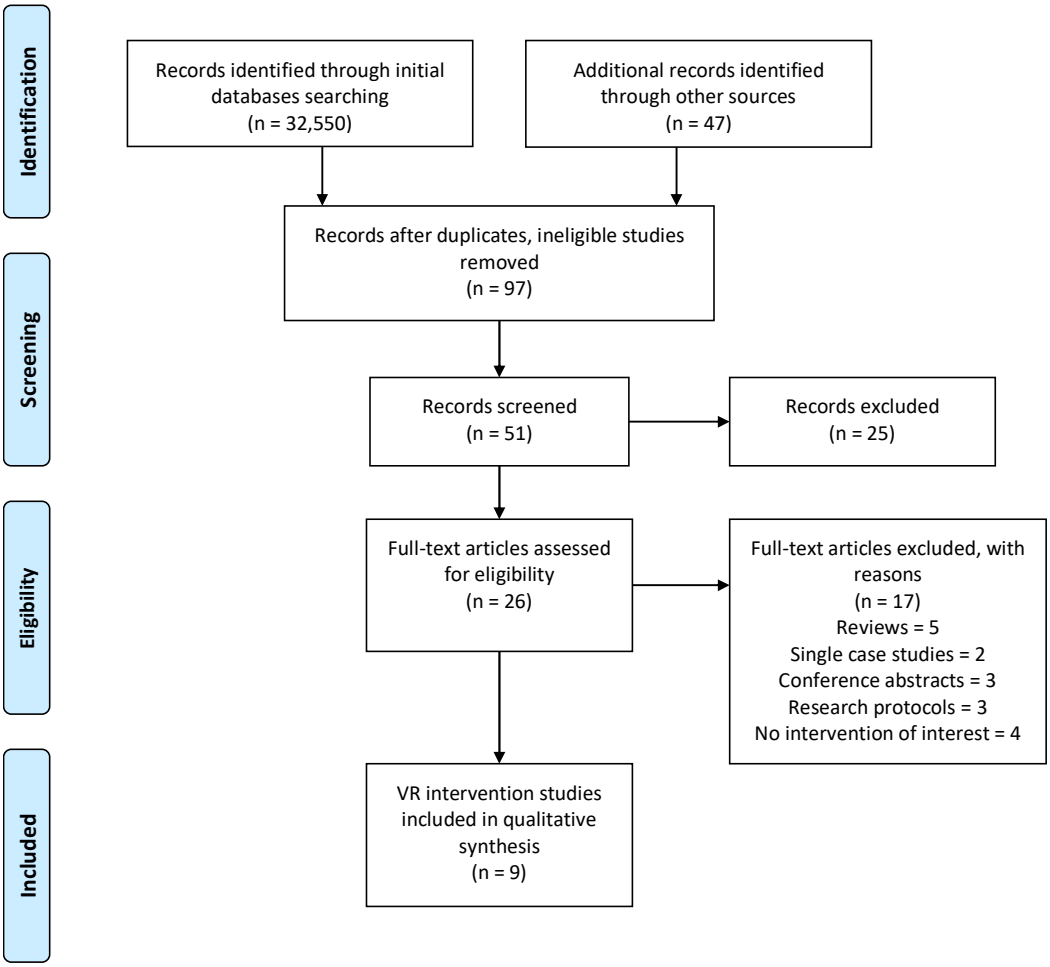


Figure 5.1 Flow diagram showing the process of study selection for systematic review

Table 5.3 Studies included in the systematic review

Studies included in the systematic review
Application of digital practice to improve head movement, visual perception and activities of daily living for subacute stroke patients with unilateral spatial neglect: Preliminary results of a single-blinded, randomized controlled trial (Choi, Shin, and Bang 2021)
Visual scanning training for neglect after stroke with and without a computerized lane tracking dual task (van Kessel et al. 2013)
The Effect of Virtual Reality Training on Unilateral Spatial Neglect in Stroke Patients (Kim et al. 2011)
Interactive virtual environment training for safe street crossing of right hemisphere stroke patients with unilateral spatial neglect (Katz et al. 2005)
Computer-Assisted Training for Improving Wheelchair Mobility in Unilateral Neglect Patients (Webster et al. 2001)
RehAtt – scanning training for neglect enhanced by multi-sensory stimulation in Virtual Reality (Fordell et al. 2016)
Validation of an immersive virtual reality system for training near and far space neglect in individuals with stroke: A pilot study (Yasuda et al. 2017)
Exploring the effects of virtual reality on unilateral neglect caused by stroke: Four case studies (Smith, Hebert, and Reid 2007)
Virtual Reality and Left Hemineglect: A Technology for Assessment and Therapy (Myers and Bierig 2000)

Levels of Evidence

Table 5.4 Evidence level (EL) results for included studies

Study reference	EL criteria	EL score
(Choi et al. 2021)	Randomised controlled trial	2
(van Kessel et al. 2013)	Randomised controlled trial	2
(Kim et al. 2011)	Randomised controlled trial	2
(Katz et al. 2005)	Randomised controlled trial	2
(Webster et al. 2001)	Non-randomised controlled cohort	3
(Fordell et al. 2016)	Follow-up study	3
(Yasuda et al. 2017)	Pilot/within-participant pre-post design	4
(Smith et al. 2007)	Case-series	4
(Myers and Bierig 2000)	Mechanism-based reasoning/preliminary trial	5

Using the OCEBM EL criteria, four studies (Choi et al. 2021; Katz et al. 2005; van Kessel et al. 2013; Kim et al. 2011) had an EL score of 2, two studies (Fordell et al. 2016; Webster et al.

2001) had an EL score of 3, two studies (Smith et al. 2007; Yasuda et al. 2017) had an EL score of 4, and one study had an EL score of 5 (Myers and Bierig 2000).

Methodological quality assessment

Only one study (Choi et al. 2021) had a good MQ score. Two studies (Katz et al. 2005; Kim et al. 2011) had a fair MQ score, whereas six studies (Fordell et al. 2016; van Kessel et al. 2013; Myers and Bierig 2000; Smith et al. 2007; Webster et al. 2001; Yasuda et al. 2017) had a low/poor MQ score.

Table 5.5 Results of methodological quality (MQ) assessment

Study reference	1	2	3	4	5	6	7	8	9	10	MQ score
(Choi et al. 2021)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8/10
(van Kessel et al. 2013)	N	N	Y	N	N	N	Y	N	Y	N	3/10
(Kim et al. 2011)	Y	N	N	N	N	N	Y	Y	Y	Y	5/10
(Katz et al. 2005)	Y	N	Y	N	N	N	Y	Y	Y	Y	5/10
(Webster et al. 2001)	N	N	Y	N	N	N	Y	Y	Y	N	4/10
(Fordell et al. 2016)	N	N	N	N	N	N	Y	Y	Y	Y	4/10
(Yasuda et al. 2017)	N	N	N	N	N	N	Y	Y	Y	Y	4/10
(Smith et al. 2007)	N	N	N	N	N	N	Y	Y	N	N	2/10
(Myers and Bierig 2000)	N	N	N	N	N	N	N	N	N	N	0/10

1 = random allocation of subjects to groups; 2 = concealed allocation of subjects; 3 = similarity of groups at baseline; 4 = blinding of all subjects; 5 = blinding of all therapists; 6 = blinding of all assessors; 7 = at least one key outcome measure obtained from > 85% of all subjects; 8 = 'intention to treat' analysis; 9 = between-group statistical comparison reported for at least one key outcome; 10 = point and variability measures reported for at least one key outcome.

Summary of included studies

Choi et al. recruited 24 stroke patients with USN and randomised them into two study groups. The experimental group (n = 12) received digital training via VR-based tasks (e.g., VR Pinch Draw, VR table tennis, virtual Rock-Paper-Scissors or RPS island) with Leap Motion controller (a small motion-tracking device normally mounted onto VR goggles or connected directly to a computer), whereas the control group (n = 12) was given conventional USN interventions (e.g., visual scanning activities, writing, figure copying, puzzles etc.). Both groups received the same length of treatment (three sessions per week, each session lasting for 30 minutes, over a 4-week period). USN was assessed in both groups at baseline and post-treatment, and key USN

outcome measures included the line bisection test, CBS, and modified Barthel index (MBI) (Choi et al. 2021).

Van Kessel et al. examined 29 stroke patients with right hemisphere stroke and semi-randomly assigned them to two groups. Although the study design was reported as an RCT, randomisation was not applied to all participants. The experimental group (n = 14) received 30 sessions of visual scanning training (a translated version of Italian Training di Scanning Visuospaziale – TSVS) consisting of four tasks (digit detection, copying/reading, drawing and figure description) and completed an additional non-immersive driving simulator task (dual tasking) during four weeks of training. The control group (n = 15) was trained using a single lane tracking task for two days per week for a period six weeks. Although the authors reported am overall training period of six week for both groups, there are significant discrepancies in terms of intervention strategies (e.g., duration of therapy) between the two groups. Outcome measures for USN included the line and letter cancellation tests, Bells test, line bisection, word reading and the Baking Tray Task (van Kessel et al. 2013).

Kim and colleagues carried out a randomised controlled trial (RCT) to assess the effectiveness of multisensory VR games as a mode of USN rehabilitation, and compared it with conventional interventions (e.g., visual scanning training). Twenty-four stroke patients were recruited, 12 of whom were randomly assigned to each of the two study groups (VR training vs. control group). Each of study group received 30 minutes training per day of the assigned intervention for five days per week over a three-week period. The study employed a number of outcomes measures, including the Catherine Bergego Scale (CBS), line bisection and star cancellation tests (Kim et al. 2011).

Katz et al. recruited 19 USN patients with right hemisphere stroke. The experimental group (n = 11) received VR training in the form of non-immersive VR street crossing tasks. The control group (n = 8) received structured, computer visual scanning training. Both groups received the

training protocol was identical for both study groups (each group received three, 45 minutes sessions per week for 4 weeks). Outcome measures included star cancellation test from the BIT, Meuslam cancellation test and the ADL checklist (Katz et al. 2005).

Webster et al. conducted a case-control study with 20 USN patients with right hemisphere stroke who received non-immersive VR training consisting of five tasks (VR visual scanning, coordinating scanning with right upper extremity movements, detection of stimuli, wheelchair simulation, and obstacle avoidance). The VR group was compared with a control group (n = 20) who were recruited in a previous study and only received conventional rehabilitation in the form of physical and occupational therapy. Outcome measures reported include random letter cancellation test, Ray-Osterrieth complex figure and real-life wheelchair obstacle course (Webster et al. 2001).

Fordell et al. conducted a pilot study with 15 USN patients with right hemisphere stroke who were trained using an immersive VR system, namely RehAtt, which involves visual scanning tasks combined with multisensory stimulation in an interactive virtual environment. All patients received three, 60 minutes sessions per week over five weeks. Therefore, each patient received a total of 15 hours of VR training during the therapy. While no control group was recruited, the study protocol involved three baseline evaluations of USN and follow-up trainings within a week and after 25 weeks from the end of VR therapy. Outcome measures included the CBS, Baking Tray task, star cancellation and line bisection tests (Fordell et al. 2016).

Yasuda et al. conducted a pilot study with 10 USN patients with right hemisphere stroke. This study did not recruit a control group. The patients recruited had USN deficits the peri-personal and far extra-personal spaces. The VR system consisted of an immersive visual scanning task which required patients to identify and collect items (e.g., a virtual burger) in the peri-personal and far extra-personal spaces. Outcome measures included four paper-and-pencil tests (e.g.,

line bisection and cancellation tests) from the Behavioural Intention Test (BIT) (Yasuda et al. 2017).

Smith et al. carried out a case study employing a single subject design. The authors recruited four stroke patients (two with right hemisphere lesions, and two with bilateral stroke). The study design employed a three-phase approach. In phase A^1, baseline USN measures were collected. Phase B involved the delivery of non-immersive VR training in the form of "Birds and Balls" game. The game consisted of 20 trials (5 X 2 trials with birds entering the screen from the right then left side, and 5 X 2 trials with balls entering from each direction). Patients had to identify and catch the birds and balls. Outcome measures included the BIT and Bells test (Smith et al. 2007).

Myers and Bierig designed proposed an application, namely the VR tracking and cueing (VRTC) programme for the assessment and rehabilitation on USN. The VRTC is an immersive virtual environment that consists of a virtual house with three rooms and a backyard. The authors reported that the right side of the virtual environment was patched to encourage patients to explore the neglected side within the virtual environment. The VRTC was reportedly able to measure the angle of head rotation, the time required to turn the head to the maximum angle in each direction, and the number of cues given to each patient to turn their head to the left. Five USN patients participated in this trial and were trained with the VRTC system. However, no control group or statistical analysis were presented in the study. Additionally, no outcome measures were reported (Myers and Bierig 2000).

Table 5.6 Characteristics of included studies

Choi et al. 2021

Study Characteristics	
Methods	RCT Country: South Korea
Participants	24 stroke patients (3 right and 21 left hemisphere stroke) VR group (n = 12), control group (n = 12) USN assessment: Line bisection test (a deviation of ≥15% to the right from the midpoint was indicative of USN) was used to confirm presence of USN prior to the random allocation of subjects Mean age±SD, years: VR group = 63.00±10.02, control group = 61.58±9.99. Gender (M/F) for VR = 5/7, control = 6/6 Time since stroke onset (mean±SD, months): VR group = 4.33±1.56, control = 4.58±1.62
Interventions	VR group: Immersive VR system using Oculus Rift DK2 (HMD/VR goggles) and Leap Motion sensory device to capture hand gestures in the virtual environment. Patient performed 10 different VR tasks/games (e.g., "Blocks, Element L, Warlock, Laser, Pinch Draw, RPS island, VR table tennis") developed by Oculus share and Leap Motion developers. Control group: Received conventional USN training, including visual scanning tasks, reading and writing, drawing and figure copying. Both groups received four weeks of allocated training, three sessions per week, each session lasting for 30 minutes.
Outcomes	Line bisection test (LBT): VR pre- vs. post-treatment (mean±SD) scores = 8.25±5.89 vs. 11.75±5.83; control pre- vs. post-treatment = 7.83±6.28 vs. 9.67±6.61 Catherine Bergego Scale (CBS): VR = 8.33±5.87 vs. 11.25±5.03; control = 9.33±6.16 vs. 10.42±6.33 Modified Barthel index (MBI): VR = 37.42±8.73 vs. 47.17±9.73; control = 38.08±9.80 vs. 44.50±10.19

Van Kessel et al. 2013

Study Characteristics

Methods	RCT (but used block semi-randomisation so randomisation was not applied to all subjects) Country: Netherlands
Participants	29 stroke patients with right hemisphere lesions VR group (n = 14), control group (n = 15) USN assessment: Letter cancellation, line bisection, line cancellation, word reading task, Grey Scales, Baking Tray task, Bells test, semi-structured scales for the evaluation of personal and far extra-personal USN, subjective USN questionnaire Mean age±SD, years: VR group = 59.07±6.08, control group = 61.86±7.75. Gender (M/F) for VR = 7/7, control = 10/5 Time since stroke onset (mean±SD, days): VR group = 157.60±117.16, control = 140.57±133.56
Interventions	Both study groups received TSVS training (three sessions per week) consisting of four tasks (digit detection, copying/reading, drawing and figure description) in weeks 1-3 of treatment. VR group: TSVS + two sessions/week of single lane tracking task + two sessions/week of non-immersive driving simulator (dual tasking) task in weeks 4-6 of treatment (discrepancies detected in duration of treatment between VR and control groups). Control group: TSVS + two sessions/week of single lane tracking task in weeks 4-6
Outcomes	Baking Tray index: VR pre- vs. post-treatment (mean±SD) scores = 0.39±0.55 vs. 0.43±0.40; control pre- vs. post-treatment = 0.36±0.59 vs. 0.19±0.57 Letter cancellation omissions: VR pre- vs. post-treatment (mean±SD) scores = 24.07±24.15 vs. 12.93±21.55; control pre- vs. post-treatment = 30.07±29.23 vs. 15.33±20.55 Line cancellation omissions: VR pre- vs. post-treatment (mean±SD) scores = 2.07±2.79 vs. 0.71±1.54; control pre- vs. post-treatment = 1.52±3.27 vs. 0.40±0.91 Bells test omissions: VR pre- vs. post-treatment (mean±SD) scores = 12.21±8.83 vs. 6.71±7.52; control pre- vs. post-treatment = 10.20±6.84 vs. 6.80±5.13

Kim et al. 2011

Study Characteristics	
Methods	RCT Country: South Korea
Participants	24 stroke patients with right hemisphere stroke VR group (n = 12), control group (n = 12) USN assessment: Star cancellation, line bisection, CBS Mean age±SD, years: VR group = 62.3±10.2, control group = 67.2±13.9. Gender (M/F) for VR = 9/3, control = 5/7 Time since stroke onset (mean±SD, days): VR group = 22.8±7.6, control = 25.5±18.5
Interventions	Both groups received physical, occupational, and cognitive therapies. Same intensity and duration of treatment were applied to both groups. VR group: Non-immersive VR training (e.g., catching flying birds, coconut etc in virtual environment using computer gloves). Treatment was administered for once/day for 30 minutes, five days/week for three weeks. Control group: Conventional rehabilitation programme including visual scanning, reading and writing, copying and drawing, and puzzles.
Outcomes	Star cancellation test: VR pre- vs. post-treatment (mean±SD) scores = 15.3±9.3 vs. 8.2±8.3; control pre- vs. post-treatment = 11.4±8.2 vs. 6.9±7.8 Line bisection test: VR pre- vs. post-treatment (mean±SD) scores = 24.9±22.2 vs. 18.9±22.6; control pre- vs. post-treatment = 10.8±9.9 vs. 5.9±8.7 CBS: VR pre- vs. post-treatment (mean±SD) scores = 20.1±7.5 vs. 11.0±5.7; control pre- vs. post-treatment = 17.9±7.1 vs. 12.2±7.6 Korean version of the modified Barthel index (MBI): VR pre- vs. post-treatment (mean±SD) scores = 28.5±15.6 vs. 47.9±15.1; control pre- vs. post-treatment = 34.4±22.1 vs. 44.9±21.8

Katz et al. 2005

Study Characteristics	
Methods	RCT Country: Israel
Participants	19 stroke patients with right hemisphere with left USN VR group (n = 11), control group (n = 8) USN assessment: Star cancellation from the BIT, Mesulam cancellation test, activities of daily living (ADL) checklist Mean age±SD, years: VR group = 62.4±14.0, control group = 63.3±10.8. Gender (M/F) for VR = 7/4, control = 5/3 Time since stroke onset (mean±SD): Unclear
Interventions	VR group: Non-immersive VR street crossing task with different levels of difficult. Treatment was administered once/day for 45 minutes, three days/week for four weeks. Control group: computer scanning task (unclear what the tasks were). Same duration and intensity of treatment as VR group.
Outcomes	Star cancellation test: VR pre- vs. post-treatment (mean±SD) scores = 9.2±9.7 vs. 14.8±12.9; control pre- vs. post-treatment = 14.6±10.4 vs. 18.1±10.2 Mesulam cancellation test: VR pre- vs. post-treatment (mean±SD) scores = 7.4±9.2 vs. 13.6±12.2; control pre- vs. post-treatment = 6.5±9.3 vs. 12.6±10.6 ADL checklist: VR pre- vs. post-treatment (mean±SD) scores = 2.2±0.5 vs. 1.4±0.6; control pre- vs. post-treatment = 1.4±0.7 vs. 0.8±0.5

Webster et al. 2001

Study Characteristics	
Methods	Quasi-experimental Country: USA
Participants	40 stroke patients with right hemisphere stroke VR group (n = 20), control group (n = 20) USN assessment: Random letter cancellation test, Rey-Osterrieth cancellation test Mean age±SD, years: VR group = 59.53±9.38, control/untrained group = 60.16±9.18. Gender (M/F) = 38/2 (unclear what the M/F ratio was in each group) Time since stroke onset (mean±SD, days): VR group = 173.32±293.45, control = 159.79±198.87
Interventions	Compared experimental group who received VR training with a control group who received conventional in-patient rehabilitation. VR group: Non-immersive VR (computer-assisted therapy in the form of simulated wheelchair) for 12 -20 sessions, each lasting for approx. 45 minutes. Control group: From a previous study. Received conventional USN rehabilitation, including physical and occupational therapy. Control subjects did not receive any additional training other than in-patient rehabilitation.
Outcomes	Wheelchair obstacle course (WCOC): No pre- vs. post-treatment data. Compared performance of trained subjects vs. untrained group. WCOC total collisions for VR group: Left side (mean±SD) = 1.26±1.91, right side (mean±SD) = 0.11±0.32 vs. Untrained group: Left side = 5.10±3.14, right side = 0.47±0.77

Fordell et al. 2016

Study Characteristics	
Methods	Follow-up/pilot Country: Sweden
Participants	15 stroke patients with right-sided ischemic infarction VR group (n = 15), no control USN assessment: Star cancellation test, line bisection test, Baking Tray task, extinction test, Catherine Bergego Scale (CBS) Mean age±SD, years: VR group = 72.8±5.7. Gender (M/F) for VR = 11/4 Time since stroke onset (mean±SD, months): VR group = 41.0±27.0
Interventions	VR group: Immersive VR RehAtt method consisting of three tasks: 1- "mental rotation task", 2- "visuo-motor exploration task", and 3- "visuo-spatial and scanning task". All patients received three training sessions per week, duration was 60 minutes/session, for five weeks. Repeated baseline measures were obtained, authors reported no test-retest effects for any of the USN tests. Post treatment measures were obtained within a week after the end of treatment. Follow-up CBS scoring was completed by each patient and their next of Kin. Follow-up CBS test took place after 25 weeks/6 months of VR treatment
Outcomes	CBS: VR pre-, post-treatment and six-month follow-up (mean±SD) scores were completed by: 1) Therapist: Baseline = 10.0±6.7, post-treatment = 5.0±3.8, follow-up = N/A 2) Next of Kin: Baseline = 10.6±6.8, post-treatment = 8.4±6.8, follow-up = 9.1±6.8 3) Patient: Baseline = 7.6±5.8, post-treatment = 2.5±1.9, follow-up = 3.5±3.8

Yasuda et al. 2017

Study Characteristics	
Methods	Pilot/within-participant pre-post design, no control Country: Japan
Participants	10 stroke patients with right hemisphere lesions VR group (n = 10) USN assessment: Letter cancellation, line bisection, line cancellation, star cancellation from the Behavioural Inattention Test (BIT). Assessment of USN in the near and far extra-personal spaces. Age (range), years: VR group (45 – 85 years). Gender (M/F) for VR = 6/4 Time since stroke onset (range): VR group = within 6 months of stroke onset
Interventions	VR group = Immersive visual scanning task. Patients to orally identify and collect items (e.g., a virtual burger) in near and far spaces. A single session treatment lasting for approx. 30 minutes. Paper-and-pencil-test scores were compared pre- and post-treatment.
Outcomes	BIT (four paper-and-pencil tests only). Scores of tests were added up and reported as median (IQR) totals. Post-VR training scores were provided, but pre-VR training scores were not. The study reported a comparison between the pre- and post-VR BIT scores using the Wilcoxon Signed-Rank test. Below are the comparison results reported: Total BIT for four conventional tests: $z = 1.3180$, $p = 0.1875$

Smith et al. 2007

Study Characteristics	
Methods	Case series Country: Canada
Participants	Four stroke patients (2 right hemisphere, 2 bilateral stroke) VR group (n = 4) USN assessment: Behavioural Inattention Test (BIT), Bells test Demographics: Patient1 (P1) = 53 years/female, P2 = 49 years/female, P3 = 55 years/female, P4= 40 years/male Time since stroke onset: P1 = 13 months, P2 = 7 years, P3 = 11 years, P4 = 4.5 years
Interventions	VR = Non-immersive VR training in the form of "Birds and Balls" game. 20 trials in total: 10 trials where birds entered the screen from the right (5 trials) and left (5 trials), 10 trials where balls entered the screen from the right (5) then left (5). Each trial lasted for about one minute. Patients had to identify and catch the objects. Patients received 6 weekly training sessions. Follow-up BIT and Bells tests were completed a week after end of therapy.
Outcomes	BIT Bells Test (No statistical analysis provided)

Myers and Bierig 2000

Study Characteristics	
Methods	Expert opinion/preliminary trial with no data Country: USA
Participants	Five stroke patients with USN (no demographic or baseline data provided)
Interventions	Immersive virtual reality tracking and cueing (VRTC) system consisting of a virtual house with a backyard. Patients had to scan the environment and identity objects. Auditory an visual cues were given to patients.
Outcomes	None reported

Discussion

The aim of this systematic review was to appraise the effectiveness of VR-based training at ameliorating post-stroke USN deficits and compare VR training with conventional rehabilitation methods. Nine studies (Choi et al. 2021; Fordell et al. 2016; Katz et al. 2005; van Kessel et al. 2013; Kim et al. 2011; Myers and Bierig 2000; Smith et al. 2007; Webster et al. 2001; Yasuda et al. 2017) met the inclusion criteria and were included in this systematic review.

Five of the nine studies (Choi et al. 2021; Katz et al. 2005; van Kessel et al. 2013; Kim et al. 2011; Webster et al. 2001) compared VR therapy with non-VR control groups. In three of these studies (Choi et al. 2021; van Kessel et al. 2013; Kim et al. 2011), the control group received conventional USN rehabilitation (e.g., visual scanning tasks, reading and writing, drawing etc). In addition to conventional rehabilitation, the control group trained by Van Kessel et al. received an additional single lane tracking task. One study (Katz et al. 2005) administered computer scanning training (the structure and details of which are unclear) to the control group, whereas the experimental group received VR street crossing training. The fifth study (Webster et al. 2001) administered no USN training to the control group. Webster et al. compared the VR group with untrained/control stroke subjects recruited in a previous study.

Of the five aforementioned studies, four employed a randomised-controlled design (Choi et al. 2021; Katz et al. 2005; van Kessel et al. 2013; Kim et al. 2011), and one employed a quasi-experimental design (Webster et al. 2001). Four of these studies used non-immersive VR systems (Katz et al. 2005; van Kessel et al. 2013; Kim et al. 2011; Webster et al. 2001), and one used immersive VR technology (Choi et al. 2021). These five studies reported mixed or inconclusive results in terms of ameliorating USN-related deficits following VR training and conventional treatment.

Choi et al. reported that patients who received VR training showed greater recovery of USN symptoms, cognitive and visuospatial abilities than the control group who received conventional rehabilitation. While within-group analyses confirmed that both groups significantly improved after they received their assigned training, the between-group analysis established that the VR group exhibited significantly greater improvements than the control group in outcome measures such as the line bisection test and degree of head rotation. However, there was no significant difference between the two groups in the remaining outcome measures, namely the CBS and MBI (Choi et al. 2021).

Van Kessel et al. reported significant improvements post-training within both study groups. However, post-intervention, there was no significant difference between the VR and control groups in any of the USN outcome measures used, including the line bisection tests, letter cancellation test, Bells test, the Baking Tray task, Grey Scales, word reading, and subjective USN questionnaire (van Kessel et al. 2013).

Kim el al. found significant within-group improvements post-training for both the VR and control groups in all four USN outcome measures (star cancellation test, line bisection test, CBS, and Korean MBI). While statical analysis showed no significant between-group differences on the line bisection test, there were significant differences in the star cancellation test and CBS, favouring VR training over conventional rehabilitation (Kim et al. 2011).

Katz et al. reported significant within-group differences for the control group (pre- vs, post-treatment) in all three USN outcome measures used, namely the star cancellation test, Mesulam cancellation test, and the ADL checklist. For the VR group, there was a significant within-group difference post-treatment in the Mesulam cancellation test and the ADL checklist, but not in the star cancellation test. Between-group statistical analysis revealed a significant difference in the

ADL checklist, but not the other two outcome measures, favouring the control group (Katz et al. 2005).

The quasi-experimental study by Webster et al. compared the performance of stroke patients who received non-immersive VR training with stroke patients who received in-patient conventional USN rehabilitation. There were significant between-group differences post-VR training in the wheelchair navigation and obstacle avoidance tasks in favour of the VR group. Within-group analysis was not reported in this study (Webster et al. 2001).

The remaining four studies included in this systematic review had no control group. Two were pilot studies that proposed and evaluated immersive VR systems for the rehabilitation of USN (Fordell et al. 2016; Yasuda et al. 2017), one was a case series in which four USN patients were trained using a non-immersive VR system (Smith et al. 2007), and one was a preliminary trial which trained five USN patients with an immersive VR system (Myers and Bierig 2000).

Fordell et al. administered a five-week training to a group of 15 USN patients using a new, immersive VR system called RehAtt. USN measures, including the CBS, were obtained at baseline and within a week of the end of training. Additionally, a follow-up CBS test was completed by the patients and their next of kin six months after the end of the VR training. There was a significant within-group differences in the CBS between the baseline and post-training scores. Significant improvements were observed following the five-week training. At six-month follow-up, the CBS completed by the patients showed a significant improvement. However, there was no significant differences in the CBS completed by their next of kin at the six-month follow-up (Fordell et al. 2016).

Yasuda et al. trained 10 USN patient with an immersive VR system designed to improve neglect symptoms in the near and far spaces. The study compared pre- and post-treatment BIT scores.

Although patients received one VR training sessions only, the study reported significant improvements in USN symptoms in the far space, post-treatment, measured by the BIT scores. However, no significant improvements were observed in the BIT scores in the near space, post-treatment (Yasuda et al. 2017).

Smith et al. used non-immersive VR to train four USN patients. While three of the four patients demonstrated improvements in the BIT and Bells raw scores following the 6-week training, no statistical analyses were provided, making it difficult to draw any conclusions (Smith et al. 2007). Similarly, the study by Myers and Bierig reported using an immersive VR system to train five stroke patients with persistent USN deficits. However, no demographic data or statistical analysis were provided in this study (Myers and Bierig 2000).

Although the literature indicates that VR telediagnosis and telerehabilitation for USN patients could be a cost-effective and time-efficient alternative to one-to-one/hospital rehabilitation (Peretti et al. 2017; Tindall and Huebner 2009), none of the included studies reported on the cost of development or purchasing the VR systems for home- or community-based use.

Limitations

There are several limitations in this systematic review. In addition to the small sample size, there was substantial variability in the VR and conventional training duration and intensity, and USN outcome measures used across the nine studies included in this systematic review.

Furthermore, only four (Choi et al. 2021; Katz et al. 2005; van Kessel et al. 2013; Kim et al. 2011) of the nine included studies employed a randomised-controlled design and had an evidence level (EL) of 2. Two studies (Fordell et al. 2016; Webster et al. 2001) had an EL of 3, an additional two studies (Smith et al. 2007; Yasuda et al. 2017) had an EL of 4, and one study (Myers and Bierig 2000) had an EL of 5 **(Table 5.4).**

Additionally, only one study (Choi et al. 2021) had a good methodological quality (MQ) score, whereas two studies (Katz et al. 2005; Kim et al. 2011) had a fair MQ score. The remaining six studies (Fordell et al. 2016; van Kessel et al. 2013; Myers and Bierig 2000; Smith et al. 2007; Webster et al. 2001; Yasuda et al. 2017) had a low MQ score due to several methodological inconsistencies **(Table 5.5).** Only one study (Fordell et al. 2016) reported long-term post-VR training results.

Finally, it was not possible to conduct a quantitative analysis of the data reported in included studies due to the variability and inconsistencies in data reporting as well as methodological discrepancies.

Summary

Only one study (Choi et al. 2021) reported moderate evidence of VR training being more effective than conventional therapy in improving USN-related symptoms. Another study (Fordell et al. 2016) reported significant improvement of USN symptoms post-VR training. However, this was a follow-up study and had no control group. Therefore, no comparison between interventions was carried out. Two studies (van Kessel et al. 2013; Kim et al. 2011) reported limited evidence of VR training a better rehabilitation method than conventional interventions. Two studies (Katz et al. 2005; Yasuda et al. 2017) reported conflicting evidence, and the remaining three studies (Myers and Bierig 2000; Smith et al. 2007; Webster et al. 2001) presented no adequate evidence of VR training being a more effective rehabilitation method for USN.

Conclusion

VR has been presented as a promising alternative to conventional therapy for the rehabilitation of USN. However, the literature on the use of this novel technology for USN treatment is quite limited. The evidence presented across the included studies is conflicting and inconclusive, making

it difficult to draw any coherent conclusions. There is a need for more evidence on the effectiveness of VR training and whether it is truly more effective than conventional USN rehabilitation. No study attempted to evaluate and compare combined VR and conventional interventions with one form of treatment or the other. Given the wide heterogeneity of USN symptoms, it is potentially beneficial to combine conventional and VR assessment and treatment methods in order to produce more comprehensive diagnosis and rehabilitation strategies.

Chapter 6
Virtual Reality Prototype: Design, Development and Evaluation

Abstract

As with similar technologies, virtual reality (VR) offers opportunities to develop a wide range of applications, albeit not without challenges. In a decade or so, technologies such as virtual, augmented, extended and mixed reality are predicated to become a fundamental component of, among many other disciplines, diagnostic, rehabilitative and therapeutic strategies. Considering the popularity and wide use of mobile phone applications, we embarked on a journey to develop VR-based applications for the assessment of post-stroke unilateral neglect (USN).

Findings of Chapters 4 and 5 were used to inform the design of our prototypes. For example, the need for versatile VR systems that can assess sensory and motor unilateral USN types and phenotypes, rather than one or the other only. Based on extensive research, we aimed to develop two virtual reality-based prototypes for the assessment of sensory and motor USN deficits.

Throughout the project, we focused on using free open-source software with the future view of encouraging the next generation of cognitive scientists, including the researcher behind this project, to acquire VR software development skills. This will significantly reduce the time and cost of development and enhance the quality of the VR applications and tools developed. To build our VR smartphone applications, we used the 3D, 2D, VR and AR real-time game engine "Unity" - rather than "Unreal" (another popular VR development software), due to its more developer/user-friendly features. Unity is a widely used cross-platform VR game engine that is free of charge for personal and educational projects. To ensure that our applications, if validated, would be widely accessible, the Google Cardboard Virtual Reality Framework was used, a technology that only requires a smartphone and a low-cost virtual reality headset which can be purchased for less than £10 on Amazon, eBay or other e-commerce websites. Several development methods, technologies and devices were employed to develop our tasks. Devices and technologies such as Kinect Xbox

One V2, Microsoft Cortana Voice Recognition and Leap Motion Controller were used as motion sensing input methods to serve the needs of our VR applications.

While the initial objective was to develop two prototypes only, safety concerns around the use of prototype one forced the researchers to develop another model of this prototype that employs voice commands, rather than physical walking. Thus, the project ended up developing three protypes which are discussed in this chapter.

Several development parameters, including the availability and cost of VR software and hardware, the effort required to develop such applications, were considered during VR prototype development. Additionally, technical parameters (e.g., application performance in different settings, user safety and experience, ease of use etc) were used to evaluate the developed applications for stroke patients.

Following the evaluation process in three different settings (home, university, and hospital), only prototype two performed satisfactorily in terms of the parameters assessed, and was thus the only prototype included in the pilot study (see Chapter 7)

Introduction

Thanks to recent advances in the field of VR technology, developing generic VR-based systems has never been more feasible (Singh et al. 2020). However, artificial intelligence (AI), which VR is a subclass of, has been developing at too rapid a pace that has made it extremely hard for clinical researchers to match, let alone fully understand and utilise the various new features and capabilities presented by new AI technologies (Kelly et al. 2019). Building task-specific VR tools for different medical disorders and syndromes requires an in-depth understanding of the medical condition, the technologies / devices currently available and their limitations – but more importantly, the cost and viability of developing such tools (Lindner 2020). At the initial stages of development, extensive research was carried out and a great deal of discussion took place between the research and development teams to determine which development platforms to use, which tools / devices to purchase and which VR scenarios and prototypes to develop. The following flowchart summarises the initial stages and steps of prototype development during this project:

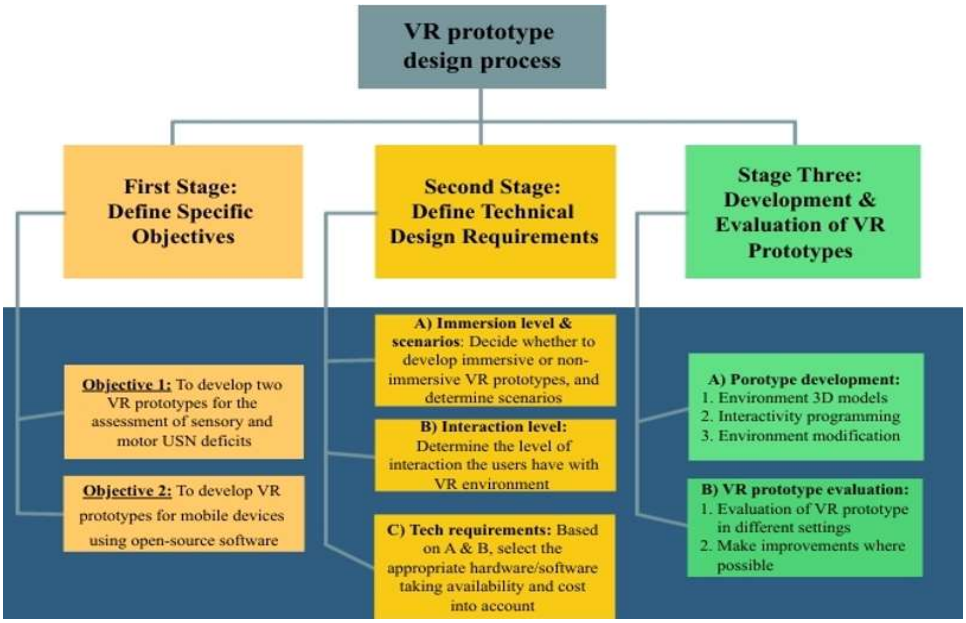


Figure 6.1 VR prototype design process

VR prototype design process

Stage one: Defining objectives

The first stage of VR prototype development (**Figure 6.1**) required defining the objectives of the VR systems that will be developed. Most of the available VR systems for USN diagnosis focus on one type or phenotype of USN. Therefore, our objective was to develop VR prototypes that assess both sensory and motor USN deficits, rather than one or the other only. An additional objective was to use open source (i.e. free of charge) software to develop VR systems that are compatible with mobile devices due to the popularity and ease of use of these devices.

Stage two: Technical design requirements

1- Immersion level and VR scenarios: The first step of stage two (**Figure 6.1**) of the development process required a decision on which type of VR system to adopt. As mentioned previously (Chapter 2 – p.27), there are three main types of VR systems: non-immersive, semi-immersive and fully-immersive – the latter being the most sophisticated of all. After extensive research and discussion, it was decided to develop fully immersive VR prototypes as immersive systems are more compatible with mobile devices. Additionally, These systems would offer more *"immersion"* whereby users may feel completely engrossed in a task due to the system's ability to shut out sensory information from the real world by placing users in a virtual environment through the medium of an HMD (VR headset) (Coburn et al. 2017).

After determining the immersion level, it was important to discuss and narrow down the different VR scenarios that could be developed. Defining the scenarios at this stage was essential for determining the interaction level we would like end users to have in the VR environment. Selecting

the scenarios would also allow us to choose the right hardware and software for prototype development.

- **VR prototype scenarios**

Rationale: VR technology enables the creation of a wide range of scenarios. The level of realism and the quality of graphics in any given scenario can vary considerably depending on resources available (e.g., budget) and time constraints. Based on the VR systems found in the literature and reviewed in Chapters 4 & 5, several scenarios were discussed and evaluated. Taking available resources and time-constrains into account, the following scenarios were agreed upon:

A- Street crossing VR scenario: Two previous studies (Katz et al. 2005; Navarro et al. 2013) had developed non-immersive street-crossing scenarios for the assessment and rehabilitation of USN. Both studies were reviewed in the initial stages of development (see Chapters 4 & 5). Based on these two studies, we decided to develop an immersive street crossing scenario for the assessment of USN that can be accessed through an application downloaded on mobile devices. Why was this decision made?

I- It is difficult to assess a USN patient's ability to cross the street safely in real life. However, this is possible in a VR environment which could also offer an enjoyable and interactive experience without posing any serious risks to the patient.

II- The previous two studies developed non-immersive VR street crossing systems. Our prototype would be fully immersive. Therefore, it could, in theory, offer a higher level of interaction with the VR environment.

III- We did not want to develop scenarios that simply replicated what conventional assessments offer already. Street crossing seemed appropriate. For example, it is common for patients who use wheelchairs to complete a paper-and-pencil test.

However, it is very difficult, if not impossible, to assess their ability to cross a busy street safely in real life. Immersive VR could make this assessment possible.

IV- Technology development and use in the private sector is light years ahead of the academic and health sectors. Since no previous study for USN developed immersive VR tools that could be accessed through applications downloaded on mobile devices, we hypothesised that piloting such approach could pave the way for telediagnosis (i.e. remote diagnosis) and telerehabilitation for USN and other stroke-related impairments in the future. This could make the diagnosis and rehabilitation of USN more cost-effective and less burdensome for patients (e.g., no need to travel) and hospitals as it would offer options such as remote/home-based diagnosis and therapy.

V- None of VR studies reviewed in Chapters 4 & 5 offered information on the accessibility of their systems. The two previous studied that developed street crossing scenarios required a sophisticated set-up (e.g., computers, monitors, haptic devices etc), we theorised that developing a street crossing scenario that can be accessed via a mobile application may enhance accessibility among stroke patients.

B- Object detection and collection: Most of the studies reviewed in Chapters 4 & 5 developed VR systems for the assessment and rehabilitation of sensory USN only. We sought to develop a scenario that could assess sensory as well as motor USN, rather than one or the other only. Why was this decision made?

I- To assess sensory and motor deficits, the scenario would require patients to use their upper extremities as well as visuospatial abilities. Based on studies discussed in Chapters 4 & 5 (e.g., Fordell et al. 2011; Kim et al. 2011), different scenarios

were proposed for this task (e.g. collecting objects in a shopping mall, picking-up pizza deliveries, object scanning and collection in a virtual house etc).

II- Budget and time constraints forced us to make a pragmatic decision. For example, 3D modelling and graphics for a shopping mall VR scenario would cost significantly more and take much longer to develop than a simple scenario.

III- Therefore, we opted for a simple living room VR scenario where patients would have to identify and collect objects placed in the three spatial frames (i.e. personal, near and far spaces) using both of their upper limbs.

2- Interaction level: The second step of stage two (**Figure 6.1**) of the development process required a decision on the level of interaction users can have with the VR environment. This would have cost and technical requirements implications. After determining the scenarios (see above) that would be developed, the interaction level/devices for end users were decided upon. The street crossing and objection collection scenarios would require interactions devices such as visual and motion sensors as well as haptic devices.

3- Tech requirements: The third and final step of stage two (**Figure 6.1**) was to select the appropriate hardware and software to develop the immersive VR scenarios discussed above. Restricted by a limited budget and time constrained, we sought to employ cost-effective technologies that are mostly free of charge (or reasonably priced) when used for educational as well as non-commercial purposes. Here, we summarise hardware and software components we used during the development process:

I- Hardware

- Street crossing scenario: Microsoft Kinect Xbox One (Kinect V2) motion sensor was selected for its relatively low cost and compatibility with the open-source software we

sought to use during prototype development (Kinect VR 2018). We reviewed studies that Kinect and other motion sensors in the literature (Coburn et al. 2017; Mousavi Hondori and Khademi 2014). Compared to other motion sensors (discussed below), Kinect was the best option for us in terms of availability and cost.

- Object detection and collection: we used Leap Motion Controller – a haptic technology that recognises hand and finger movements and allows the use of hand gestures in a virtual environment. This haptic device is relatively inexpensive and has been used in previous studies (Cikajlo and Peterlin Potisk 2019; Kim et al. 2017)

II- Software

- Unity Gaming Engine: a cross platform gaming engine [i.e. works on various devices including Android and IOS operating devices], that is used to develop VR and AR mobile games / applications (Unity 2018). In our VR tasks, the first programming language (FPL) used was the C Sharp (C#) programming / coding language. The C# was used to link the hardware sensors with the software side of our design. The C# programming language is considered an easier coding language to master and read even by beginners when compared to the other main programming language, namely the C++ (sometimes referred to as C with classes) (Farooq et al. 2014).
- Node.JS: a JavaScript engine which is used for network real-time applications. It uses the event-driven non-blocking Industrial / Organisation (I/O) model of communication, which significantly enhances the exchange of messages in real-time. Node.JS is a cross-platform

engine (works on various devices). Its main function is to "*build scalable network applications*" (Node.js 2018).

- WebSocket: a mechanism of communication between two devices using a certain protocol, which allows a two-way connection between a device / computer (i.e. user's browser) and a server (WebSocket API 2018).
- Speech Recogniser: a library embedded within certain operating systems designed to recognise certain words in the dictionary specified by the developer. The speech recognition process uses the device's microphone (in our context, the smartphone's microphone) to recognise a set of words to execute a certain action (words such as "*go*" and "*stop*" in the street-crossing task). We used Microsoft Cortana – a virtual digital assistant developed by Microsoft to perform a variety of functions including recognising voices / commands to execute tasks (Microsoft Cortana 2014).
- The Model-View-Controller (MVC): a programming approach used to design flexible applications in which the code, used to build a certain application, can be reused efficiently and flexibly and parallel application developments can be executed (MVC 2017).
- Event-Driven Programming (EDP): a programming paradigm used to develop video games. It comprises dozens of interactive events that mimic real life scenarios. The EDP's objective is to detect and communicate events as they happen and process them using a set of specified "event-handling procedures" (Event-Driven Programming 2017).

Development and evaluation of VR prototypes

A) **Prototype development:** After the completion of stages one and two of the design, the first step of stage three (**Figure 6.1**) started with the development of the first scenario

involving a street crossing task in an immersive virtual environment. The prototype, scenario, tech requirements and evaluation outcomes are discussed below.

Prototype One: Street-Crossing VR Task using Kinect V2 & Google VR Cardboard

VR Environment / Scenario

This street crossing VR task involves crossing streets in a virtual environment that, to a certain extent, mimics a real street-crossing environment in which patients / users have to explore the environment and assess whether it is safe to cross the street having looked to the left and right. If the user decides it is safe to cross the street, they then have to physically walk to cross the street in the virtual environment in the same manner that they would cross a street in real life. We used three types of vehicles in this task – cars, buses and trucks. It was theorised that using different types of vehicles with varying sizes may offer a more realistic VR experience and could also indicate whether the type or size of vehicle might improve the user's ability to detect it. The colour of all vehicles was set to black to accommodate individuals with colour blindness (however, we added a feature that would allow researchers / users to change the vehicle colour from the settings). Visual cues in the form of flashing yellow arrows (used to guide users to the correct direction of movement) and a yellow ball at the end of the crossing task (this indicates the end of the task) were used. Additionally, auditory cues (for example, the words *"go"* and *"stop"*) were used to indicate the start and end of the task.

The accident scenario in this task was changed several times to ensure that no trauma would occur when a user fails to cross the street successfully (i.e. a collision occurs, and a user crashes with / gets hit by a vehicle). Initially, we accompanied collisions with a *"bang"* graphic and sound. However, that was deemed somewhat traumatic, and was thus removed. Instead, we opted for a softer scenario whereby when a "car accident" occurs, the collision is accompanied by a soft sound

of screeching brakes as the vehicle approaches the user's position, followed by a horn sound. The screen then fades out to indicate failure.

The task was designed in a manner that would make it extremely flexible and easily manipulated via the settings to create a number of different scenarios whereby the velocity, vehicle span, direction of vehicle flow, number of streets, number of lanes per street and so on can be easily adjusted to accommodate different conditions and levels of abilities. For example, following a collision, the researcher or administrator can determine whether the user would return to the pavement of the street where the collision occurred and get a second chance to cross the street successfully, or move forward to the next crossing.

Figure 6. 2 Prototype one testing [Prototype one involved having to walk towards the motion sensor (Microsoft Kinect) to cross the road / avoid vehicles in a virtual environment. We used internal (VR environment) and external cameras to capture this video].

The Technology

Development Engine

The first stage of development required a cross-platform engine that would allow us to experiment and develop various scenarios including the abovementioned prototypes. A number of major game engines, including Unreal (Unreal Engine 2014) and Unity (Unity 2018), were available . Unity game engine was deemed the most suitable for a variety of reasons due to its more developer/user-

friendly features (Sutherland et al. 2019; Wheeler et al. 2018). Unity, a cross-platform engine developed by California-based Unity Technologies and released in 2005, offers many attractive features that makes it the go-to platform when it comes to developing VR applications, especially for those with limited VR development skills (Cikajlo and Peterlin Potisk 2019; Coogan and He 2018). This engine is used by more than 120 million users per month and supports more than 20 platforms including those most widely used such as Android, IOS, Windows, Google Cardboard, Xbox One, PlayStation VR and several others (Unity Stats 2019). In other words, it supports most modern gadgets including computers, mobiles and VR tools. In terms of programming languages, Unity supports the most commonly used coding language including C#. The licencing options include free and paid subscriptions (Unity Subscription 2020). In 2016, Unity Technologies changed its subscription model and offered individuals using the engine for personal or educational purposes as well as small companies earning less than $100,000 per annum a free license. Additionally, in 2010, Unity launched an Asset Store (similar to Google Play and IOS App Store) through which developers can create 2D and 3D models and either sell or offer them free of charge to other Unity users. Unity also provides step-by-step tutorials to build various applications (Coogan and He 2018). By the time we started developing our prototypes in early 2018, Unity had been employed to develop more than half of the mobile games and approximately 60% of VR and AR content available on the market, with over 40 million downloads from the Asset Store worldwide (Unity Stats 2019).

Motion Sensor

In the second stage of development, we sought to find a suitable motion sensor to detect, monitor and record movements inside the virtual environment. A number of motion sensors were commercially available to execute the street-crossing VR scenario.

Following extensive research on various devices and taking cost into account, Microsoft Kinect Xbox One (Kinect V2) motion sensor was selected. Kinect is a motion-sensing system that was the fruit of a collaboration between Microsoft and the now defunct Israeli Tech company PrimeSense (the latter was purchased by Apple Inc. in 2013 for $360 million) (Mousavi Hondori and Khademi 2014).

The Kinect device **(Figure 6.3)**, produced by Microsoft for Xbox 360 video game console, first appeared in 2010 and included hardware devices developed by PrimeSense (Kinect VR 2018; Levac et al. 2015).

Figure 6. 3 Capture of Microsoft Kinect Xbox One (Kinect V2)

Kinect is a horizontal motion-sensing device with built-in RGB cameras, Infrared Red (IR) cameras and detectors combined with a processing chip, which all together generate a grid mapping the depth of every frame it captures through calculating time of flight or structured light – the latter is a process of projecting a well-defined and known shape. An additional hardware is a built-in microphone used as an auditory sensor. Kinect combines the aforementioned hardware with artificial intelligence and software produced by Microsoft to create a motion-sensing system capable of recognising body movements, gestures and speech for up to four users, all in real-time. The Kinect system we used, which is placed atop the video display like a webcam, can recognise

near and far objects or patterns of movement in 3D space for up to 6 feet (other versions of this device detect movement up to 3 feet). At the time of purchase (January 2018), the cost of Kinect V2 used for the development of prototype one was £56.99 for the device plus an additional £131.95 for the adaptor – an essential piece of equipment used to connect the Kinect sensor with the computer (Kinect VR 2018).

Figure 6. 4 Capture of Microsoft Kinect adaptor

VR Headset / Goggles (HMD)

As one of the main aims of this project was to develop fully immersive prototypes, a VR platform was required to ensure that users would be completely engrossed in the virtual environment. Google Cardboard (Google VR) technology was selected to develop our prototypes as it is affordable, reliable and widely accessible. Google developed the VR Cardboard technology – a low-cost VR platform released in 2014 to facilitate and encourage the development of various VR applications (Schwebel et al. 2017). The system requires a viewer (VR headset) which can either be built manually by the developer (**Figure 6.5**) using low-cost and simple equipment (Google provide free of charge step-by-step instructions on how to assemble the Cardboard) or purchased (pre-assembled) online (Google Cardboard 2014).

Figure 6. 5 Google Cardboard or Google VR headset / goggles

Google also released a software development kit (SDK) which allows developers and users to embed their content into VR applications. Google's SDK supports Android and IOS devices (Google VR 2018). Once a VR application is developed, and headset is assembled or purchased, a smartphone is inserted into the headset. The VR application, which must be compatible with Google Cardboard technology, divides the smartphone's display into left-and-right split screen display (a single image for each eye / lens). This produces a stereoscopic 3-D display (wide field of view) that allows a user to rotate their head in all directions in a fully immersive VR environment.

Figure 6. 6 Capture of Shinecon VR headset used in this project

Google has given permission to third party companies to manufacture various VR headsets using specifications provided by the tech giant. For the development of our prototypes, we used Shinecon (G01 3-D VR Glasses) classical design (**Figure 6.6**), a simple low-cost VR headset that is compatible with Google Cardboard technology and assembled according to the specifications published by Google (Shinecon VR 2018). The cost at the time of purchase was £9.89. This VR headset was used for all three prototypes.

VR Headset – Product Details

VR Shinecon G01 Classical Design Immersive 3D VR Headset for Smartphone (Shinecon VR 2018)

Table 6. 2 VR Shinecon Headset specifications

G01—Classical design	
Features	**Specifications**
"1. Pupil distance, Object distance adjustable 2. Field of View (VOF) 70-90° 3. High Definition lens Shortcomings: many fake models in the market	Item Size: 202*140*100 mm Weight: 380g Material: ABS (RoHS) Colour: Black/White OEM Lens: HD Optical Blu-Ray Resistance Lens Lens Diameter: 32mm IPD Scale: 58mm ~ 72mm Compatible with 3.5-6.0-inch smartphones. (Length max: 154mm; Width max: 82mm)"

B) Prototype evaluation: We carried out prototype one evaluation in three different settings (home, community/university and hospital) with a control group of users (friends, university students and staff, and nurses) using a simple questionnaire. The questionnaire consisted of four questions/parameters that were answered by test volunteers using a

simple, 3-point scale. The parameters and scale used as well as comments from control users for prototype one are summarised in the table below.

Table 6.2 Prototype one evaluation outcomes
(Three-point scale: + = good, 0 = neutral, – = poor)

Parameters	Evaluation settings			User comments
	Home	University	Hospital	
Immersion	+	+	+	Young adult: "*I know it is not real, but it also feels real when I see the cars approaching"*
Ease of use	+	–	–	University staff: "*It is not easy to use"*
System responsiveness (e.g. Sensory/haptic feedback)	0	0	–	*Nurses*: "*I keep moving out of the specified range"* & "*System keeps disconnecting*"
Mobility, user safety and experience	–	–	–	All control users found it difficult to walk whilst having the VR headset on.

Across the three settings, the performance of the prototype was deemed poor, especially in terms mobility and user safety and experience. When having the VR headset on, users had to physically walk to cross the roads inside the virtual environment. Users asked to be physically supported and guided (e.g., their arms were held whilst completing the task) as they felt they might fall or trip whilst walking towards the other end of the road. After a few trials, younger adults in the home environment were able to overcome their fear of falling or tripping as the test room was completely cleared of cables and objects and they became familiar with the walking distance and VR environment. However, the object-free, home setting could not be recreated at university or hospital. For example, nurses advised the researcher to rethink and modify the prototype as stroke patients will certainly struggle to complete the task, particularly as younger/able adults struggled with walking whilst having the VR headset on. Some users suggested installing handrails along a track created for patients/users to walk through for safety reasons. However, this was not possible.

Conclusion

Based on the data presented in **Table 6.2,** and discussed thereafter, prototype one did not pass the evaluation test across the three settings. Taking the advice of stakeholders (e.g., stroke nurses) into consideration, this Kinect-based VR street-crossing scenario was excluded from the pilot study as it was deemed unsafe for use in clinical settings and potentially risky for stroke patients. An attempt was made to modify prototype one to ensure safety, and improve system responsiveness and ease. This modification attempt led to the development of prototype two.

Prototype Two: Street-Crossing VR Task using Microsoft Cortana Voice Recognition Technology

A) Modification of prototype one

Taking the limitations of prototype one into account, we sought to modify the original prototype. The mofided version would involve a similar VR street-crossing scenario but a different technology, and task completion steps. To overcome the motion sensor limitations and addressed safety concerns, Kinect was replaced by voice recognition [speech-to-text] technology. We used a similar VR environment to that used in prototype one, but instead of walking to cross the street in the VR environment, the task would be completed using verbal commands that control the movement inside the VR environment.

To achieve this modification, we substituted the Kinect sensor with a speech recogniser that identifies a set of specified terms such as "*Go*" and "*Stop*" to control the crossing movement inside the VR environment. The speech recogniser uses the smartphone's microphone to detect the abovementioned terms which allow the user to perform the street-crossing task. We used Windows Cortana Speech recognition technology to build the library of terms required to complete this task.

Whilst the research and development teams agreed that using verbal commands may reduce the "realness" of the task, it was theorised that the voice recognition approach would allow the research team to assess a wide range of stroke patients with different abilities including those with motor deficits and /or using wheelchairs, and would therefore be more inclusive. Finally, prototype two was deemed a safer scenario for stroke patients as the task would be completed from a sitting position with no movement (other than head rotation) required to complete the task. Therefore, the risk of injuries, unlike in prototype one, is minimal.

VR Environment / Scenario

The verbal command directed VR street-crossing task attempts to mimic a real-life street-crossing scenario and takes place in a fully immersive environment (i.e. involves wearing adjustable VR goggles) where participants attempt to complete a street-crossing task successfully without any accidents. Like prototype one, three types of vehicle were used in this task: cars, trucks and buses. The vehicles' 3D models varied in size in an attempt to establish an understanding of whether using different vehicle sizes may affect the user's ability to detect them. The default colour of the vehicles was set to black to accommodate individuals with colour blindness. Nonetheless, a feature that would allow the researcher / user to change the vehicle colour was added to the settings.

Once the task starts, the participant first explores the virtual environment and assesses whether it is safe to cross the street. The participant navigates the environment and movement inside the game through voice commands. When the user deems it safe to move / cross the street, they say "*go*" – as a result, the view (i.e. the subject's position inside the VR environment) moves forward instantly. When the participant decides it is time to stop the movement – for example, when a car is approaching and must be avoided – they say "*stop*" and the movement inside the VR environment freezes immediately.

The “accident / collision” scenario was changed several times to ensure that no trauma would occur as a result of a collision / failure to cross the street successfully. We opted for a soft collision scenario where, if the participant fails to cross the street (i.e. a collision occurs), the collision is signalled by a soft sound of screeching brakes as the vehicle approaches the user’s position, followed by a horn sound. The screen then fades out to indicate failure and the task restarts at the beginning of the same crossing that the user failed to complete successfully. This allows us to collect data on the number of times required for a user to complete each crossing successfully, and whether they struggled with a certain crossing or type of vehicle.

As with prototype one, visual cues in the form of flashing yellow arrows (to indicate the starting location of the task and point the user to the correct direction of movement inside the VR environment) and a yellow ball (to indicate the destination to be safely reached to end the task), were used in prototype two.

The Technology

Development Engine

We used Unity VR game engine to develop prototype two. Whilst some parts of the VR environment developed for prototype one were used in this modified version, a significant restructuring of the development codes and environment was required to accommodate the replacement of the Kinect sensor with the Voice Recognition Technology in prototype two.

Microsoft Cortana Voice Recognition Technology

Microsoft Cortana, initially released in 2014, is a virtual voice assistant developed by tech giant Microsoft. Cortana can execute several functions including music recognition, setting reminders and recognising natural voices and auditory commands without any input from a keyboard. Cortana can also use results gathered from Bing (Microsoft’s search engine) to answer various

questions put forward by a user (Microsoft Cortana 2014). This virtual assistant supports numerous platforms and devices including Windows 10, Windows 10 mobile, IOS, Android, Xbox One and Windows Mixed Reality. The system is currently available in 8 languages including Chinese (simplified Mandarin Chinese), English (American, Australian, British and Indian accents) and Spanish. Cortana is among the most widely used virtual voice assistants worldwide. Furthermore, other prominent voice assistants have been developed by tech giants / Microsoft competitors such as Amazon's Alexa, Apple's Siri and Google Assistant. Microsoft reported that 800 million people had accessed Cortana in 2019 alone, with more than 18 billion questions asked by users since the service's initial launch in April 2014 (Amazon Alexa 2016; Apple Siri 2011; Microsoft Cortana 2014).

Tech giants including Microsoft, Amazon and Apple have been in fierce competition to win the battle of which voice assistant is best for healthcare applications (Arogyaswamy 2020; Koon, Blocker, and Rogers 2019). Studies have reported that voice assistants can help reduce the time spent by medical staff on administrative tasks such as documentation, which would in turn increase the time available for other more important tasks such as focusing on patients (Kumah-Crystal et al. 2018; Lee Ventola 2014; Willis et al. 2020).

To develop prototype two and incorporate the voice recognition technology, a series of machine learning experiments was carried out. TensorFlow, which is an open-source machine learning / computing framework, was used in combination with Microsoft Cortana to develop a library of keywords / commands that the system recognises and accurately implements inside the virtual environment (TensorFlow 2015). The smartphone's microphone was used as the input method for Cortana, meaning that it detects voice commands and transfers them back to the operating system. The VR voice recognition system was developed in a manner that would allow Cortana (built-in

voice recogniser for Windows 10) to recognise the pre-specified commands ("*Go*" & "*Stop*") – then send voice data over a Wi-Fi network back to the operating system (Windows 10) which is tasked with decoding voice commands. Once the commands are decoded, a User Datagram Protocol (UDP), which is a communication protocol / channel between computer applications, sends decoded messages to the VR system resulting in either movement (for voice command *Go*) or immediate motionlessness (for voice command *Stop*), meaning that the avatar / camera (which represents the user inside the VR environment) either moves or freezes depending on the command uttered by the user (**Figure 6.7**).

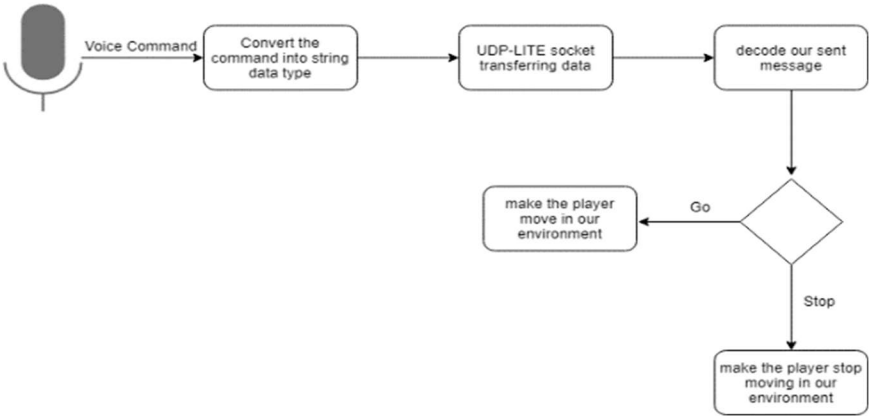


Figure 6. 7 Event-driven programming used in the VR prototypes

B) **Prototype evaluation:** Prototype two evaluation was carried out in three different settings (home, community/university and hospital) with a control group of users (friends, university students and staff, and nurses) using a simple questionnaire. The questionnaire consisted of four questions/parameters that were answered by test volunteers using a

simple, 3-point scale. The parameters and scale used as well as comments from control users for prototype one are summarised in the table below.

Table 6.3 Prototype two evaluation outcomes
(Three-point scale: + = good, 0 = neutral, – = poor)

Parameters	Evaluation settings			User comments
	Home	University	Hospital	
Immersion	+	+	+	University student: *"the graphics can be improved, but the environment feels real to a certain extent"*
Ease of use	+	+	+	Same nurse who tested prototype one: "*much easier to use than the previous version, although the use of voice of commands will exclude patients with aphasia"*
System responsiveness (e.g. Sensory/haptic feedback)	+	–	–	*Nurses*: "*there is a lag every now and then, I'm saying 'go' and 'stop' but sometimes there is no movement at all"*
Mobility, user safety and experience	+	0	+	University staff: *"The use of voice commands for walking is strange, but there is no safety concerns"*

Limitations

I- Problem A: Whilst Cortana has a reported accuracy of over 90% for recognising 10 words or less, the accuracy tends to drop as the number of commands / words specified increase. Also, Cortana's accuracy of voice recognition appears to decrease in cases where an individual has an ambiguous or heavy English accent.

II- Problem B: A lag was detected at the university and hospital between the moment a voice command was uttered and the execution of the command inside the VR environment.

Solutions

I- Solution for problem A: To avoid a significant drop in accuracy, two words / commands (*Go & Stop*) only were used to control movement inside the virtual environment. A

Library of various English accents (e.g., American, Australian, British, Canadian, Indian etc) for the abovesaid commands was put together and incorporated into the system. Following several rounds of testing and improvement, a rate of 93% accuracy was attained for the recognition of the two commands required for the completion of the street-crossing VR task. Whilst prototype two was initially designed for English speakers only, other languages can be added to the system but only when a library of terms from a given language is accurately incorporated into the system.

II- Solution for problem B: The lag was thoroughly investigated. The investigation ascertained that the Wi-Fi network was the reason behind the observed lag between voice commands and execution. As mentioned previously, the design of prototype two involved using a Wi-Fi network to transfer voice data from the mobile's microphone back to the operating system for decoding, movement planning and execution inside the VR environment. When connected to a public Wi-Fi network (e.g., hospital), the connection within the VR app was unable. This is because there is huge pressure on the network as hundreds of users normally connect to public Wi-Fi networks as there is no 3/4G connection inside the hospital/some universities. To overcome this lag, a private connection (Wi-Fi hotspot) using the hospital's public network was established. The use of a private Wi-Fi hotspot meant that only one user is connected to the network, and therefore, a stable connection can be established. This tweak resolved the lag observed previously with the public Wi-Fi network.

Conclusion

Prototype one was modified to address the limitation and safety concerns that arose during prototype evaluation. This modification attempt led to the development of prototype two. Based

on the data presented in **Table 6.3**, and after applying solutions to the problems discussed above, prototype two passed the evaluation test across the three settings, and was thus eligible for inclusion in the pilot study with stroke patients.

Prototype Three: Objects Detection and Collection VR Task using Leap Motion Controller technology

A) **Prototype development:** The first step of stage three (**Figure 6.1**) started with the development of the second scenario involving the detection and collection of objects in an immersive virtual environment. Prototype three was developed with the intention of creating an assessment for USN-related motor deficits as well as visual impairments. Herein, we sought to construct a VR scenario that would allow us to observe, monitor and collect data on the behaviour and deficits of stroke subjects, particularly focusing on an individual's attention capacity as well as the ability to follow specific instructions. The prototype, scenario, tech requirements and evaluation outcomes are discussed below.

VR Environment / Scenario

Prototype three consists of a fully immersive VR environment that places a user in a well-lit room which, to a certain extent, mimics a generic design of a living room. The subject is presented with 12 coins placed on a virtual table (six on each side), clearly divided by a yellow-coloured midline. The user's height is added to the settings prior to the start of the task to ensure that the virtual table appears at an appropriate height for each individual. Out of the six coins on each side of the table, three coins are numbered (numbers 1-9 are generated at random each time the task is performed). Users are then given auditory instructions via the speaker of the smartphone inserted into the VR headset they wear to enter (via a virtual calculator which appears every time a user orients upwards toward the ceiling and disappears once the user drops their head down to the virtual table level)

three numbers corresponding to the three coins on the right, and the three on the left side of the virtual table, clicking "*append*" to finish once they have entered all numbers.

Should participants make a mistake in entering the correct number, they will be given the chance to correct it through the "*clear*" button on the virtual calculator. Once the correct numbers are entered, patients are instructed through the headset to pick up the coins using their hands, which is made possible through the use of the Kinect Sensor and the Leap Motion VR Bundle technology – the latter being a motion sensor that allows the use of hands gestures in a virtual environment (Leap Motion 2018). Users are instructed – via the smartphone's speaker – to use the left hand to collect coins placed on the right side and the right hand to collect coins placed on the left side of the virtual table. The aim of this strategy is to avoid using the same hand to collect coins on either side of the table which would make it difficult to properly assess the presence of any motor deficits. The collection process involves a brief click on each of the numbered coins. In addition to its potential ability to detect subtle motor deficits, this VR task may be able to detect subtle visual deficits in the three spatial frames mentioned below. The three numbered coins on each side of the virtual table are generated at the following distances (Kerkhoff 2001):

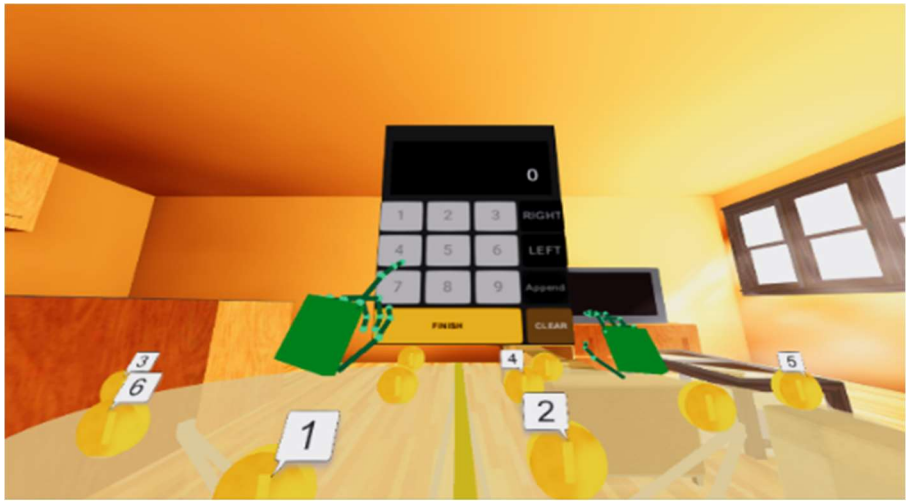


Figure 6. 8 Coin detection and collection VR task

1- First coin: 0 - 0.3m – personal space
2- Second coin: 0.3 – 0.7m – peripersonal or near extrapersonal space
3- Third coin: > 0.7m – far extrapersonal space

The aim of this VR task is to diagnose potential attention deficits in any of the abovementioned spatial frames, as well as any subtle motor deficits – as some stroke patients may use the same hand to pick up objects on both sides.

The Technology

Development Engine

We used Unity VR game engine to develop prototype three and incorporated the Kinect Sensor as well as Leap Motion Controller / Sensor (haptic technology) into the task to detect and allow hand gestures inside the VR environment.

Motion Sensor

To develop prototype three, which is a fully immersive task, we used a combination of the Kinect Sensor (to detect joint and spine movement) and the Leap Motion Controller – a haptic technology that is able to recognise hand and finger movements as well as allowing the use of hand gestures in a virtual environment. Whilst a number of VR haptic tools are commercially available, we opted for the Leap Motion controller as the best option in terms of cost-effectiveness (Coburn et al. 2017; Kim et al. 2017; Leap Motion 2018). Other more sophisticated haptic tools, including the 5DT Data Glove Ultra ($5,495 per glove excluding shipment) (5DT Data Glove 2020), Noitom Hi5 VR Glove ($999.00 excluding shipment and custom taxes) (Hi5 VR Glove 2018) and Sensor VR Glove ($599 excluding shipment and custom taxes) (Sensoryx 2019), are commercially available. However, we opted for a cheaper option to experiment with due to a limited budget, and thus

purchased the Leap Motion Controller ($80 - excluding postage charges and taxes - at the time of purchase in February 2018) (Leap Motion 2018).

Developed by Ultraleap – a start-up tech company based in San Francisco – the Leap Motion Controller (first released in 2013) is a haptic technology that facilitates the tracking of hand and finger gestures with a reportedly good accuracy and low latency. The device is able to project hand gestures inside a 3D VR environment using a USB cable connected to a PC (Cikajlo and Peterlin Potisk 2019; Leap Motion 2018).

The Leap Motion Controller is a 0.5" x 3.2" small USB device that can be either placed on a desktop or mounted onto VR googles (image right). The device consists of two monochromatic infrared (IR) cameras and three light emitting diodes (LEDs). This device detects gestures within an interaction zone of around an “arm’s length” or 80cm, with the cameras generating nearly 200 frames per second of imitated data. The Leap Controller is powered by a USB cable which also acts as the communication channel through which hand movement data is transferred from the controller to the operating system (e.g. computer) for analysis. The process of analysing hand movement data involves using what the developers described as “complex maths.” However, the Leap developers have not yet disclosed what this complex maths model is precisely, or how it actually works.

Figure 6. 9 Leap Motion sensor connected to VR headset /laptop to hand gestures

“Leap Motion Specifications”

Below is a list of the “Leap Controller specifications published by Ultraleap (Leap Motion 2018).

	Height	Width	Depth	Weight
Metric	13mm	80mm	30mm	32g
Imperial	0.5"	3.2"	1.2"	1.15oz
Description:	Specialised sensor			
Power supply:	Leap Motion Controller for hand tracking			
Data connection:	USB			
Ingress protection:	USB 2.0 (packaged with USB 2/3 hybrid cable, but can be used with any certified USB cables with the Hi-Speed USB 2.0 logo featured on the packaging			
Mounting methods:	Splash resistant			
Interaction zone:	May be placed on a desktop, mounted on a VR headset using the Leap Motion VR Developer Mount, or recessed into a larger hardware installation			
Cameras	60cm (24") or more, extending from the device in a 120×150° field of view (approximately 8 cubic feet or 0.2 cubic meters of interactive space)			
Camera interface:	Experimental Universal Video Class (UVC) release provides access to low-level controls such as LED brightness, gamma, exposure, gain, resolution, etc.; examples in C, Python, and Matlab, as well as OpenCV bindings			
LEDs:	Three, spaced on either side and between the cameras, baffled to prevent overlaps			
Range:	Arm’s length, up to roughly 80 cm; varies depending on hand perspective conditions			
Construction	Aluminium and scratch-resistant glass			
Ambient operating temperature:	32º to 113º F (0º to 45ºC)			
Storage temperature:	14º to 122º F (-10º to 50º C)			
Relative Humidity:	5% to 85% (non-condensing)			
Operating Altitude:	0 to 10,000 feet (0 to 3048 meters)			
Compliance:	CE, FCC, CAN ICES-3			

Minimum system requirements (desktop)	Windows® 7+ or Mac® OS X 10.7 (note that OSX is no longer formally supported); AMD Phenom™ II or Intel® Core™ i3/i5/i7 processor; 2 GB RAM; USB 2.0 por
Minimum system requirements (VR)	Windows 7 SP1 64 bit or newer; Intel® Core™ i5-4590 equivalent or greater; 8GB+ RAM; 3x USB 3.0 port; NVIDIA GTX 970 / AMD R9 290 equivalent or greater with compatible HDMI 1.3 video output"

Table 6. 4 Leap Controller specifications

B) **Prototype evaluation:** Prototype three evaluation was carried out in three different settings (home, community/university and hospital) with a control group of users (friends, university students and staff, and nurses) using a simple questionnaire. The questionnaire consisted of four questions/parameters that were answered by test volunteers using a simple, 3-point scale. The parameters and scale used as well as comments from control users for prototype one are summarised in the table below.

Table 6.5 Prototype three evaluation outcomes
(Three-point scale: + = good, 0 = neutral, – = poor)

Parameters	Evaluation settings			User comments
	Home	University	Hospital	
Immersion	+	–	0	University staff: *"the colours are too bright; I think the graphics need more work for the environment to look more real"*
Ease of use	–	–	–	All users complained about the difficulty and complexity of this task. A nurse said "*It will be too difficult for stroke patients to complete this task in its current format"*
System responsiveness (e.g. Sensory/haptic feedback)	0	–	–	University student: "*The app seems to confuse my right hand and left hand. When I use my right hand, it appears as my lift hand inside the environment"*
Mobility, user safety and experience	0	–	–	Young adult: "*I think after trying it a few times, my experience slightly improved. I think it might be okay for young users, but too complicated for older individuals"*

Across the three settings, the performance of prototype three was poor. The Leap Motion controller appeared to confuse the right and left hands, as it incorrectly detected the left as right

and vice versa. This issue was less common in the home setting, but consistently appeared during prototype evaluation sessions at the university and hospital. Although attempts were made to investigate the coding and fix this issue, the Leap controller failed to detect the correct hand and finger gestures inside the VR environment. It also showed a lag between hand gestures outside the environment and the correct imitation inside the virtual environment.

Conclusion

Based on the data presented in **Table 6.5**, and considering the budget and time constraints, prototype three did not pass the evaluation test across the three settings. We could not further investigate and fix the technical issues within the timeframe and budget (in the context of the PhD) we had. Therefore, prototype three was not included in the pilot study.

Prototype two and cognitive domains

As only prototype two (street-crossing VR task using Microsoft Cortana voice recognition technology) passed the evaluation process, this section aims to discuss the cognitive domains that are assessed by this VR task.

Traditionally, simple screening tests such as the Mini-Mental State Examination (MMSE) (Wallace and Kurlowicz 1999) and Montreal Cognitive (Nasreddine et al. 2005). However, studies reported that these screening tests are quite limited, and are only able to detect severe to moderate cognitive impairments. For example, the MMSE may accurately assess cognitive domains such as attention, memory and orientation, but it has been found to be less sensitive in identifying executive function deficits and mild cognitive impairment (MCI) (Kim et al. 2014).

More recently VR has been used to screen for cognitive deficits (Gamito et al. 2017). Although prototype two was specifically designed and developed to assess visuospatial abilities/deficits of patients with post-stroke USN, it can in theory assess other cognitive domains. For example,

during the street-crossing task, patients would have to look to the left and right, and cross the street at the right moment to avoid any collisions with vehicles in the virtual environments. This means that patients would have to assess the environment before making decisions about crossing the street safely. This involves analysing and understanding gaps in the traffic and the speed of vehicles and making accurate judgements. Hence, this is a complex task that involves cognitive domains such as attentional, executive, cognitive, and perceptual functions. Therefore, this VR task can assess in theory cognitive domains such as executive function, complex attention, and social cognition.

Further, this task uses voice commands to control movement inside the virtual environment. This means that patients need to remember the voice commands, scan the environment by turning left and right, collect and process information from the environment before making a judgement to either move forward or remain in position or move then stop by using the voice commands "*go*" and "*stop*". Therefore, this task could also assess a number of cognitive functions, including verbal working memory, spatial working memory, reaction time, language and speech and spatial orientation.

VR Prototypes: Programming Structure & Language

At the initial stages of development, it was crucial to build a game infrastructure that would allow dynamic addition and removal of various features, with the intention of building a user / researcher-friendly task with an associated VR environment which could be easily recreated and adapted for different scenarios and conditions.

We used the Kinect V2 sensor and Kinect-VR framework to manage the connections between the sensor and the smartphone inserted into the VR headset. The sensor detects and transfers the player's movements to the server and records all relevant data automatically. Additionally, a Node.JS, which is a real-time JavaScript framework, was used in prototype one due to its ability to handle a large number of queries in real-time. The Role of the Node.JS server is to transfer data within the system using a pre-specified Wi-Fi network. This allows the smooth transfer of the player's data between the Kinect sensor and the VR network/platform (**Figure 6.10**).

Prototype one

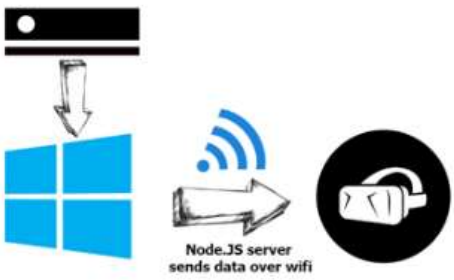


Figure 6. 10 Prototype one - basic structure

MVC architecture was employed to make the structure more flexible in terms of adding new features or editing existing ones. We added visual cues in the form of flashing arrows to guide the player towards the end of one crossing and the start of another as well as a yellow ball to mark the finishing line**.** Furthermore, we used a combination of delegates and event-driven

programming in the C# language to detect and manage the environment's dynamically changing events **(Figure 6.11).**

Additionally, event-driven programming was used to ensure the development of a flexible VR system structure.

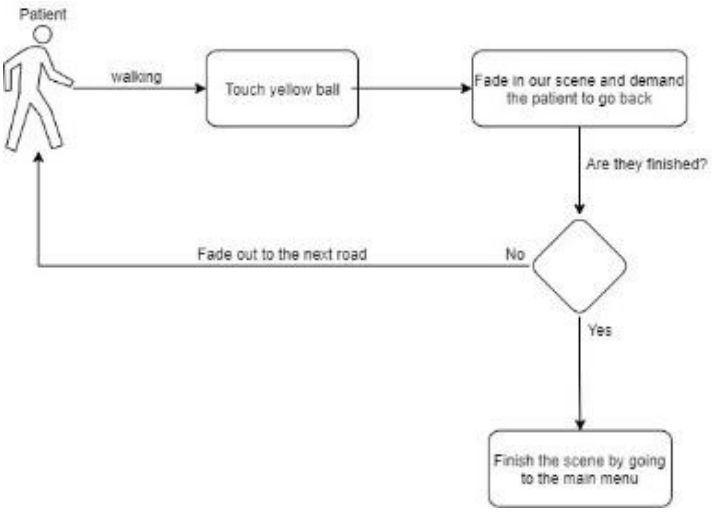


Figure 6. 11 Prototype one scenario - yellow ball [visual cue] used to guide the user

Prototype two

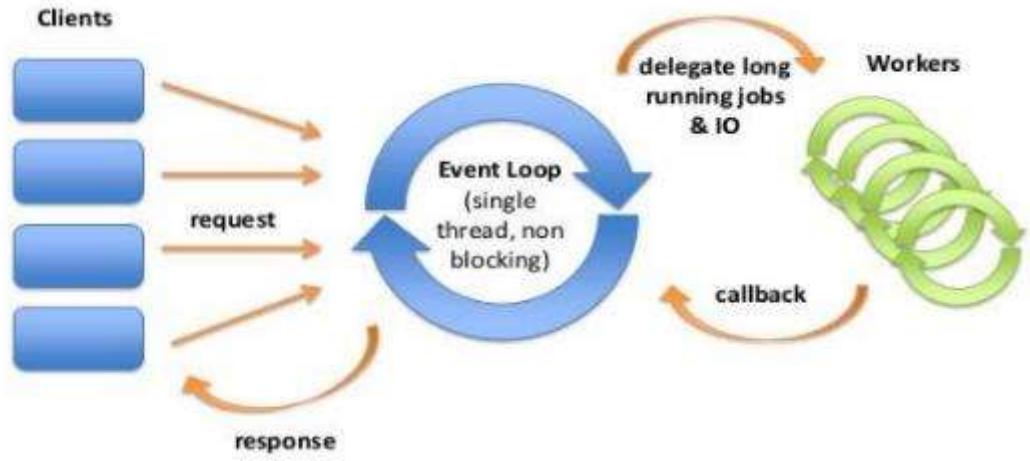


Figure 6. 12 Prototype two - voice recognition process (Street-Crossing - voice commands)

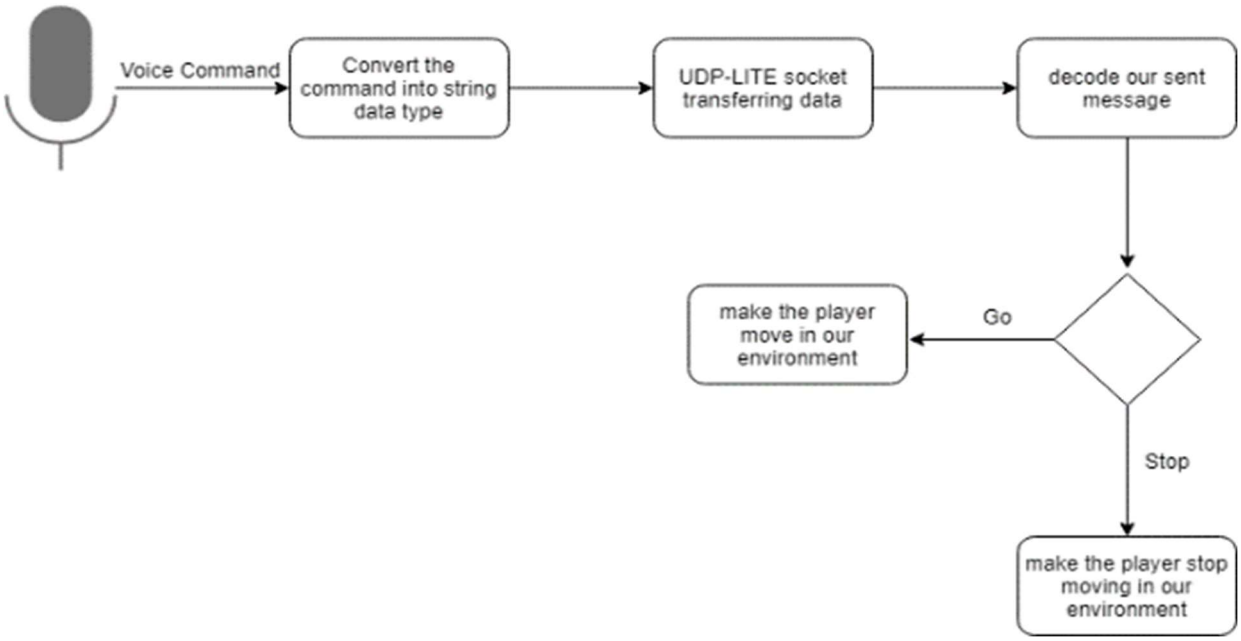


Figure 6. 13 Event-driven programming used in prototype two

Prototype three

Figure 6. 14 Prototype three - coin collection task, information flow through the network

Artificial Intelligence & Machine Learning

Artificial intelligence (AI) and machine learning (ML) were employed in the development of the above-discussed prototypes. Whilst various definitions and theories of AI – also known as machine intelligence – exist in the literature, AI generally refers to a process whereby a computer is taught

to mimic “intellectual processes characteristic of humans, such as the ability to reason, discover meaning, generalise or learn from past experiences” (Bali, Garg, and Bali 2019).

ML, however, is a subset of AI and involves the use of complex algorithms and statistical models that allow computer systems to perform various complex tasks. ML simply means that a machine is trained to enhance computational power, storage and memory capacity as well as the ability to handle enormous volumes of data. ML has been increasing and successfully employed in academia and industry, which has led to a significant increase in the production and quality of AI-based products. Thanks to ML approaches, including the ability to collect and process large volumes of data as well as making accurate predictions based on a wide range of data sources, AI-based products have become an integral part of our daily lives (Amisha et al. 2019; Bini 2018; Toh, Dondelinger, and Wang 2019).

ML was used in the three prototypes developed to help assess, predict and classify stroke patients with USN tendencies and those without. We also used ML to analyse various data points collected during the VR tasks to help improve the VR systems’ prediction / diagnostic ability (current thesis) and employment as rehabilitation tools (future studies). Furthermore, ML was used to test new data points for each prototype to further improve the computational power and ability of the VR systems as well as the process of data collection and analysis.

Systematic Analysis of Development

We employed a waterfall model (**Figure 6.15**) in the development of the VR prototypes, meaning that the project was divided into several stages (Dillibabu 2014). This meant that the completion of each stage would trigger the start of the next one, and thus, the three prototypes were developed systematically. This approach has a number of advantages including:

1. The development process is kept simple. The work was divided amongst the research and development teams and each developer / researcher was assigned a certain task.
2. Each stage was clearly defined, and specific tasks for each team member were determined prior to the start of the development process.
3. The waterfall model has linear sequential phases with no parallel working phases, meaning that if an error occurred with a specific task assigned to a certain team member, it would not affect the completion of other tasks assigned to other team members.
4. This model allows a faster execution of individual tasks due to the linear nature of the phases.

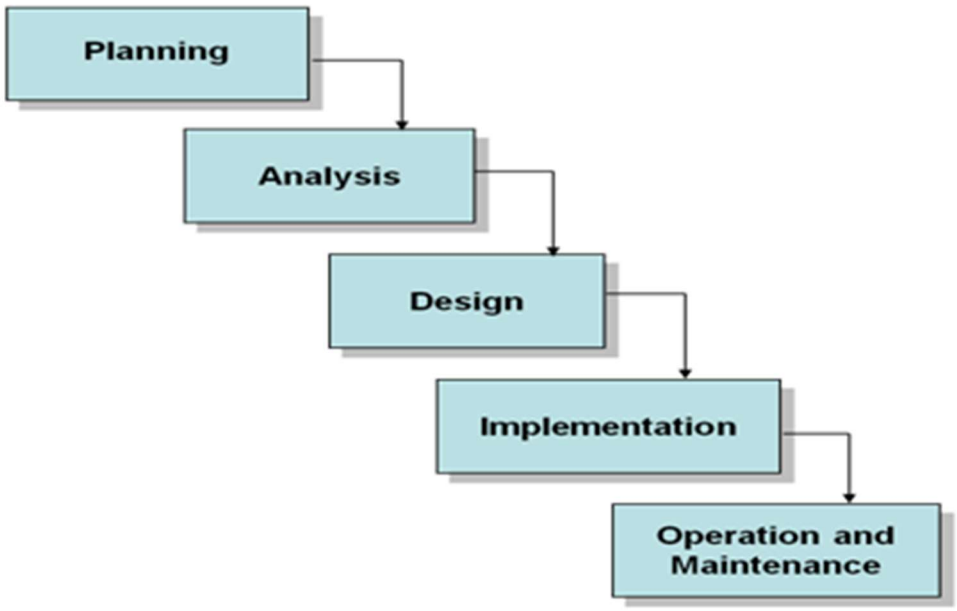


Figure 6. 15 Diagram showing the stages of the waterfall model

Smartphone App & User Interface

Building a flexible user interface (US) was a real challenge in terms of creating a user / researcher-friendly interface that would allow an easy change of settings as well as task management and execution. The UI, including the settings, play a key role in collecting basic user information as

well as determining the structure and features of the VR environment. The UI was created in a manner that would allow two levels of interaction depending on the user (average user, researcher and admin). The average user would be able to perform the following actions when the UI appears:

1. Browse the application and choose a level / mode (easy, medium, difficult)
2. Store basic information such as name, settings etc
3. Change settings according to preference

In addition to the above, a researcher / admin would be able to perform the following actions:

1. Suggest and add various new features to the VR tasks
2. Perform quality control on the data collected
3. Check missing data values if any
4. Carry out comprehensive analysis of the stored data which can also be visualised using data analysis and visualisation tools such as Tableau

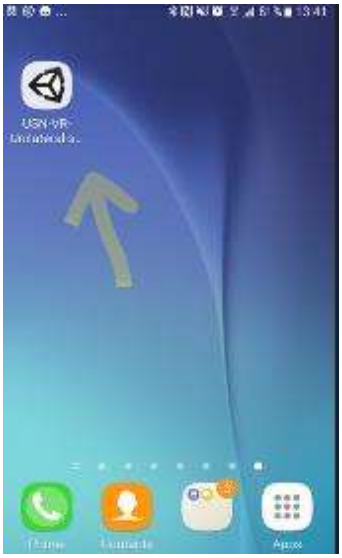


Figure 6. 16 USN-VR smartphone application developed and used in the pilot study

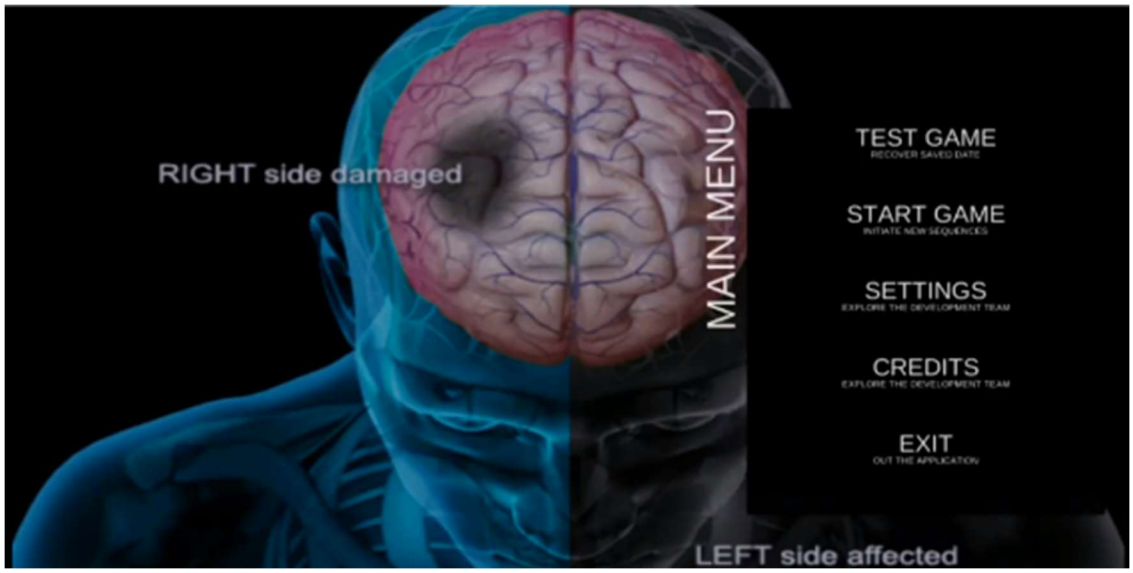


Figure 6. 17 USN-VR user interface (UI) presented upon entering the application

Summary of User Interface Interaction

The following tables provide examples on the levels of interaction with the UI and how the latter can be used and adjusted by different users.

Average User / Patient

Scenario 1

Scenario	Change Settings
Brief Description	Allow user to change Settings
Trigger	Click *Settings* button
Actor	User
Basic Flow	User enters app User chooses settings button User changes the settings User clicks on save button to save the settings
Alternative Path	In step 4, user can discard the changes and use the default parameters
Post-USN Test	User creates their own settings

Table 6.6 Instructions on how to change the settings of the USN-VR application for an average user / patient

Scenario 2

Scenario	Choosing Different Levels
Brief Description	User chooses a level among different options available
Trigger	Click the level button
Actor	User
Basic Flow:	User enters the app User chooses a level User enters the VR environment and completes the task
Alternative Path	In step 2, a user can click Test Game or Start Game button on the UI to trigger the start of the task
Post-USN Test	User enters a level according to preference

Table 6. 7 Instructions on how to enter the virtual environment of the USN-VR application for an average user / patient

Scenario 3

Scenario	Enter Name & Record Data
Brief Description	Collect user's data
Trigger	User enters their name
Actor	User
Basic Flow	User enters the app User enters their name User chooses a level Complete the task
Alternative Path	In step 2, user can choose whether they want to enter their name or leave the name field blank
Post-USN Test	After finishing the session, the real-time and one-time data records will be stored in the database for analysis

Table 6. 8 Explanation of how real-time and one-time data is stored for average user / patient

Researcher

Scenario 1

Scenario	Change Settings
Brief Description	Allow researcher to change *Settings*
Trigger	Click *Settings* button
Actor	Researcher
Basic Flow	Researcher enters app Researcher clicks *Settings* button Researcher changes the settings Researcher clicks save to save the preferred settings

Alternative Path	In step 4, the researcher can discard the changes and use the default parameters
Post-USN Test	Researcher creates suggested settings for a user / patient to try

Table 6. 9 Instructions for researchers on changing the settings of the USN-VR application

Scenario 2

Scenario	Choosing Testing Level
Brief Description	Researcher chooses a level
Trigger	Click the level button
Actor	Researcher
Basic Flow	Researcher enters the app Researcher chooses a level Researcher enters the VR environment
Alternative Path	In step 2, researcher can click Test Game or Start Game button on the UI to trigger the start of the task
Post-USN Test	Researcher enters the level and evaluates the basic immersive experience to ensure readiness for the patient

Table 6. 10 Instructions for researchers on patient testing in the virtual environment

Scenario 3

Scenario	Data Analysis
Brief Description	Collecting the patient's data for observing
Trigger	Researcher retrieves data stored on the app
Actor	Researcher
Basic Flow	Researcher enters the app Researcher clicks on data export button Data is imported and ready for analysis
Alternative Path	In step 2, data is sent to a secure database via web server for storage
Post-USN Test	Data is imported and researcher can perform quality control and analysis

Table 6. 11 Instructions for researchers on data collection and storage

Admin

Scenario 1

Scenario	Adding New Parameters
Brief Description	Adding new parameters suggested by researcher
Trigger	Suggested parameters added depending on the research question
Actor	System Admin

Basic Flow	System admin accesses the project's files on Unity engine Add new *Settings* parameters to the system Link new parameters with existing data structure Evaluate the addition of new parameters
Alternative Path	In step 2, new parameters can be added / edited / removed depending on the nature of the research question
Post-USN Tests	All new parameters are added and ready for deployment

Table 6. 12 Explains how an admin can add new settings / parameters to the USN-VR application

Scenario 2

Scenario	Data Quality Control
Brief Description	Ensure the data is complete and no errors recorded during the experiment
Business Trigger	N/A
Actor	System Admin
Basic Flow	System admin enters the database management program System Admin ensures the dataset is complete with no data is missing Export data in a suitable format for the researcher to analyse (e.g. CSV format)
Alternative Path	N/A
Post-USN Tests	Data is imported and ready for quality control and analysis

Table 6. 13 Data quality control

Deep Dive into Unity Workflow

During the development phases of the USN-VR app, we employed the standard approaches published by Unity (Unity Learn 2018). This involved combining artistic design with task-specific coding to enable the creation of a sound virtual environment. To achieve this, we used various built-in features and tools offered by Unity as well as other free open-source software, including:

- Unity editor: The editor is the main workspace interface for the developer / learner. It is a developer-friendly interface for working on visible 3D / 2D environments and observing the different components / behaviours interacting inside a "virtual scene" – the latter being a collection of different "game objects" programmed to behave in a certain manner. The
- objects (e.g. the tree, roads, building shown in the figure below) are normally designed by artists to enable the creation of 3D / 2D environments inside the engine.

Figure 6. 18 Unity Editor used in the development of the USN-VR application

- Source code editor: The text editor tool is designed for writing / editing the source code. It is a key tool when programming Unity projects. It includes syntax highlighting, indentation and autocomplete functionalities for more robust coding during development. The editor

also allows developers / learners to run a compiler, interpreter and debugger for the source code. Unity supports a large number of source code editors such as Microsoft Visual Studio and Microsoft Visual Code (Unity Learn 2018). During prototype development, we used the Microsoft Visual Code editor due to its robust workspace in terms of coding experience and debugging Unity C# code.

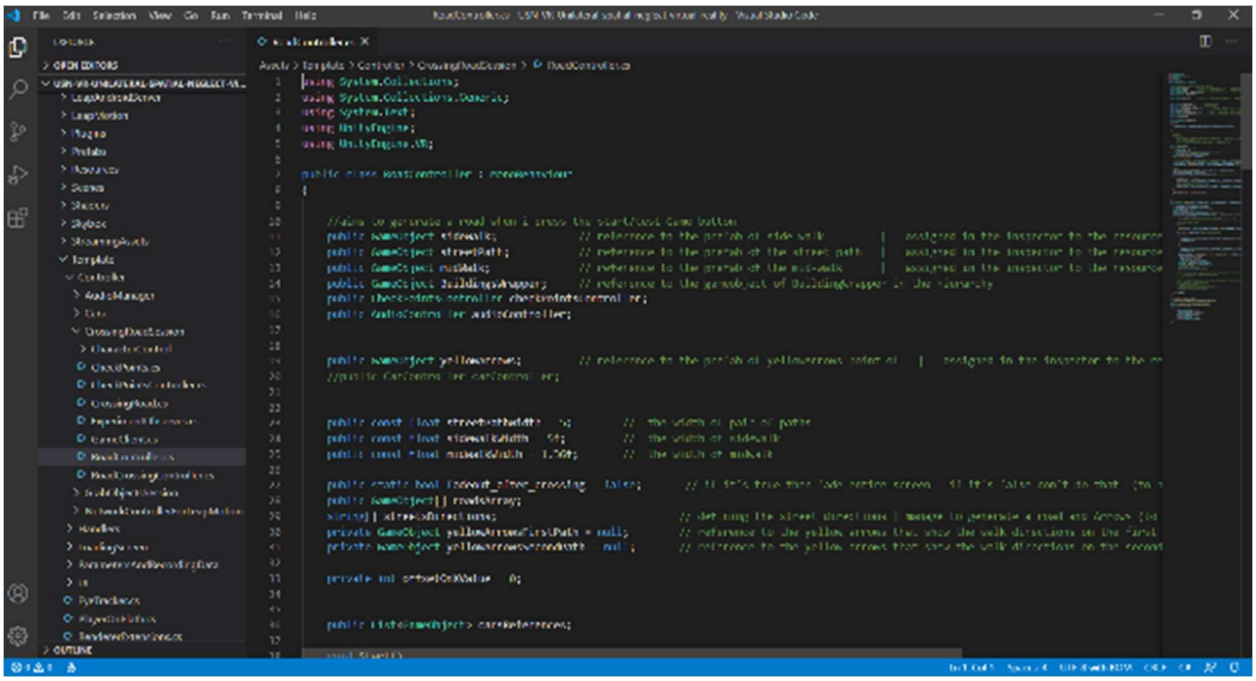


Figure 6. 19 Capture from Microsoft Visual Code editor used in the USN-VR application

Reusability of Task Coding and Structure

The development team employed the MVC approach in the development of the three prototypes to ensure that most of the components are reusable. The MVC approach permits addition, editing and removal of various features which makes it ideal for developing VR applications.

Additionally, the development process of each prototype was thoroughly documented and maintained. The game documentation was created and stored in a manner that makes it easily

readable and usable by other developers. It also means that the coding and structure of the current project can be employed in future projects for different research purposes (**Figure 6.20**).

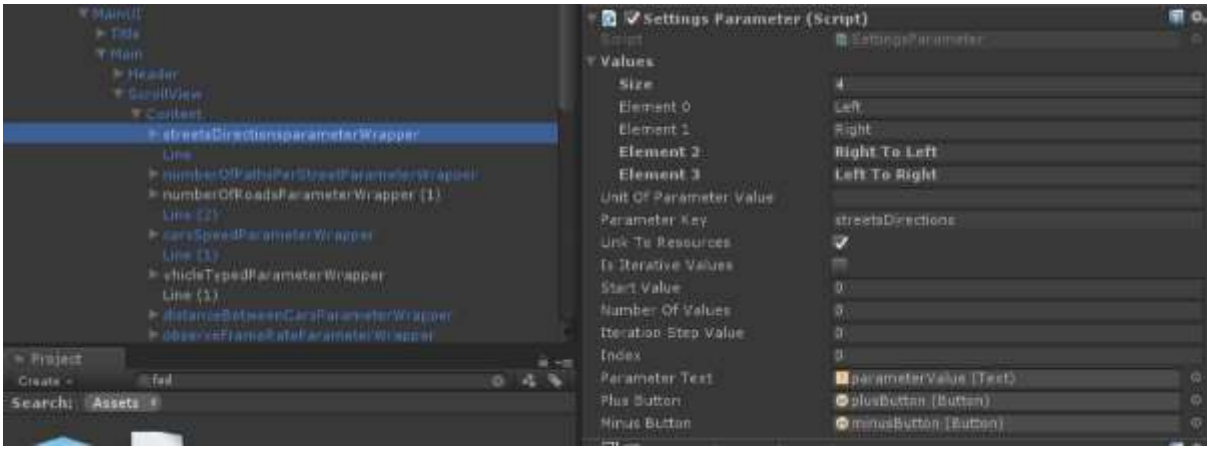


Figure 6. 20 Example of VR tasks' coding structure, documentation and potential reusability

VR Prototype Prototypes - Settings & Parameters

The settings presented below can be altered and adjusted as desired by the researcher or the user (**Figure 6.21**)**.** The VR environment can be recreated to mimic different street-crossing scenarios.

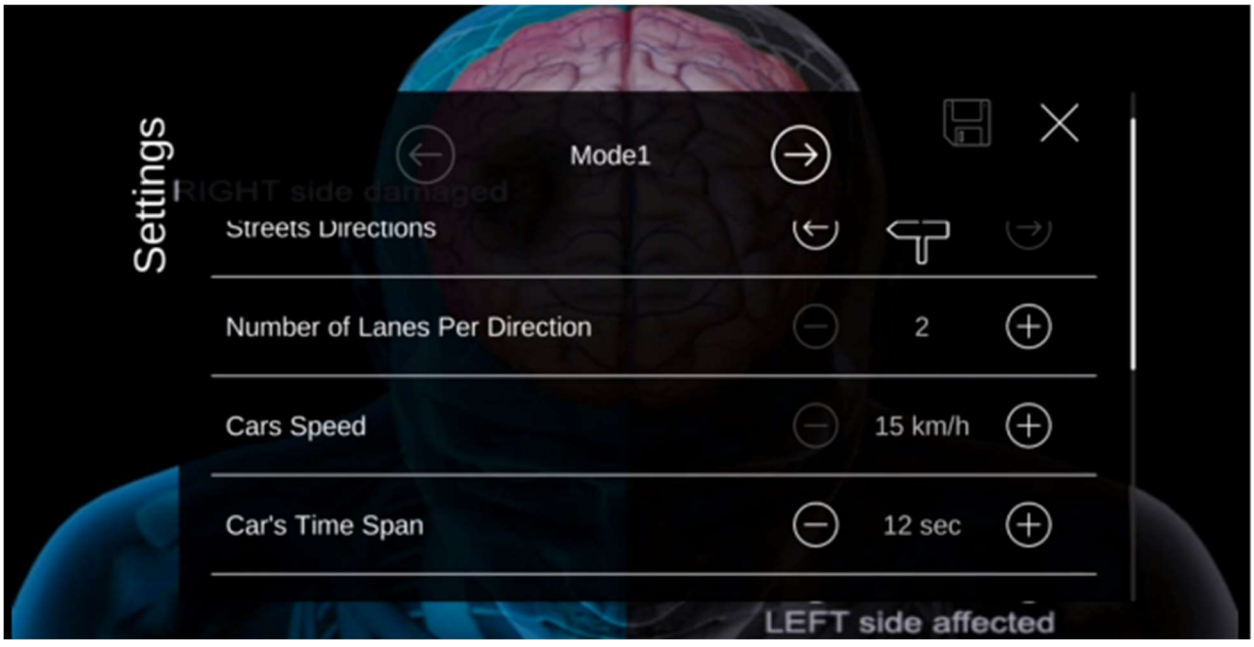


Figure 6. 21 Sample of the USN-VR prototype settings

Settings

1. Gameplay id: refers to a certain gameplay for a player
2. Street directions: determines which direction vehicles approach from (left only, right only, or both on two lanes – one left and one right)
3. Lanes per Direction/Road: number of lanes in a single road
4. Number of roads
5. Car/vehicle speed in kph
6. Car/vehicle span (seconds): distance between vehicles by taking timespan into consideration (vehicles can either move together or with intervals)
7. Sound Mode: the direction of sounds (left/right/both)
8. Player name (optional)
9. Player's height (optional)

USN-VR Application - Data Collection

The following data were collected automatically by the VR system:

- ID: primary key for each observed data.
- Gameplay ID
- Traffic Towards Flow: the current street direction.
- Current timespan: time elapsed since the game started
- Gazing car (vehicle)
- Current distance vs. nearest car
- Gazing nearest car: did the patient see the car while crossing
- After collision frame: a trigger to record whether the player had an accident with a car or not
- Person X, Y, Z: user's coordinates in 3D space described as the following:

Figure 6. 22 User coordinates in 3D space

- The red arrow: x axis in 3D space.
- The blue arrow: z axis in 3D space.
- The green arrow: y axis in 3D space.

Head rotation y: user's Y axis/head rotation in 3D space described as the following:

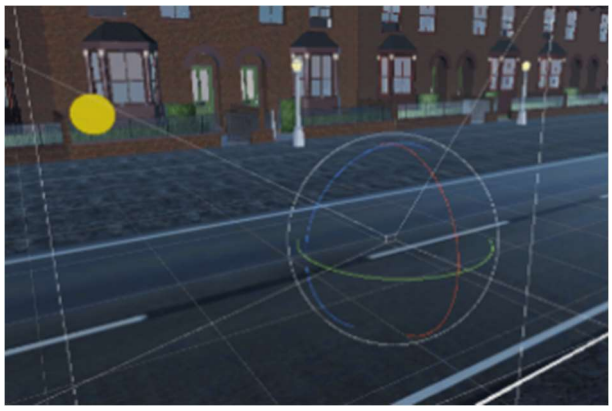


Figure 6. 23 Head rotation in 3D space

- The red circle: x axis in 3D space.
- The blue circle: z axis in 3D space
- The green circle: y axis in 3D space.

	Name	Data type	Primary Key	Foreign Key	Unique	Check	Not NULL	Collate	
1	street_crossing_data_id	INTEGER							NULL
2	gameplay_id	INTEGER							NULL
3	traffic_flow_towards	STRING							NULL
4	current_time_span	DOUBLE							NULL
5	current_distance_nearest_car	DOUBLE							NULL
6	gazing_car	BOOLEAN							NULL
7	gazing_nearest_car	BOOLEAN							NULL
8	after_collision_frame	BOOLEAN							NULL
9	person_x	DOUBLE							NULL
10	person_y	DOUBLE							NULL
11	person_z	DOUBLE							NULL
12	head_rotation_y	DOUBLE							NULL

Table 6.14 Data collection keys

In conclusion, prototype two was deemed adequate for inclusion in a pilot study following several rounds of testing. This task was also considered safe to perform and more inclusive than prototype one, as stroke patients with different abilities, including those using wheelchairs, can perform this task in a safe and controlled virtual environment

USN-VR Prototypes – Codes

The USN-VR prototypes developed employ dynamic and robust event-driven programming approach whereby the different controllers of the virtual environment are independent of each other. This allows the overall architecture of the virtual environment to be more “isolated”. In other words, this made it easier add new features while maintaining the original architecture of the virtual environment we wanted keep.

Furthermore, the ability to add, edit, record and/or delete different paraments related to the researcher’s as well as the future user’s scenario of the virtual environment / task is controlled through classes of codes developed during the project. In simple terms, the classes of codes would

allow any change in the application settings by the researcher or the user to be executed inside the virtual environment as soon as the new settings are saved, and the user enters “test game” or “start game” and recorded once the VR task is complete. The code classes are:

1. **Road controller class (street-crossing prototypes)**

This class is responsible for generating roads for the street-crossing task inside the virtual environment. It does so by translating the codes below which take into account the different parameters chosen by the user in the settings tab found in the user interface. These parameters include the number of roads, lanes per direction, street direction type and so on.

The “generateRoads()” code below is activated and deployed as soon as the user clicks “test/start game”. This function changes with any new change of settings and generate the appropriate number of roads, lanes and tags the flow of vehicle direction as specified by the researcher / average user.

```
public void generateRoads()
    {
        //Assigning number of paths from the UI
        int pathGenerateIndex = 0;
        int numberOfPathsInSingleRoad = ExperimentParameters.lanes_per_direction;
        int numberOfRoads = ExperimentParameters.numberOfRoads;
        carsReferences = new List<GameObject>();
        // using string builder to rename the roads into a correct format just to make it easy reaching them
        float lastPosition = sidewalkWidth + midwalkWidth + (streetPathWidth / 2) + streetPathWidth * (numbe
rOfRoads);
        yellowArrowsFirstPath = Instantiate(yellowArrows, new Vector3(sidewalkWidth + (streetPathWidth / 2),
 -1.999f, -8.98f), Quaternion.identity);

        //Road #1
        roadsArray = createDirection(sidewalkWidth + (streetPathWidth / 2), ref pathGenerateIndex, 0);
        Debug.Log("after generate the first road");
        Debug.Log(ExperimentParameters.streetsDirections);
        streetsDirections = ExperimentParameters.streetsDirections.Split(' ');
        if (streetsDirections.Length > 1)
        {
            Debug.Log("generate the second road");
```

```
            Instantiate(midWalk, new Vector3(sidewalkWidth + (midwalkWidth / 2) + streetPathWidth * (numberO
fRoads), -2.0f, 0.0f), Quaternion.identity);
            yellowArrowsSecondPath = Instantiate(yellowArrows, new Vector3(lastPosition, -1.99f, -
8.98f), Quaternion.identity);

            //Road #2
            roadsArray = createDirection(sidewalkWidth + (streetPathWidth / 2) + midwalkWidth + (streetPathW
idth * (numberOfRoads)), ref pathGenerateIndex, 2);
            Instantiate(sidewalk, new Vector3((sidewalkWidth) + (midwalkWidth) + streetPathWidth * (numberOf
PathsInSingleRoad), -0.0012f, 0.0f), Quaternion.identity);
        }
        else //one direction usecase
        {
            Debug.Log("generate side walk in else condition");
            Instantiate(sidewalk, new Vector3((sidewalkWidth) + (streetPathWidth * (offsetOnXValue / 2)) + (
midwalkWidth * numberOfRoads) - midwalkWidth, -0.0012f, 0.0f), Quaternion.identity);
        }

        BuildingsWrapper.transform.position = new Vector3((sidewalkWidth * 2) + (midwalkWidth * numberOfRoad
s) + (streetPathWidth * (offsetOnXValue / 2)), 0, 0);

    }
```

Figure 6. 24 Road controller class of code for the function of “generateRoads()”

Also, part of the “road controller” class is the “createDirection” code below, which uses “generateRoad()” parameters but also conducts several calculations to determine the position of each lane in the virtual environment.

```
    public GameObject[] createDirection(float startPositionAtX, ref int pathGenerateIndex, int indexOfD
irection)
    {
        int numberOfRoads = ExperimentParameters.numberOfRoads;
        int numberOfLanes = ExperimentParameters.lanes_per_direction;
        Vector3 RoadMeasure = Vector3.zero;
        GameObject generatedRoad = null;
        GameObject[] roadsArray = new GameObject[numberOfRoads * numberOfLanes / 2];
        Debug.Log("Roads array length " + roadsArray.Length);
```

```
        streetsDirections = ExperimentParameters.streetsDirections.Split(' '); //to be able to name the
 streets
        for (int i = 0; i < numberOfRoads; i++)
        {
            if (i != 0)
            {
                Debug.Log("offsetOnXValue  = " + (offsetOnXValue / 2) + " AND i = " + i);
                Instantiate(midWalk, new Vector3(sidewalkWidth + (midwalkWidth / 2) + (streetPathWidth
* (offsetOnXValue / 2)) + (midwalkWidth * (i - 1))    /* (numberOfRoads)*/, -
2.0f, 0.0f), Quaternion.identity);

            }
            for (int j = 0; j < (numberOfLanes / 2); j++) //generate each  road
            {
                if (j == 0)
                {
               RoadMeasure = new Vector3(startPositionAtX + (streetPathWidth * offsetOnXValue / 2) +
(midwalkWidth * i), -2.0f, 0.0f);
                generatedRoad = Instantiate(streetPath, RoadMeasure, Quaternion.identity) as GameObject;
                offsetOnXValue += 2;

                }
                else
                {

                    RoadMeasure = new Vector3(startPositionAtX + (streetPathWidth * offsetOnXValue / 2)
 + (midwalkWidth * i), -2.0f, 0.0f);
                    generatedRoad = Instantiate(streetPath, RoadMeasure, Quaternion.identity) as GameOb
ject;
                    offsetOnXValue += 2;
                }
                int offsetTotal = (offsetOnXValue / 2) - 1;

                if (offsetTotal < roadsArray.Length)
                {
                    roadsArray[offsetTotal] = generatedRoad;
                }
                StringBuilder stringBuilder = new StringBuilder();
                stringBuilder.Append("Road " + offsetOnXValue / 2);
                generatedRoad.name = stringBuilder.ToString();
            }

        }
        return roadsArray;
```

```
}
```

Figure 6. 25 Road controller class of code for the function of "createDirection"

2. Experiment observes class (street-crossing prototypes)

This class is used to record all movement data inside the virtual environment from the user's position. Such movement parameters include the head rotation and current traffic flow direction at a certain time in seconds. It starts recording as soon as a user enters the virtual environment until the task is completed (i.e. user exists the virtual environment) and send the collected data to our local database. The data collection and recording process is activated using the "Initialize()" and "onFrame" code. We initialise the arrays which represent each data point collected with the codes below.

```
public void Initialize()
{
    //initialize the framerate value
    float frameRateInitialize = float.Parse(ExperimentParameters.observeFrameRate);
    observeFrameRate = frameRateInitialize / 30; //now getting the invoke reapeting rate

    //those arrays are here for recording the data to DB every 2 invokes (performance matter)
    playerPositions = new Vector3[3];  //player position array for recording
    playerHeadRotations = new float[3]; //player head rotation as array for recording purpose
    traffic_towards_flow = new string[3]; //recording the current road the player is on
    isLookingAtCar = new bool[3]; //is he looking to a car
    current_time_span = new float[3]; //time span since OnFrame() started
    is_hit_by_car = new bool[3];
    distance_nearest_car_in_lane = new float[3];

    //getting the initial state of the first road
    leftSideString = ExperimentParameters.streetsDirections.Split(' ')[0][0].ToString();
    current_traffic_towards_flow = leftSideString;
    //time since touching the first yellow point
    timeSinceReachTheFirstYellowPoint = Time.time;
    parents2DArray = carController.parentsWithCars2DArrayRefernces;
    //invoke the method
    InvokeRepeating("searchOnPlayer", 1f, observeFrameRate);
}
```

```
    void OnFrame()
    {
        //recording the data
        angle = mainCamera.transform.localRotation.eulerAngles.y;
        playerPositions[frameIndex] = SpineMid.transform.position;
        playerHeadRotations[frameIndex] = angle;
        traffic_towards_flow[frameIndex] = current_traffic_towards_flow;
        current_time_span[frameIndex] = Mathf.Abs(Mathf.Round((Time.time - timeSinceReachTheFirstYellow
Point) * 1000) / 1000);
        isLookingAtCar[frameIndex] = CarMove.numberOfRenderedCars > 0;
        is_hit_by_car[frameIndex] = checkPointsController.isHitByCar;
        distance_nearest_car_in_lane[frameIndex] = finalDistanceResult;
        frameIndex++;
        if (frameIndex == 2)   // you can use this as the index of the lists above
        {
            observedData = new ObservedData
(playerPositions, playerHeadRotations, isLookingAtCar, traffic_towards_flow, current_time_span, is_hit_
by_car, distance_nearest_car_in_lane);
            //connection to database in a thread
            Thread connectionDBThread = new Thread (() => ConnectionToDB());
            connectionDBThread.Start();
            if (!connectionDBThread.IsAlive)
            {
                connectionDBThread.Abort();
            }
            frameIndex = 0;     // back to zero after each send
        }
    }
```

Figure 6. 26 Experiment observes class of codes for the functions of Initialize()" and "onFrame"

Table controller (coin detection prototype - not relevant to street-crossing)

This class is used specifically for the object detection and collection (VR prototype three). This class is responsible for generating / initialising the coin detection and collection VR task in the pre-specified order of personal, peri-personal, far extra-personal space. Using the "RecordCollectedObjectsToDB()" code below, the performance of each user is recorded and collected data is sent to the local database.

```
public void RecordCollectedObjectsToDB()
    {
        for (int i = 0; i < instantiatedTableActiveGameObjects.Length; i++)
```

```
        {
            dbgrabconnection.CreateCollectedObjectsRow(instantiatedTableActiveGameObjects[i].GetCompone
nt<TableObject>().collected_Objects);
        }
    }
```

Figure 6. 27 Table controller code for the functionality of "RecordCollectedObjectsToDB()"

3. DataService class (street-crossing prototypes)

The DataService class is responsible for connecting and recording all results from different experiments and sending them to the local database. The "CreateRoadCrossingData()" functionality uses the various real-time and one-time data collected during the "experiment observes" phase to create a table that includes all relevant data in a readable manner (.csv format) that would enable a quality control exercise and data analysis.

```
    //create a crossingroaddata row in the db
    public void CreateRoadCrossingData(ObservedData observedData)
    {
        StreetCrossingData streetCrossingData;

        for (int i = 0; i < 2; i++)
        {
            streetCrossingData = new StreetCrossingData
            {
                gameplay_id = ExperimentParameters.gameplay_id,
            //storing from the static variable in the class
                traffic_flow_towards = observedData.traffic_towards_flow[i],
                current_time_span = double.Parse(observedData.current_time_span[i].ToString("F3")),
                current_distance_nearest_car = (double)observedData.nearest_distance_for_lane[i],
                gazing_car = observedData.isLookingAtCar[i],
                gazing_nearest_car = false,
                after_collision_frame = observedData.is_hit_by_car[i],
                person_x = (double)observedData.playerPositions[i].x,
                person_y = (double)observedData.playerPositions[i].y,
                person_z = (double)observedData.playerPositions[i].z,
                head_rotation_y = (double)observedData.playerHeadRotations[i]
            };
            _connection.Insert(streetCrossingData);
        }
    }
```

Figure 6. 28 DataService class of code for the functionality of "CreateRoadCrossingData()"

Chapter 7

Virtual Reality Smartphone Application for the Assessment of Post-Stroke Unilateral Spatial Neglect: A Pilot Study

Abstract

Background

Unilateral spatial neglect (USN) is a common and disabling post-stroke deficit. Conventional paper and pencil assessments are traditionally used to assess USN despite several limitations including the inability to detect milder forms of USN. Virtual reality (VR) is a novel technology that has been increasingly used to screen for USN.

Objectives

The objective of this pilot study was to develop and evaluate a simple street crossing task in a virtual environment for the assessment of stroke patients with USN. It was hypothesised that the VR task will distinguish between stroke patients with and without USN.

Methods

Twenty-four stroke patients (12 USN+, 12 USN-) and eight healthy controls (HC) were tested using conventional USN tests (line bisection and bells tests) as well as the USN-VR street-crossing task to assess their ability to cross the street safely and negotiate moving vehicles in a virtual environment. Performance of the three groups was compared on conventional assessments and USN-VR in terms of head rotation, accident rate, successful crossings, head turns, and time taken to complete the tasks.

Results

For the left-side trials, neglect patients showed a higher accident rate per trial and a lower rate of successful crossings and number of left head turns compared to non-neglect and healthy control subjects. No difference was observed between the three groups on the right-side trial in terms of number of accidents and successful crossing. There was a good correlation between paper and pencil tests and a simple VR street crossing task.

Conclusion

This pilot study showed that the ability of the VR street crossing task to detect USN was similar to the line bisection and bells tests. However, it was not possible to carry out a diagnostic test

accuracy analysis to compare the two methods as there is no gold standard assessment battery for USN. This study had several limitations, chief among them is the small sample size and the study design. Future studies should consider a randomised test design and recruit a larger sample size. The heterogeneity of USN symptoms and absence of consensus on gold standard assessments should encourage researchers with experiment with hybrid models of USN assessments that combine conventional tests, ecologically valid assessments, and VR-based tools.

Introduction

Stroke is one of the leading causes of death and disability worldwide (Feigin et al. 2014). In the UK, an estimated 100,000 strokes occur each year (Stroke Association 2018). Stroke survivors suffer from a wide range of physical and cognitive impairments (Al-Qazzaz et al. 2014). These impairments include unilateral spatial neglect (USN) which scientifically hinders stroke survivors' chances of regaining independence and performing simple everyday activities (Aretouli and Brandt 2010; Bowen and N. Lincoln 2007; Buxbaum et al. 2004).

The first recorded definition of USN, a syndrome characterised by spatial awareness deficits, dates back to the second half of the nineteenth century (Jackson 1932; Vallar 2001). By the start of the current century, hundreds of studies had thoroughly investigated USN and related phenomena and developed various modes of assessment and rehabilitation strategies (Gammeri et al. 2020). The last decade saw a significant increase in the number of USN-related studies, mostly due to recent advances in neuroimaging techniques (Adair and Barrett 2008).

Unilateral spatial neglect (USN) is a highly prevalent post-stroke clinical consequence affecting approximately 25-30% of all stroke survivors in the acute stage (Corbetta and Shulman 2011). Of those affected by USN, the vast majority (estimates vary between 80-90%) have right hemisphere lesions (Li and Malhotra 2015; Ringman et al. 2004). Chronic USN impacts 5-17% of stroke survivors with right hemisphere lesions (Karnath et al. 2011b; Ringman et al. 2004). USN patients fail to detect, report, respond or orient to stimuli presented on the contralesional side of space, and symptoms indicate impairments in visual, auditory and tactile channels. USN-related deficits are associated with a wide range of lesions in both cortical and subcortical regions (Corbetta and Shulman 2011; Hillis et al. 2005).

Lesions in the right hemisphere are far more likely to lead to severe and enduring neglect than those in the left hemisphere. This may be because one of the dominant functions of the left hemisphere is language processing (in right-handed people). Therefore, it is less involved with visuoperceptual function, and damage results in dysphasia which allows earlier self-detection and treatment (Kleinman et al. 2007). However, a number of other factors are probably involved in hemispheric differences in USN (Li and Malhotra 2015).

USN can be classified into three main categories - sensory (visual and auditory), motor and representational deficits (Gammeri et al. 2020). Additional USN subtypes affecting different spatial arrays (personal, near extrapersonal, far extrapersonal) and spatial frames (egocentric and allocentric) are well-documented in the literature (Bowen and N. Lincoln 2007; Cléry et al. 2015; Leyland et al. 2017). It is common for some authors to combine the above-mentioned classifications, as sometimes near and far extrapersonal USN are described in terms of sensory deficits whereas personal USN is often described as somatosensory deficit (Berti and Frassinetti 2000; Neppi-Mòdona et al. 2007). In clinical settings, however, an overlap of USN subtypes is often seen among stroke patients who typically show mixed symptoms (Aimola et al. 2012; Chatterjee 1994).

Sensory neglect is the most common subtype of USN and accounts for most cases. This subtype is a high-order, multi-sensory cognitive impairment affecting spatial orientation and response to contralesional stimuli following a brain injury (Kleinman et al. 2007; Zebhauser et al. 2019). A hallmark of visuospatial (sensory) neglect is the selective unawareness of contralesional stimuli combined with reduced attention and exploration ability which leads to a failure in responding to stimuli presented contralesionally (Adair and Barrett 2008; Ronchi et al. 2014). Sensory USN symptoms are the most visible and are normally easily detected in clinical settings (Buxbaum et

al. 2004; Kerkhoff 2001). The importance placed on detecting sensory neglect symptoms stems from their effect on patient prognosis in terms of neurorehabilitation and Activities of Daily Living (ADLs) (Chen et al. 2015; Dobkin 2004). Typical sensory USN symptoms are most obvious during ADLs such as eating, walking, washing and shaving. USN patients may eat food on the ipsilesional side and neglect the contralesional side of the plate, bump into furniture or objects located in the contralesional hemi-space and males may shave only the ipsilesional side of the face (Gerafi et al. 2017; Kerkhoff and Schenk 2012; Di Monaco et al. 2011).

Traditionally, conventional paper and pencil tests such as line bisection, target cancellation, object drawing and copying tasks are the most common mode of USN assessment (Azouvi et al. 2002; Plummer, Morris, and Dunai 2003). These conventional assessments use static 2D targets to assess USN-related deficits. The line bisection and cancellation (e.g. letter, star, bell) tests are frequently used in clinical practice to assess USN among stroke patients due to their simplicity and ease of administration (Ferber and Karnath 2001; Gauthier, Dehaut, and Joanette 1989; Rorden and Karnath 2010). Nonetheless, most paper and pencil assessments lack tasks that mimic ADLs. Additionally, conventional tests include visual scanning tasks that can be learned and mastered with practice. Furthermore, some patients can compensate on conventional tests with practice despite showing no improvement on ADLs (Bowen and N. Lincoln 2007). Thus, conventional tests can sometimes paint a misleading picture and lead therapists and clinicians to deem patients USN-free based on conventional test scores which often fail to detect subtle USN deficits (Agrell, Dehlin, and Dahlgren 1997; Eschenbeck et al. 2010; Kim et al. 2011; Weiss et al. 2003). Conventional paper-and-pencil assessments may be sufficient for the assessment of USN in the acute stage of the disorder. However, they are deemed inadequate for the assessment of milder forms of USN, particularly in the chronic stage

The limitations of said conventional tests have led researchers to develop various new USN tests / batteries that can assess both sensory and motor deficits. Chief among them is the Rivermead Behavioural Inattention Test (BIT), a 15-item (nine behavioural and six conventional subtests) behavioural psychometric battery of tests for the assessment of USN (B. Wilson, Cockburn, and Halligan 1987). The BIT includes behavioural assessments of everyday skills such as menu reading, telephone dialling and card sorting as well as conventional assessments such as the line bisection and star/letter cancellation tests (Halligan et al. 1989; Luukkainen-Markkula et al. 2011). Despite becoming one of the most frequently used clinical assessments of USN, the BIT has a number of limitations including lengthy duration of administration and scoring which makes it time-consuming for clinicians and tiresome for USN patients, especially those with severe attention deficits (Azouvi 2017; Di Monaco et al. 2011). Additionally, the BIT can only be administered by well-trained therapists and clinicians which can in turn limit the utility of the test in clinical practice (Navarro et al. 2013).

Recent and ongoing advances in technology have made it possible for medical researchers to develop new and innovative methods of assessment and rehabilitation for various medical conditions including USN (Bohil et al. 2011a). Over the past decade, advanced technologies such as virtual reality (VR), augmented and mixed reality have been introduced to the field of neurological assessment and rehabilitation (Cipresso et al. 2018; Wright 2014). VR has gradually laid the foundations for the development of various new assessment and rehabilitation tools for cognitive impairments including USN (Gamito et al. 2017; Ogourtsova et al. 2017). VR-based tools offer an alternative to conventional modes of assessment and rehabilitation as they could potentially overcome the limitations of conventional tests and interventions by introducing new

features that are otherwise not possible in traditional methods (Hung et al. 2014; Pedroli et al. 2015; Sala 2007).

Using VR systems, which are essentially computer-simulated environments, various real-life scenarios can be recreated in a safe, ecological and patient / condition-specific manner (Bohil, Alicea, and Biocca 2011b). VR uses 3-D images to create virtual tasks that require dynamic responses unlike conventional paper and pencil assessments which use static 2-D visual training tasks that can be learned with practice (Cox 2003; Fordell et al. 2011a; Rizzo, Schultheis, et al. 2004). Furthermore, VR tools offer a flexibility that is seldom seen on conventional tests, where a virtual environment can be recreated and adjusted easily (by both researchers and users) to suit the different needs of each patient. This flexibility makes VR-based tools much more researcher / user-friendly than conventional assessments and interventions.

One of the major advantages of VR tools is the ability to deliver a high dose of task-specific training in a safe and controlled virtual environment which is otherwise very hard to administer in real-life (Perez-Marcos, Bieler-Aeschlimann, and Serino 2018; Stanmore et al. 2017). For example, USN patients tend to bump into furniture and objects – increasing their risk of falls and fractures – and neglect the left hemi-space when crossing the street which can be very risky. Whilst it is extremely difficult to assess patients' navigation and street-crossing abilities in real life situations due to the risk associated with such activities, VR tools can provide an excellent alternative where tasks such as navigation, object detection and crossing the street can be performed safely and with minimal risk (Buxbaum et al. 2012; Navarro et al. 2013; Peskine et al. 2011). Additionally, VR assessments can provide new insights into each patient's performance and attentional ability including head rotation in space, eye movement tracking and behavioural

responses. These measures are not possible to gauge using conventional assessments (Aravind and Lamontagne 2018; Ulm et al. 2013).

Over the past few years, VR-based tools have increasingly been used for the assessment of post-stroke cognitive impairments including USN. Researchers have designed various VR-based assessments for USN, some of which intend to mimic life scenarios while others rely on invented scenarios (Duffy, Cushman, and Stein 2008; García-Betances et al. 2015; Laver et al. 2017).

Currently, VR assessments for USN reported in the literature include navigation, obstacle avoidance, VR target cancellation, and street-crossing tasks (Aravind and Lamontagne 2017; Buxbaum et al. 2008; Kim et al. 2011; Navarro et al. 2013; Peskine et al. 2011). Five studies have previously used street-crossing scenarios in their design, three as a mode of assessment of USN (Kim et al. 2010; Navarro et al. 2013; Peskine et al. 2011) and two as a rehabilitation tool (Katz et al. 2005; Weiss et al. 2003). However, none of the abovementioned studies reported the cost of the VR systems and accessibility for stroke patients in clinical and non-clinical settings. Additionally, none of the systems developed previously had a researcher as well as an average user functionality in the same VR application / system. Therefore, we aimed to design, develop, and evaluate a new low-cost VR street-crossing mobile application (USN-VR) that uses voice commands for the assessment of USN that can be safely used by researchers and clinicians as well as average users, patients and their relatives in clinical and non-clinical settings. Whilst our VR system was intended as an assessment tool, it has the potential to be used as a rehabilitation tool in future studies. However, this study only intends to discuss the assessment capabilities of the USN-VR tool. The VR task employs a simple design using voice instructions (e.g., words such as *"go"* and *"stop"*) and was deemed potentially more inclusive as it can be used with patients of varying abilities such as those in a wheelchair or who are bedbound.

We hypothesised that the number of accidents, successful crossings and number of left head turns in the virtual street-crossing task would distinguish between stroke patients with (USN+) and without USN (USN-).

Methods

Participants

The aim was to recruit stroke patients with and without USN. The inclusion criteria for neglect patients (NP) were: 1) right hemisphere ischemic or haemorrhagic stroke confirmed by a CT or MRI scan; 2) age > 18; 3) time since stroke > 4 weeks; 4) clinical diagnosis of USN on conventional paper and pencil assessments including the line bisection test; 5) reasonably good cognitive ability – Montreal Cognitive Assessment (MoCA ≥ 20); 6) ability to participate in a test session for one hour confirmed by a healthcare professional (e.g., stroke nurse). The inclusion criteria for the stroke control (patients without USN) group were the same as the stroke group with USN except the absence of clinical diagnosis of USN on conventional paper and pencil assessments including the line bisection test. The exclusion criteria for both groups were: 1) patients with severe aphasia; 2) patients with visual field defect; 3) patients with severe cognitive deficits; 4) patients with severe mental illness; 5) patients with epilepsy; 6) patients with hearing loss. After screening for patients using the abovementioned inclusion and exclusion criteria, 26 stroke patients with right hemisphere lesions (20 ischemic and 6 haemorrhagic) were initially recruited for this study. Two patients (1 male and 1 female) did not complete the VR assessment – one due to feeling unwell on the day and the other due to motion sickness. Twenty-four stroke patients completed the assessments and were divided into two groups:

1. Stroke patients with USN (USN+) group: 12 patients (7 males and 5 females), 63.1 ± 10.0 years (mean age ± SD), 373.9 ± 366.3 days (chronicity ± SD) and 11.8 ± 2.7 years of education.
2. Stroke patients without USN (USN-): 12 patients (8 males and 4 females), 60.7 ± 10.6 years (mean age ± SD), 207.4 ± 294.5 days (chronicity ± SD) and 11.5 ± 3.2 years of education.

In addition to the stroke groups, a healthy control (HC) group which met the criteria of no history of stroke, substance abuse, epilepsy or hearing loss and matched age, education and cognitive condition was recruited. Eight healthy participants (4 males and 4 females), 58.9 ± 9.0 (mean age ± SD) and 12.8 ± 1.0 years of education were recruited **(Table 7.1).**

Table 7. 5 Characteristics of participants

	Control Group	**Experimental Group**	
	HC ***N=8***	**Neglect (USN+)** ***N=12***	**Non-Neglect (USN-)** ***N=12***
Gender (*n*, %)			
Male	4 (50%)	7 (58%)	8 (67%)
Female	4 (50%)	5 (42%)	4 (33%)
Age (years)	58.9 ± 9.0	63.1 ± 10.0	60.7 ± 10.6
Education (years)	12.8 ± 1.0	11.8 ± 2.7	11.5 ± 3.2
Chronicity (Days)	N/A	373.9 ± 366.3	207.4 ± 294.5
Stroke Type			
Ischemic	N/A	10 (83%)	9 (75%)
Haemorrhagic		2 (17%)	3 (25%)

Materials

Hardware

The fully immersive VR Street-crossing system is composed of a standard desktop or laptop (for the researcher – average user version does not require a desktop), a smartphone [minimum system requirement: Android Operating System Marshmallow 6.0 or above or iPhone 6 or above – Samsung Galaxy S6 (Android 6.0) was used in this study (S6 2015)], standard headphones as well as an HMDI - Shinecon G01 3-D VR Glasses (Shinecon VR 2018) were used in this study. However, any Google Cardboard VR goggles would work).

Software

The VR Street-crossing system is a smartphone application that can be downloaded on any of the abovementioned smartphones. The verbal commands VR street-crossing task attempted to mimic a real-life street-crossing scenario, albeit with certain modifications including the use of voice commands rather than physical movement. The task took place in a fully immersive environment [i.e. involved wearing adjustable VR goggles for immersion] where participants attempted to complete a street-crossing task successfully without any accidents.

The scenario consisted of three roads, each with two lanes and a pavement between every two roads. Three types of vehicles were used in this task: cars, trucks, and buses. The vehicles' 3D models varied in size in an attempt to establish an understanding of whether using differently sized vehicles may affect the user's ability to detect them. The default colour of the vehicles was set to black to accommodate individuals with colour blindness. Nonetheless, a feature that would allow the researcher / user to change the type of vehicle and colour was added to the settings.

At the start of the task, the participant first explores the virtual environment to establish familiarity and assess whether it is safe to cross the street. The participant navigates the environment and movement inside the game via voice commands. When the participant deems it safe to move /

cross the street, they say "*go*" – as a result, the camera inside (i.e. the subject inside the VR environment) moves forward instantly.

When the participant decides it is time to stop the movement – for example, when a car is approaching and must be avoided – they say "*stop*" and the movement (i.e. camera) inside the VR environment stops immediately. Participants were able to use verbal commands at any point during the task (i.e. not necessarily at the pavement).

Several studies have reported that the average speed of stroke patients ranges from 0.2 to 0.8 meter/second when patients were walking comfortably (Bohannon 1992; Jonkers, Delp, and Patten 2009; Jonsdottir et al. 2009; Turnbull, Charteris, and Wall 1995). Taking different walking abilities into account, it was agreed that the speed of movement (i.e. crossing the street) inside the virtual environment would be slow to ensure it matched the stroke patients' walking speed in real life and also to give the patients enough time to explore the environment and enhance their chances of avoiding vehicles. Therefore, the speed of movement inside the VR environment was pre-specified by the researcher at 0.3 meter/second. The VR system uses Microsoft Cortana Voice Assistant to decode and implement verbal commands inside the virtual environment (**Figure 7.1**).

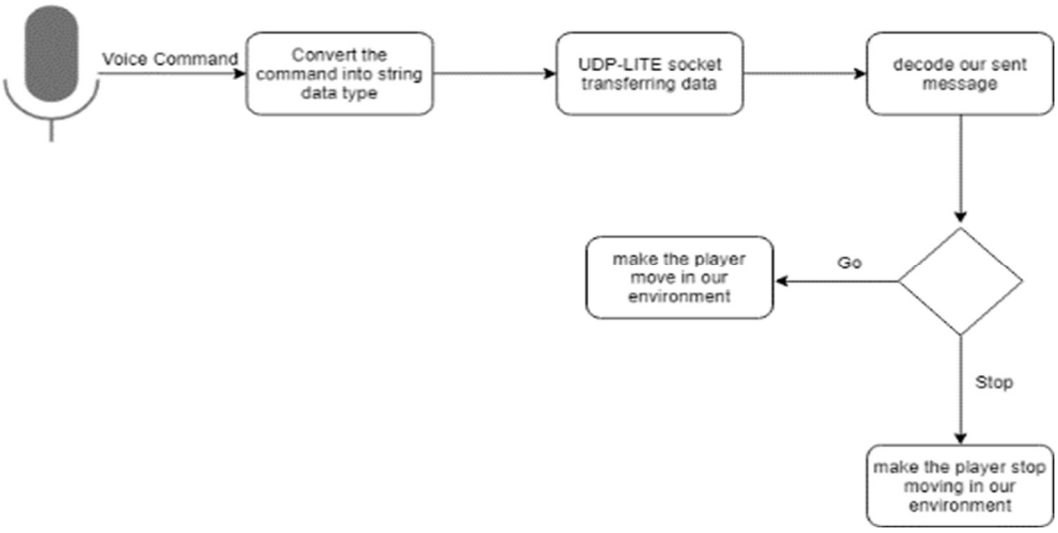


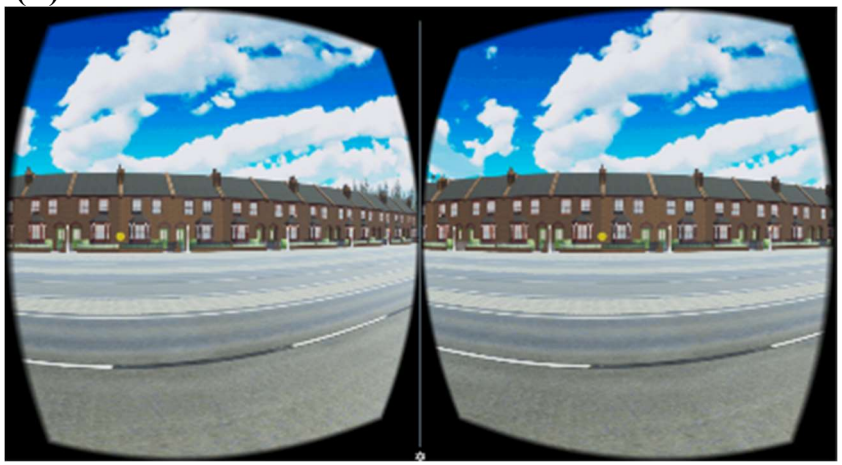
Figure 7. 4 Voice recognition process used in the street-crossing VR task.

Collision / accident Scenario

A soft collision scenario was adopted to ensure no trauma would occur as a result of failure to cross the street successfully. When participants failed to cross the street [i.e. a collision occurred], the collision was accompanied by a soft sound of screeching brakes as the vehicle approached the participant's position, followed by a horn sound. The screen then faded out to indicate failure and the task restarted at the beginning of the same crossing the participant failed to complete successfully. This allowed us to collect data on the number of times required for each participant to complete each crossing successfully, and whether they struggled with a certain crossing or type of vehicle.

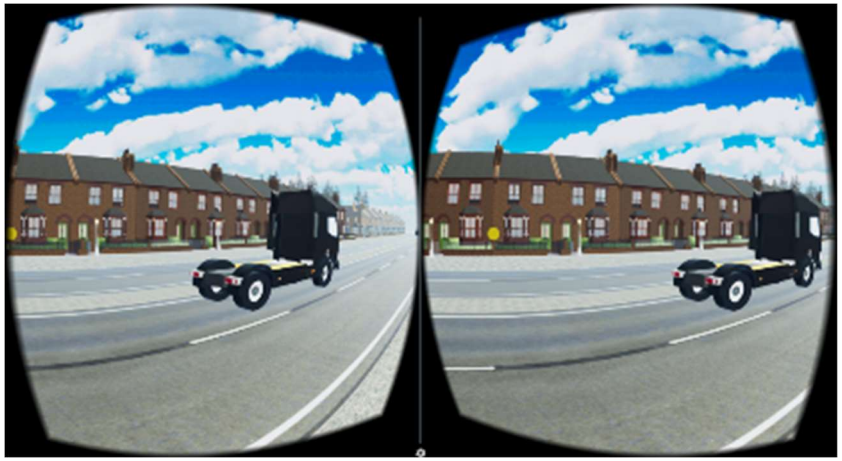
Visual cues – in the form of flashing yellow arrows (to indicate the start of the task and point the user to the correct direction of movement inside the VR environment) and a yellow ball (to indicate the end of the task), were used in this task (**Figure 7.2).**

(A)



(B)

(C)



(D)

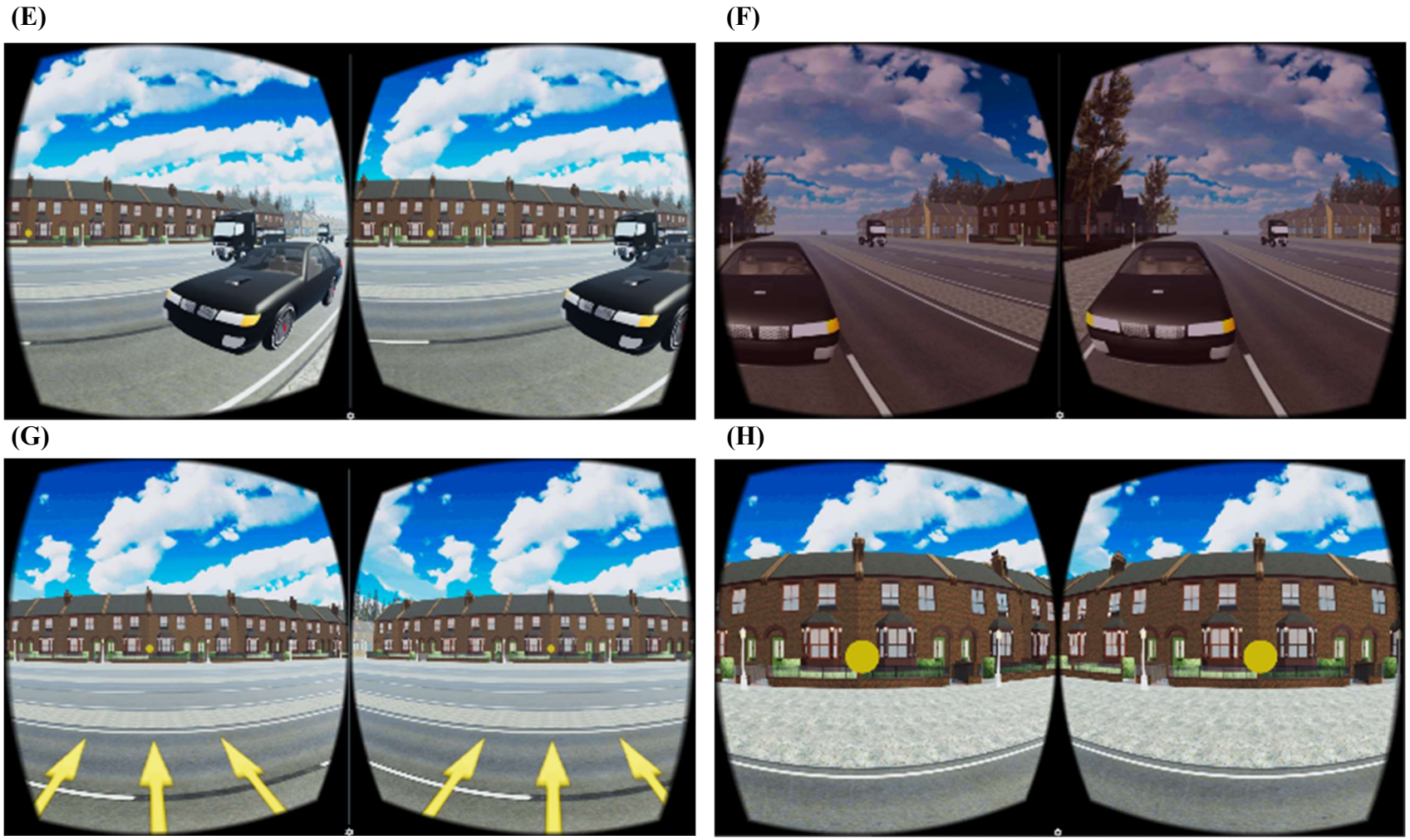


Figure 7. 5 USN-VR street-crossing virtual environment

(A) VR demo with no vehicles – patients were asked to explore and familiarise themselves with the VR environment and cross the street in the absence of vehicles. (B) Left trial - first crossing with cars approaching from the left. (C) Left trial - second crossing with trucks approaching from the left. (D) Left trial – third crossing with buses approaching from the left. (E) Right trial – street-crossing

with vehicles (in the aforementioned order) approaching from the right. (F) Accident / collision scenario – collision accompanied with a soft sound of screeching brakes and horn beeping before screen fades out to indicate failure (G) Visual cue in the form of flashing yellow arrows at the start of the task to indicate the direction of movement. (F) Visual cue in the form of a yellow ball at the end of the third crossing to indicate the end of the street-crossing task.

Figure 7. 6 Study participants completing the USN-VR street-crossing task

Procedure

The testing sessions took place in a quiet room in Ashford and St. Peters and Charing Cross Hospitals. The room was chosen carefully to ensure attentional distractors were kept to a minimum. Patients were first seated and given an introduction to the tasks with particular emphasis on VR technology and related equipment such as VR googles including safe usage, how to adjust the googles and what to do in case patients suffer motion sickness. The testing session consisted of a number of cognitive and USN assessments including the VR street-crossing task. The assessments were administered in the following order:

The Montreal Cognitive Assessment (MoCA): the MoCA is a brief cognitive test developed by Nasreddine and colleagues (2005) to screen for mild cognitive impairment. The MoCA comprises eight subtests that examine the following cognitive areas: visuospatial ability/executive function, naming, memory, attention, language, abstraction and orientation.

Administration time: 10 minutes

The line bisection test is a quick measure to assess the presence of USN. Using a pencil, patients are required to approximately denote the centre of three horizontal black lines, each 8-inch long and 1-mm thick, displayed on an A4 sheet in a staircase order. The mean deviation from the true midpoint of the horizontal lines is measured in mm. Patients with right-hemisphere lesions (i.e. left neglect) typically deviate to the right (ipsilesional side) (Parton et al. 2004a). The line bisection test was administered before and after the VR street-crossing task.

Administration time < 5 minutes

The Bells cancellation test is a cancellation test used to quantitatively and qualitatively assess USN. Using a pencil, patients are required to scan, locate and circle 35 bells presented among 280 distractors on an 8.5" x 11" sheet of paper placed at the individual's midline. An omission of 6 or

more bells indicates left-sided neglect (Gauthier et al., 1989). The bells test was administered before and after the VR street-crossing task.

Administration time < 5 minutes

VR Street-Crossing Task

Prior to the start of VR testing, the researcher offered each patient an introduction to VR technology and provided detailed instructions on how to complete the VR street-crossing task. Patients were asked to communicate with the researcher if they experienced discomfort, motion sickness or dizziness. Participants were given short (1-2 minutes) breaks between VR trials if they wished to and were asked whether they would like to withdraw or continue the task following the completion of each VR trial. The USN-VR task was performed in the following order:

1. **VR Demo** – Exploring the virtual environment with no vehicles. Participants were asked to wear the VR headset to explore the virtual environment and learn how to complete the street-crossing task. Participants were encouraged to ask questions and give feedback before the start of the next phase which involved crossing the street with vehicles. Data from the VR demo was excluded from the analysis.

   Administration time: 5 minutes

2. **VR task 1: Left trials, performed three times** -– Street-crossing with vehicles approaching from the left side. In this task, there were three crossings (each with two lanes and a pavement to separate the streets) with a different type of vehicle in each crossing [cars, trucks and buses, respectively].

Administration time: 10-15 minutes

3. **VR task 2: Right trial, performed once –** Street-crossing with vehicles approaching from the right side. In this task, there were three crossings (each with two lanes and a pavement

to separate the streets) with a different type of vehicle in each crossing [cars, trucks and buses, respectively]. This task was performed once to confirm the absence of USN in the right side of space as patients.

Administration time: 5 minutes

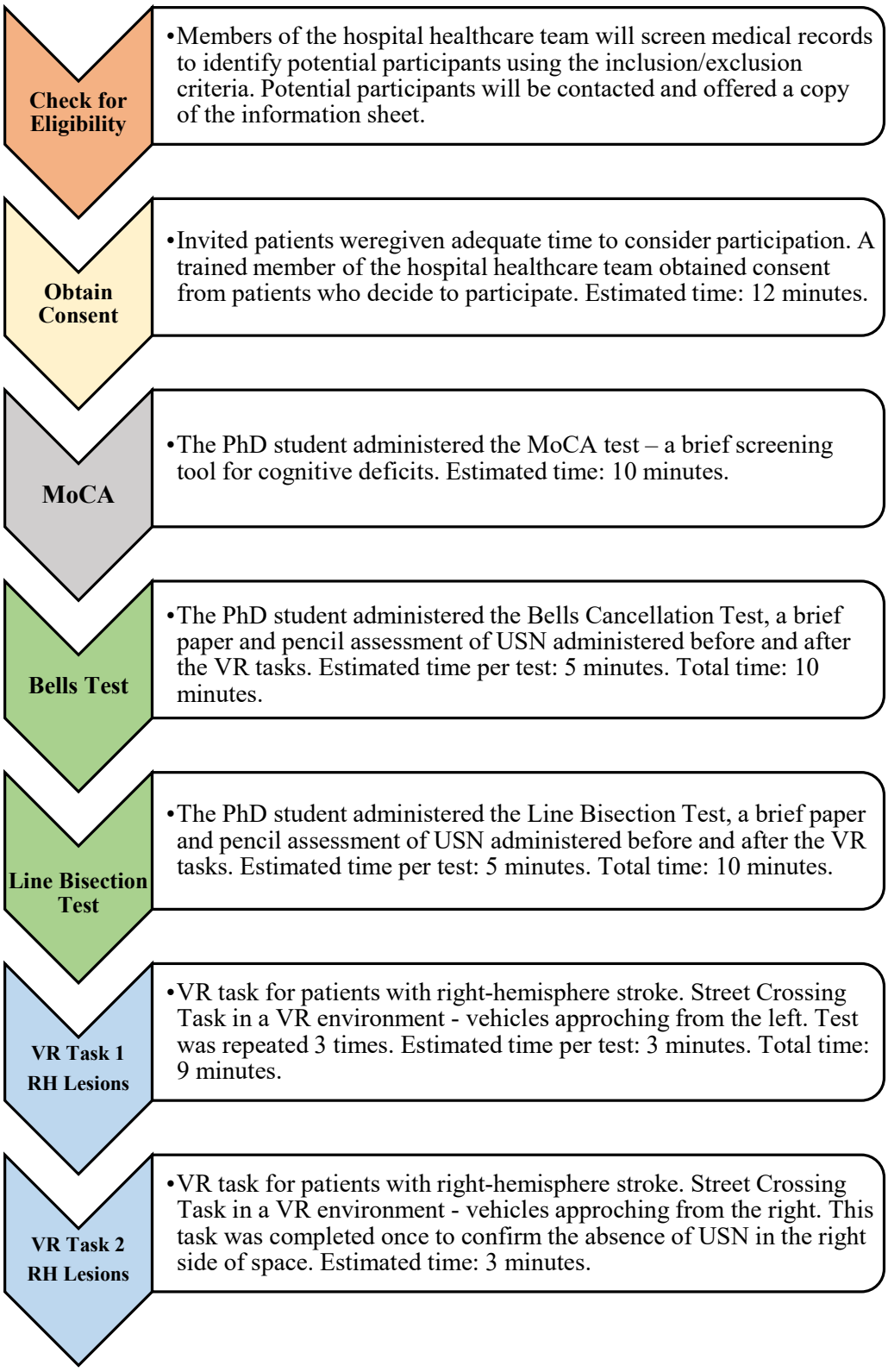


Figure 7.4: Test session procedure

Sample size calculation

Twelve patients with spatial neglect and 12 without will be recruited. The use of VR in this population is novel and there is limited data available on the likely distribution of primary outcome (number of accidents) of the study. The proposed sample size will be sufficient with 80% power at the 5% significance level to detect a large effect size in terms of the difference between the two groups assuming that the difference in means is at least 1.2 times the pooled standard deviation. In order to detect a difference between groups in the % with number of accidents with 80% power at the 5% significance level, the sample size is sufficient to detect differences of 60% or greater (assuming a rate of 20% in the no neglect arm).

Statistical analysis

Question 1: Compare the performance of the study groups (neglect, non-neglect, healthy controls) on paper and pencil tests before and after the VR task?

Statistical analysis was performed using R v 3.6.2. Mean ± standard deviation was used to summarise the distribution of continuous variables. Counts and percentages were used to summarise the distribution of categorical variables. Test parameters were compared across three groups using either Chi-square test of independence or one-way ANOVA. Post-hoc pairwise comparisons were performed using paired t-test. Hypothesis testing was performed at 5% level of significance.

Question 2: Do the VR task scores correlate with the scores of the paper and pencil tests for the two stroke groups?

Spearman's correlation was used to assess the association between the USN-VR task and the paper and pencil tests.

Question 3: Compare the performance of the three study groups on the VR task?

3.1 For three trials where vehicles approached from the left

Statistical analysis was performed using generalised least squares with autoregressive covariance structure to take into account multiple measurements per participant. Post-hoc contrast analysis was performed to compare each pair of groups.

a. For one trial where vehicles approached from the right

Statistical analysis was performed using one-way ANOVA. Post-hoc comparisons were performed using unpaired t-test.

Q4: Compare the effectiveness of the paper and pencil tests as well as the VR task in differentiating between the study groups?

Receiver operating curve (ROC) was used to assess the effectiveness of paper and pencil assessments as well as the VR task in differentiating healthy controls from stroke patients. They were also used to assess the performance of the VR task as well as the paper and pencil technique in differentiating stroke patients with and without neglect.

Results

A total of 63 stroke patients attending Ashford & St. Peter's and Charing Cross hospitals fulfilled the eligibility criteria and were considered as potential study participants. These patients were contacted and invited to participate in the study. Out of the 63 patients contacted, 24 patients agreed to take part in this study.

Twenty-four stroke patients (12 USN+ & 12 USN-) and eight healthy controls completed the paper and pencil assessments as well as the USN-VR street-crossing task. The performance of the three groups on paper and pencil tests, which were administered before and after the USN-VR task, were compared. Additionally, data collected form the USN-VR task including the mean head rotation, number of accidents per trial, number of successful crossings, number of right and left head turns as well as the time taken to complete the task were compared amongst the three groups.

Question 1: Compare the performance of the study groups (neglect, non-neglect, healthy controls) on paper and pencil tests before and after the VR task?

Results showed that the average MoCA was significantly higher in healthy controls (HC) compared to stroke patients without neglect (USN-) and stroke patients with neglect (USN+). The average value for bells test was significantly different between HC and USN+ ($P < 0.001$) as well as between USN- and USN+ ($P < 0.001$). The average value for Bells test was not significantly different between HC and USN- ($P = 0.094$). The post-test results for Bells test were similar to the pre-test results which indicates consistency in performance. The time required to complete the pre-test was lower in HC compared to the USN- and USN+ groups. The mean line bisection test showed similar findings as patients with neglect had significantly lower scores compared to HC ($P < 0.001$) and USN- ($P < 0.001$).

Table 7. 6 Performance on paper and pencil tests

	HC	USN+	USN-	F Statistic	P	HC vs. USN+	HC vs. USN-	USN+ vs. USN-
	N=8	*N=12*	*N=12*					
MoCA (/30)	27.8 (1.98)	24.4 (1.56)	23.8 (2.86)	**8.14**	**0.002**	**0.007**	**0.002**	0.799
Bells Test (Pre-VR)	34.8 (0.46)	27.6 (3.53)	32.3 (1.78)	**22.88**	**<0.001**	**<0.001**	0.094	**<0.001**
R Omissions (Pre-VR)	0.25 (0.46)	1.83 (1.70)	1.08 (1.31)	**3.38**	**0.048**	**0.038**	0.373	0.369
L Omissions (Pre-VR)	0.00 (0.00)	5.58 (2.71)	1.42 (1.16)	**26.88**	**<0.001**	**<0.001**	0.220	**<0.001**
Time (S) (Pre-VR)	124 (42.1)	191 (48.7)	181 (44.4)	**5.63**	**0.009**	**0.009**	**0.029**	0.849
Bells Test (Post-VR)	34.6 (0.74)	29.2 (2.98)	33.2 (1.11)	**21.11**	**<0.001**	**<0.001**	0.261	**<0.001**
R Omissions (Post-VR)	0.12 (0.35)	2.17 (2.04)	0.58 (0.67)	**6.88**	**0.004**	**0.006**	0.734	0.018
L Omissions (Post-VR)	0.25 (0.46)	3.75 (2.26)	1.25 (0.97)	**14.47**	**<0.001**	**<0.001**	0.339	0.001
Time (S) (Post-VR)	110 (42.4)	152 (39.1)	140 (63.7)	1.65	0.209	0.186	0.424	0.822
Mean Line Bisection mm (Pre-VR)	0.31 (1.33)	6.44 (3.32)	0.52 (2.19)	**21.04**	**<0.001**	**<0.001**	0.983	**<0.001**
Lines Missed (Pre-VR)				**17.79¶**	**<0.001**	**0.006**	1.000	**0.006**
0	8 (100%)	3 (25.0%)	11 (91.7%)					
1	0 (0.00%)	4 (33.3%)	1 (8.33%)					
2	0 (0.00%)	5 (41.7%)	0 (0.00%)					
Time (S) (Pre-VR)	62.8 (29.9)	74.2 (21.5)	68.7 (38.1)	0.34	0.714	0.694	0.907	0.897
Mean Line Bisection mm (post-VR)	0.57 (0.91)	5.18 (2.28)	0.78 (1.24)	**27.4**	**<0.001**	**<0.001**	0.959	**<0.001**
Lines Missed (Post-VR)				3.49¶	0.647	0.885	1.000	0.885
0	8 (100%)	9 (75.0%)	11 (91.7%)					
1	0 (0.00%)	2 (16.7%)	1 (8.33%)					
2	0 (0.00%)	1 (8.33%)	0 (0.00%)					
Time (S) (Post-VR)	50.5 (12.9)	57.4 (15.2)	59.8 (32.9)	0.39	0.678	0.792	0.661	0.967

HC: Healthy Controls; USN+: stroke patients with USN; USN-: stroke patients without USN; MoCA: Montreal Cognitive Assessment; VR: virtual reality.
F statistic is shown for all tests except for the lines missed where the X^2 statistic is shown (denoted by ¶)

Question 2: Do the VR task scores correlate with the scores of the paper and pencil tests for the two stroke groups?

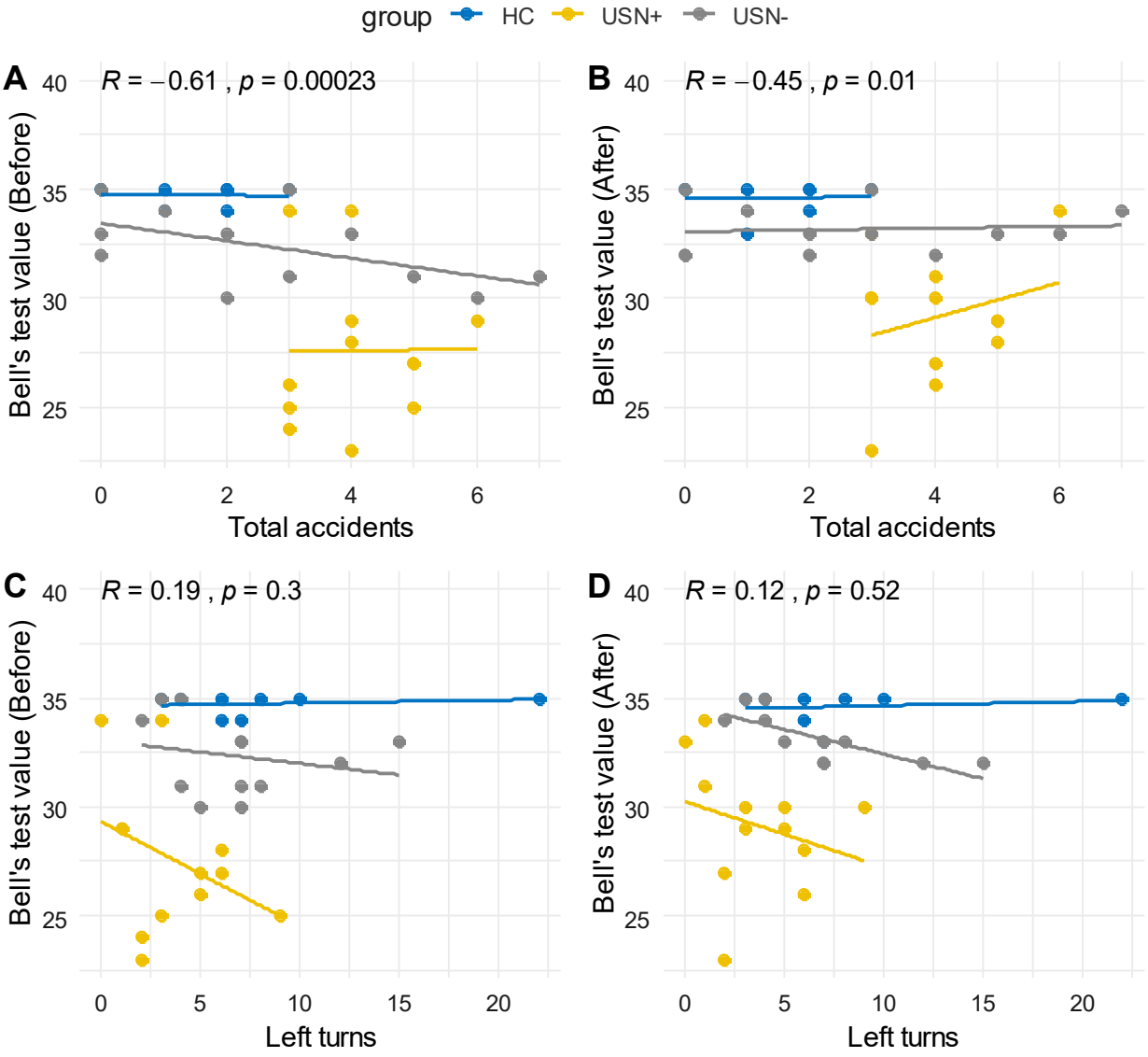


Figure 7. 5 Correlation between bells test results and the overall VR task results

Results showed that the total number of accidents, for all subjects including healthy controls, was significantly correlated with the pre-VR task value for bells test ($r = -0.61$, $P < 0.001$) as well as the post-VR task value for bells test ($r = -0.45$, $P = 0.01$) . The total number of left head turns

across trials was not significantly correlated with bells test values (P > 0.05 for pre-VR and post-VR tasks).

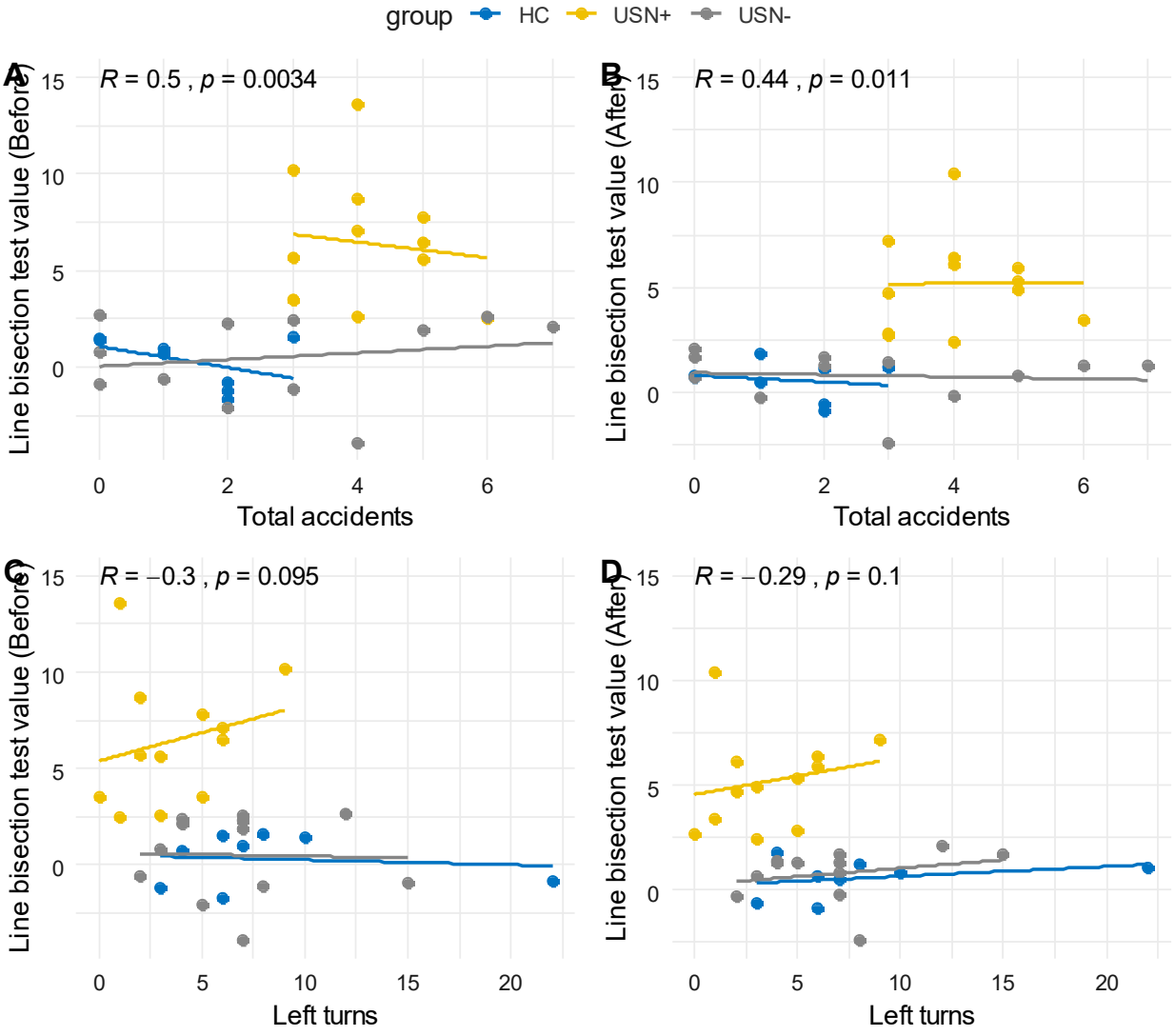


Figure 7. 6 Correlation between line bisection test results and the overall VR task results

Results showed that the total number of accidents was significantly correlated with the pre-VR task value for the line bisection task (r = 0.5, P < 0.05) as well as the post-VR task value for bells

task ($r = 0.44$, $P < 0.05$). The total number of left head turns across trials was not significantly correlated with the line bisection test values ($P > 0.05$ for pre-VR and post-VR tasks).

Question 3: Compare the performance of the three study groups on the VR task?

3.1 VR task performance for left trials

Participants performed three trials during which vehicles approached from the left side only. The left trials were performed first with breaks in between when required. Data from the three left trials comparing the three groups are presented in Table 5.3.

Statistical analysis was performed using generalised least squares with autoregressive covariance structure to take into account multiple measurements per participant. Post-hoc contrast analysis was performed to compare each pair of groups. The trials with vehicles approaching from the right side was excluded from this analysis.

Table 7. 7 VR task performance for left trials (three trials - vehicles approaching from the left)

`	HC *N=8*	USN+ *N=12*	USN- *N=12*	P	HC vs. USN+	HC vs. USN-	USN+ vs. USN-
Mean Value - Head Rotation	-28.04 (19.3)	-17.62 (22.6)	-21.51 (24.2)	0.602	0.574	0.801	0.906
Mean no of accidents/3 trials	0.46 (0.35)	1.36 (0.33)	0.92 (0.79)	**0.0004**	**0.0001**	0.132	**0.0088**
Mean no of success/3 trials	0.62 (0.28)	0.17 (0.17)	0.44 (0.38)	**0.0009**	**0.0003**	0.15	**0.0149**
Mean no of left turns/ 3 trials	8.25 (5.97)	3.58 (2.64)	6.75 (3.72)	**0.042**	**0.02**	0.6855	**0.0315**
Time/3 trials	62.4 (21.0)	85.4 (29.9)	83.7 (56.2)	0.420	0.166	0.21	0.89

HC: Healthy Controls; USN+: stroke patients with USN; USN-: stroke patients without USN. Statistical analysis was performed using generalised least squares

Results showed a statistically significant difference in the average number of accidents per trial, successful crossings and average number of left turns between the neglect and non-neglect groups as well as between the neglect and healthy control groups. The average MVHR was not significantly different between healthy control and non-neglect groups. The average time / trial was not significantly different between the three groups.

3.2 VR task performance for control (right) trial

Participants performed the control trial (vehicles approaching from the right) once only after they completed the left trials task. Data from the control trial comparing the performance of the three groups on the USN-VR task are presented in Table 7.4.

Table 7. 8 VR task performance for control trial (one trial - vehicles approaching from the right)

`	HC *N=8*	USN+ *N=12*	USN- *N=12*	P	HC vs. USN+	HC vs. USN-	USN+ vs. USN-
Mean Values Head Rotation (MVHR)	30.2 (25.5)	32.2 (8.20)	27.2 (29.0)	0.860	0.980	0.953	0.848
Number of Accidents / Trial	0.38 (0.74)	0.58 (0.79)	0.50 (0.52)	0.805	0.787	0.917	0.953
Number of Successful Crossing / Trial	0.75 (0.46)	0.50 (0.52)	0.50 (0.52)	0.493	0.536	0.536	1.000
Numbers of Left Turns	3.62 (3.20)	1.00 (1.04)	0.92 (1.00)	**0.005**	0.009	0.007	0.993
Number of Right Turns	4.00 (3.25)	3.08 (1.73)	2.58 (2.15)	0.422	0.669	0.390	0.860
Time / Trial (S)	61.8 (30.1)	54.1 (17.6)	92.4 (61.1)	0.081	0.915	0.260	0.081

HC: Healthy Controls; USN+: stroke patients with USN; USN-: stroke patients without USN. Statistical analysis was performed using one-way ANOVA. Post-hoc comparisons were performed using unpaired t-test

Results showed that there was no significant difference between the three groups in terms of mean head rotation, number of accidents, successful crossings, number of right head turns, and the time taken to complete the trial. However, the number of left head turns was significantly different between the healthy controls and neglect patients as well as the healthy control and non-neglect groups

Performance by trial

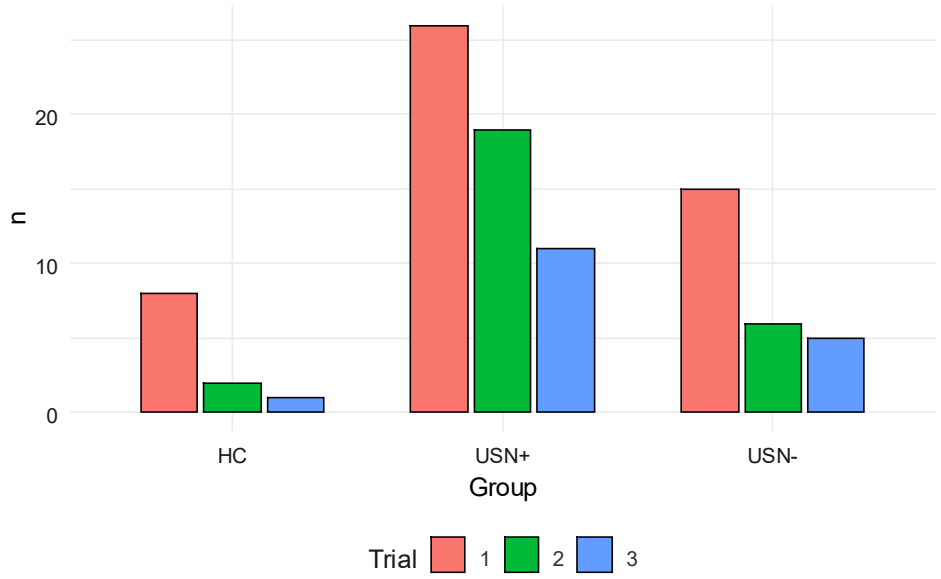


Figure 7. 7 Distribution of number of accidents across groups stratified by trial

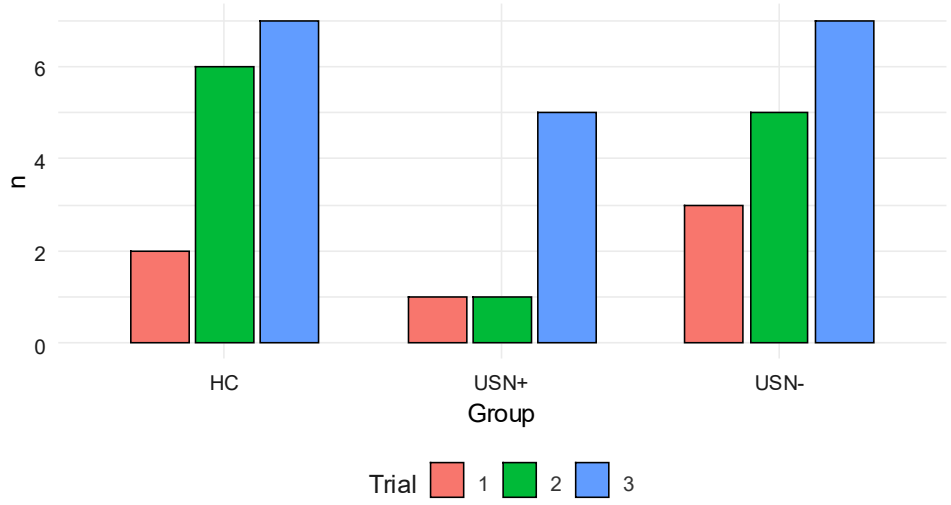


Figure 7. 8 Number of successful crossings across groups stratified by trial

Predictive power of the VR task

A predictive model was developed based on the total number of left turns and accidents across the three trials. Binary logistic regression was used to develop the model. A nomogram was constructed to predict the probability of neglect based on the model results. The probability of neglect was defined according to the inclusion criteria of the line bisection (a deviation of 6mm to the right from the midpoint) and bells test (an omission of 6 or more bells on the left side of the test) Receiver operating curve (ROC), and its components like AUC, sensitivity, and specificity, was used to assess model performance with higher AUC indicating higher ability of the model to distinguish cases from controls. Model validation was performed using bootstrapping (1000 bootstrapped samples). The accuracy of the validated model was assessed using R^2 and Somer's index (Harrell and Lee 1985; Miller, Hui, and Tierney 1991). Somers' D is a measure of association between the predicted and observed values. Somers' D takes values between -1 (when all pairs of the variables disagree) and 1 (when all pairs of the variables agree). The model correctly identified all USN+ patients.

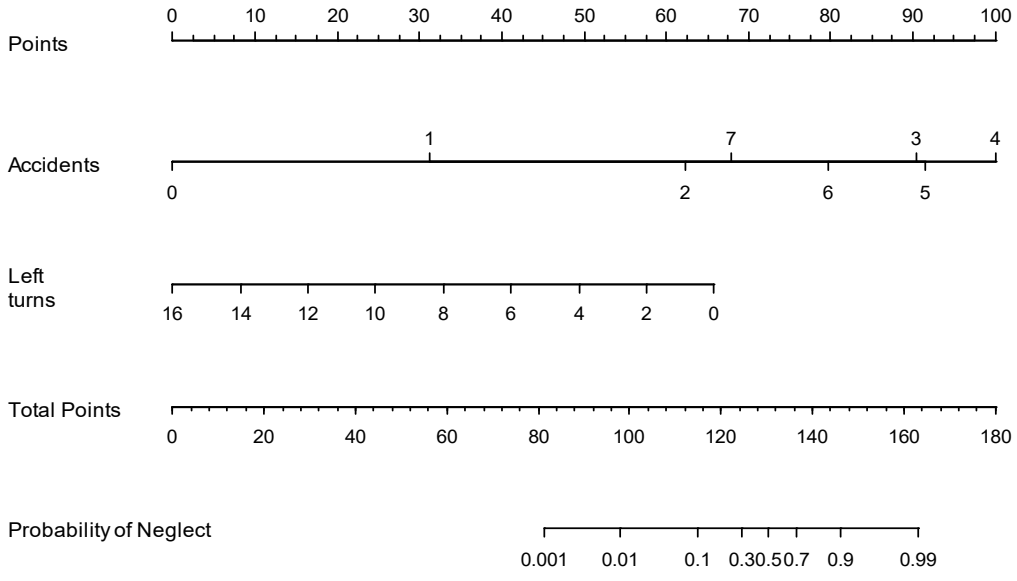


Figure 7. 9 Nomogram to predict the probability of USN from the VR task

According to the predictive model, two USN- patients appeared to have USN deficits on the VR task that went undetected on the bells and line bisections tests (see examples for calculations of the probability of USN using the nomogram below).

	index.orig	training	test	optimism	index.corrected	n
Dxy	0.8611	0.8758	0.7991	0.0767	0.7844	1015
R2	0.6956	0.7425	0.6205	0.1220	0.5736	1015
Intercept	0.0000	0.0000	0.0136	-0.0136	0.0136	1015
Slope	1.0000	1.0000	0.6334	0.3666	0.6334	1015
Emax	0.0000	0.0000	0.1032	0.1032	0.1032	1015
D	0.6958	0.7792	0.5921	0.1871	0.5088	1015
U	-0.0833	-0.0833	0.8198	-0.9031	0.8198	1015
Q	0.7792	0.8625	-0.2277	1.0902	-0.3110	1015
B	0.1073	0.0850	0.1386	-0.0536	0.1609	1015
g	5.9146	14.1701	4.9548	9.2153	-3.3008	1015
gp	0.4497	0.4373	0.4173	0.0200	0.4297	1015

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Figure 7. 10 Model validation results

Results showed that the model had a corrected R^2 of 57.4% and a corrected Somers' D of 0.78. which indicates good concordance between the predicted and observed values.

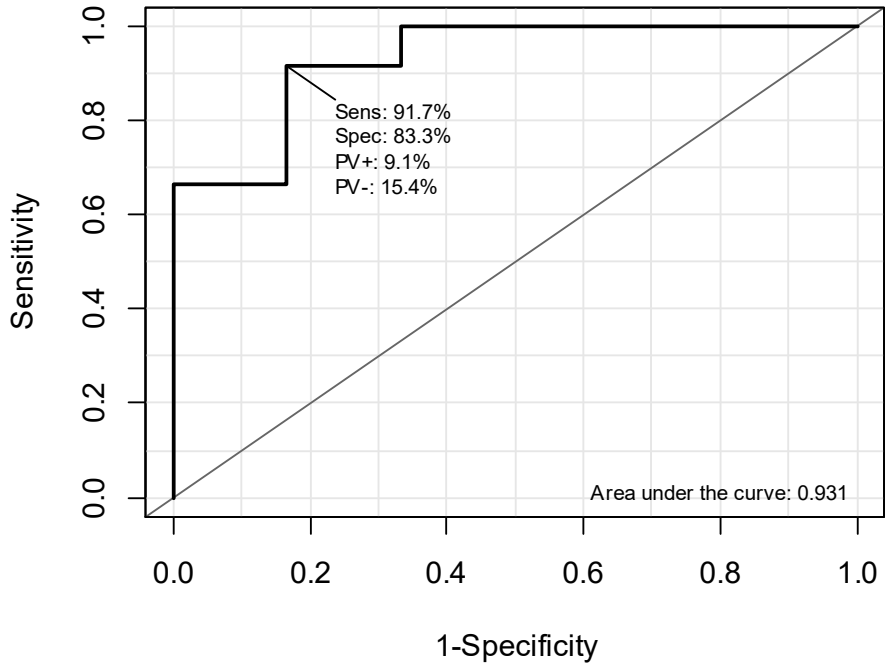

Figure 7. 11 Model performance

The resulting model had an AUC of 0.93 (95% CI 0.83, 1 using 1000 bootstrapped samples).

Examples of neglect and non-neglect patients

Performing calculations using the nomogram

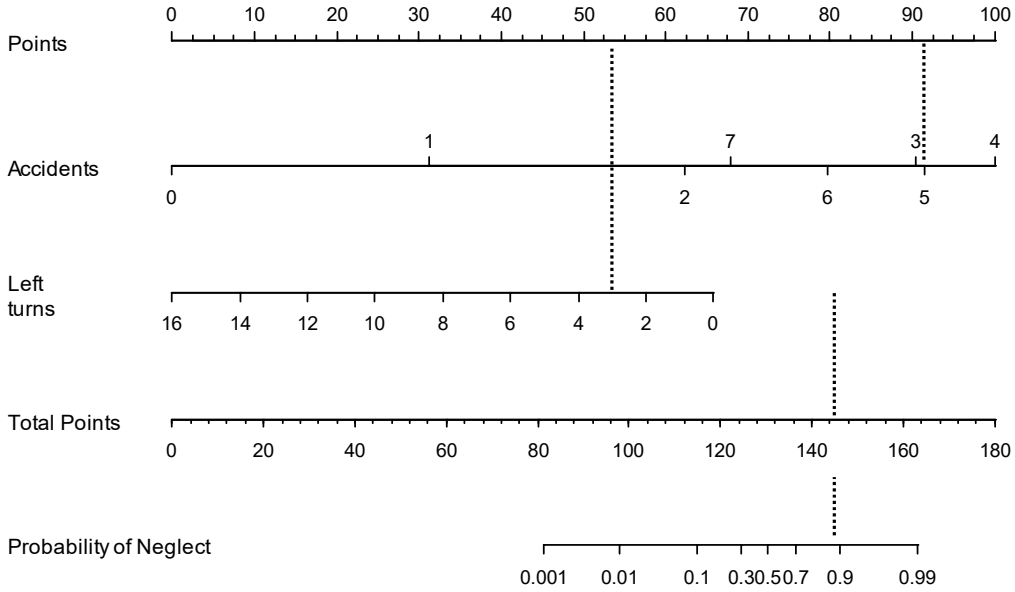

Figure 7.12 Example nomogram calculations for a neglect patient

Table 7. 5 Example for a neglect patient

	USN+7	Points	Probability
Total accidents	5	93 points	
Left turns	3	53 points	
Total Points		146	~ 0.9 or 90%

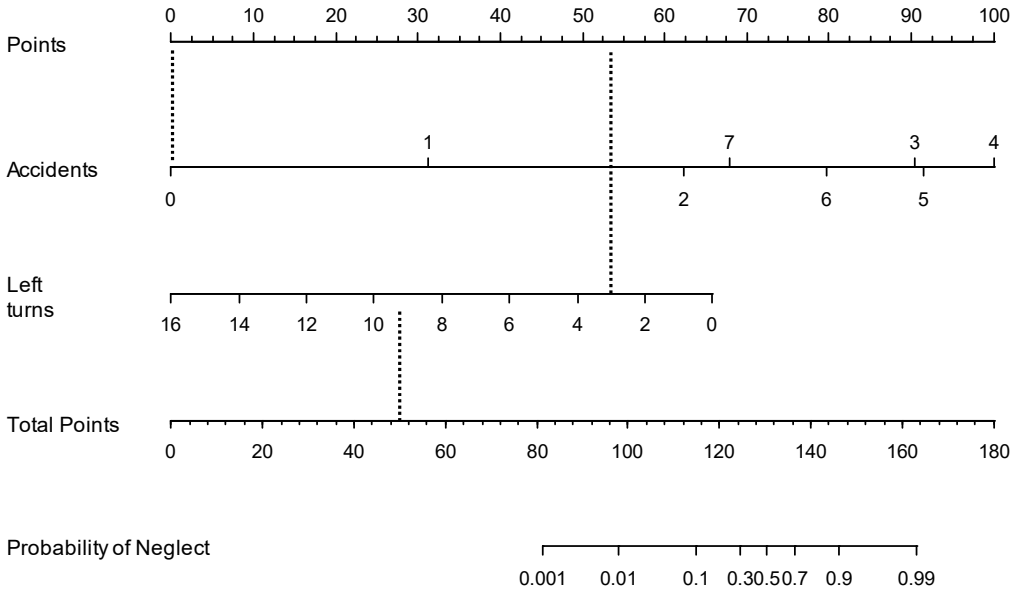

Figure 7.13 Example nomogram calculations for a non-neglect patient

Table 7. 6 Example for non-neglect patient

	USN-4	Points	Probability
Total accidents	0	0 points	
Left turns	3	53 points	
Total Points		53	< 0.001 or < 1%

Discussion

This pilot study presents the findings of a new, fully immersive virtual reality (VR) smartphone application – a low-cost, easily accessible VR street-crossing task using voice commands, for the assessment of post-stroke unilateral spatial neglect (USN). The study compared the performance of stroke patients (with and without hemispatial neglect) and healthy controls on conventional paper and pencil assessments (line bisection and bells tests) as well as a simple VR street-crossing task.

Generally, the results of this pilot study demonstrate that stroke patients with neglect (USN+) performed significantly worse than stroke patients without neglect and healthy controls on conventional paper and pencil tests as well as the VR street-crossing task. On the line bisection and bells tests, the pre- and post-VR task performance was significantly different amongst healthy controls and neglect patients as well as non-neglect stroke patients and neglect patients. This finding is consistent with previous studies which reported similar results (Kim et al. 2010; Navarro et al. 2013; Peskine et al. 2011). Additionally, the pre- and post-VR task performance was consistent among the three groups, with neglect patients showing slight but not significant improvement on the line bisection and bells tests post-VR task. This could be due to the learning effect reported in several studies which have shown that performance on visual scanning tasks such as the bells test is likely to improve with repetition despite the absence of associated improvement on activities of daily living (ADLs) (Bowen and N. B. Lincoln 2007; Buxbaum et al. 2012; Navarro et al. 2013).

With regards to performance on the VR task, there was no significant difference in the mean head rotation, number of accidents, successful crossings and time taken to complete tasks between the three groups in the control trial [performed once with vehicles approaching from the right (non-neglected) side]. However, the number of left head turns was significantly

different between healthy controls and neglect patients as well as healthy controls and non-neglect stroke.

The overall VR performance on the left trials [three trials performed with vehicles approaching from the left (neglected) side], was significantly different between the three groups. In terms of the number of accidents/trial, successful crossing/trial and left head turns, neglect patients performed significantly worse than healthy controls and non-neglect stroke patients. No difference was observed in the time taken to complete trials between the three groups **(Table 7.3).** One unexpected finding in all trials (left and right) was the lack of significant difference in the mean head rotation between neglect patients and healthy controls as well as non-neglect stroke patients. In the control trial, neglect patients showed a deviation of 2º and 5º to the right compared to healthy controls and non-neglect patients, respectively **(Table 7.3).**

In the left trials, neglect patients showed a mean head rotation to the left of -17.62º compared to -21.52º (non-neglect stroke patients) and -28.04º (healthy controls). Whilst discrepancies in the ability to rotate to the left were observed amongst the groups, statistical analysis yielded no significant difference in head rotation. This contradicts findings of previous studies which reported that the head rotation could be used to distinguish neglect from non-neglect patients. A number of factors may have contributed to this finding. Chief among them is the small sample size in our pilot study and the method used to calculate head rotation values.

The present pilot study used Euler Angles, a model in which 3-dimensional rotation in space can be represented by performing separate rotations around individual X, Y and Z axes. The Euler Angles model is integrated within Unity, the gaming engine used to develop our VR tasks and was thus integrated within the VR street-crossing application to calculate head rotation (Hasan et al. 2018; Shah, Saha, and Dutt 2012). This model is very different to methods used in previous studies (Buxbaum et al. 2008; Kim et al. 2010; Navarro et al. 2013; Peskine et al. 2011) which employed external sensors (e.g. infrared camera) to estimate values of head

rotation. Using Euler Angles to estimate head rotation was intended to reduce the complexity and cost of our VR system and potentially increase the accessibility and future use of the VR system as, unlike other systems, our VR tool does not require sophisticated/costly gadgets to operate which potentially makes it more inclusive and researcher/user-friendly. Although the difference in head rotation was not significant, discrepancies were indeed observed among the stroke and healthy control groups. This suggests that more studies with a larger sample size are required to verify findings of this pilot study.

Regarding the number of accidents per VR trial, it was initially hypothesised that the number of accidents / trial (primary outcome) on the VR task would be significantly worse for neglect patients compared to healthy controls and non-neglect stroke patients. As expected, neglect patients performed significantly worse on the VR task compared to the other groups. The number of accidents among healthy participants dropped gradually between the first and third trials, whereas non-neglect patients showed a relatively high number of accidents in the first trial followed by significant drop in the second and third trials (**Figure 7.7**). Indeed, the pattern for both healthy and non-neglect subjects was fairly predictable as by learning to navigate the virtual environment and avoid vehicles, the number of accidents would be expected to decrease (the number of successful crossings would therefore increase) by the third trial. This could be due to learning effects or potentially because other cognitive functions are being recruited over time. While neglect patients showed a similar pattern – that is a decreasing number of accidents from the first to the third trial, the number of accidents reminded significantly higher than the non-neglect subjects and healthy controls. Neglect patients had more than double the number of accidents compared to non-neglect patients across all three trials. This suggests attentional impairment combined with the inability to sustain vigilance for a prolonged period. This finding broadly supports the work of other studies in this area linking neglect with impaired vigilance and a reduced ability to maintain performance for an extended period following right

hemisphere injury (Broeren et al. 2007; Fordell et al. 2011b; Riestra and Barrett 2013; Tsirlin et al. 2009).

In terms of head turns, all three groups performed similarly for right head turns. However, in VR trials where vehicles were approaching from the left side, neglect patients showed a significantly lower number of left head turns compared to healthy controls and non-neglect stroke patients **(Table 7.3).** Indeed, this finding suggests that stroke patients with neglect were unable to perform appropriate scanning on the left side. This can be explained by the lack of awareness and inability to orient to stimuli on the neglected side, which – consistent with the literature, is a typical observation among neglect patients and has been reported in several studies (Azouvi 2017; Buxbaum et al. 2008; Peskine et al. 2011; Zebhauser et al. 2019). Therefore, the number of accidents, successful crossings as well as left head turns successfully distinguished between neglect and non-neglect subjects as the results showed an expected pattern and supported the initial hypothesis.

As for the correlations between the outcomes of the VR street-crossing task and conventional assessments (line bisection and bells tests), there was a significant correlation between the total number of accidents on the VR task and the pre- and post-VR values for the line bisection. However, the total number of left head turns was not significantly correlated with the pre- and post-VR line bisection test **(Figure 7.6).** Similarly, the total number of accidents was significantly correlated with the bells test, whereas the number of left head turns was not (**Figure 7.5**). This could be due to impaired scanning strategies not possible to gauge on conventional assessments. Furthermore, two neglect patients whose performance on the bells test was relatively good (yet performed dissatisfactory on the line bisection test) showed a low number of left turns and higher numbers of accidents. It was not possible to carry out a comprehensive assessment of these two patients. Therefore, it is difficult to make any cohesive conclusions about the presence of mild USN deficits. This is because it was not possible to

organise follow-up/comprehensive assessments in pilot study. Future studies should consider inviting patients who perform well on paper tests, but not on VR, for follow-up/comprehensive assessments.

Taking all three trials (vehicle approaching from the left) into account, a predictive model for the VR task was developed by means of binary logistic regression using the total number of accidents and left head turns. To predict the probability of neglect, a nomogram (**Figure 7. 9**) was constructed along with a ROC curve to assess model performance with higher AUC indicating higher ability of the model to distinguish neglect from non-neglect cases. Bootstrapping (1000 bootstrapped samples) was used to validate the predictive model. Bootstrapping is a resampling technique used in statistics which relies on random and independent sampling with replacement using a small, existing sample of data. Bootstrapping uses the same sample size (n) and performs statistical inference among the resampled set of data, where a large sample of small, existing samples of the same size is repeatedly drawn, with replacement (meaning that each bootstrap sample drawn from existing sample data is highly unlikely to be identical to the original sample). To assess the accuracy of the validated model, R^2 and Somer's index were used. The validated model had a corrected R^2 of 57.4% and a corrected Somers' D of 0.78 which indicates good concordance between the predicted and observed values. Moreover, the validated model had a sensitivity and specificity of 91.7% and 83.3%, respectively. The AUC was of 0.93 (95% CI 0.83, 1 using 1000 bootstrapped samples). Using the predictive model, two stroke control patients (USN-3 and USN-9 – 17% of the sample n=12) who showed no signs of neglect on paper and pencil assessments appeared to have neglect-related deficits on the VR street-crossing task which suggests that a future study with a larger sample is required to confirm this finding and validate whether the results of the current pilot study can be generalised to other populations.

Technology

On the topic of technology, the task used in this study is the first VR-street-crossing system of its kind to employ verbal commands in a fully immersive environment for the assessment of USN. Previous USN assessment studies employed non-immersive technology combined with a joystick to control movement (Navarro et al. 2013) or immersive (involved wearing an HMDI) with a mouse to navigate the task (Peskine et al. 2011), whereas rehabilitation studies used non-immersive tasks on a desktop or projection screen with a keyboard or external sensors to detect movements (Katz et al. 2005; van Kessel et al. 2013; Kim et al. 2011). None of the previous studies reported on the cost or applicability of the VR systems in clinical as well as non-clinical settings. The VR system used in this study can be accessed on a smartphone application, and, providing that the user owns a smartphone, the system only requires an HMDI to operate – the latter can be purchased online for as little as £10 (Headset 2018). Our fully immersive VR system uses verbal commands rather than external sensors to complete the task and navigate the virtual environment. This design was adopted to ensure that the system would be widely accessible and cost-effective for potential future users. It also means that the system can be safely used in non-clinical settings such as homes and community settings as it does not require sophisticated equipment or advanced training. However, as with any of the aforementioned VR systems, our VR system has a number of advantages and disadvantages. Indeed, the use of verbal commands as a motion controller helped reduce the cost of development and it was hypothesised that it would enhance the accessibility of the system since it does not employ external sensors.

Additionally, employing verbal commands as a motion controller meant that any patient with a reasonably good cognitive ability and no aphasia could perform this task regardless of physical disability - for example, patients who are bedridden or in a wheelchair could use the system without having to move, thus, it was hypothesised that this type of VR system could be

more inclusive and user-friendly as it can be administered with the help of healthcare professional, a family member or even self-administered following a period of training. Nonetheless, the use of verbal commands has some disadvantages including the inability to control the speed of motion (for example, when using the word "*go*").

The speed used when uttering verbal commands was pre-specified prior to the start of testing. Therefore, patients could not increase or decrease the speed of motion, which otherwise can be controlled using a joystick or a keyboard.

Limitations

This pilot study had several shortcomings – chief among them being the small sample size included in the analysis which may have weakened the statistical power. This limitation is best reflected in the ROC curve analysis. Although the predictive model performance yielded a high sensitivity and specificity (91.7% and 83.3%, respectively), the positive predictive value (PPV+) and negative predictive value (PPV-) were quite low indicating a USN prevalence of around 50% in the sample tested. However, one cannot expect such prevalence in real-life. Future studies should include larger sample sizes to overcome this limitation.

There were additional limitations. While a wide variability of study subjects' characteristics is often preferred to test the acceptance and usability of a new tool such as VR, this variability makes it difficult to interpret the VR performance data with a good degree of accuracy and confidence. Further, the line bisection and bells tests were performed before and after the VR task. These tests were not randomised. Three VR trials where vehicles approached from the left were completed by each study subject. The number of accidents (**Figure 7.7**) dropped from the first to the third trial. Similarly, the number of successful crossings (**Figure 7.8**) increased with each trial. Once again, the confounding factors must be considered, as training and/or session effects cannot be excluded. The methodological flaws in this study may have contributed to some of the findings. Therefore, it is important for future studies to consider a

randomised study design and recruit a larger sample size to account and control these cofounders.

With regards to the mean age of participants, there were not many elderly patients recruited. While every attempt was made to invite and recruit a representative sample of stroke patients, including elderly patients, those who agreed to participate were relatively young. Elderly patients were contacted and invited. However, many cited their unfamiliarity with VR technology and declined to participate. Therefore, patient selection bias cannot be excluded.

As for other confounding factors, the MOCA scores were significant across the three study groups. We did not account for confounding factors (e.g., age, language etc). This may have biased the results and must be considered as a limitation.

Conclusion

The findings of this pilot study showed that there was a good correlation between paper and pencil tests and a simple VR street crossing task. However, it was not possible to carry out a diagnostic test accuracy analysis to compare the two methods as there is no gold standard assessment battery for USN. This study had several limitations, chief among them is the small sample size and the study design. We only used two paper and pencil tests. Future studies should employ several methods (e.g., CBS and eye tracking) to assess for USN. A future study with a better study design (e.g., randomised test design) and a larger sample size is needed to confirm findings of this pilot study. Finally, no study has yet attempted to use a hybrid model of assessment that combines conventional tests, ecologically valid assessments, and technology-based tools for USN. Experimenting with this hybrid model may contribute to addressing the wide of variability of USN symptoms and the lack of gold standard assessments.

Chapter 8

Stroke Patients' Experience of a Virtual Reality Application for the Assessment of Unilateral Spatial Neglect: A Thematic Analysis of Semi-Structured Interviews

Abstract

Purpose

The purpose of this thematic analysis was to evaluate USN patients' experience of a VR street crossing task and its usability.

Methods

Semi-structured interviews were conducted with 24 stroke patients (15 men and 9 women) who completed the USN-VR assessment involving a street crossing task in a virtual environment. Patients' responses were recorded and transcribed digitally. A thematic analysis was carried out using Braun and Clarke's six-stage approach.

Findings

The thematic analysis revealed three main themes: 1) unfamiliarity with VR technology; 2) the need for more engaging scenarios; and 3) the importance of patient involvement before and during prototype design. Findings showed that majority of sample recruited was unfamiliar with VR technology. Findings further highlighted the need for scenarios that integrate storytelling elements and techniques, and the importance of engaging stroke patients in the early stages of development and during VR scenario and task design.

Conclusions

Overall, the acceptance of the VR street crossing task was good. Patients found it relatively enjoyable and engaging. This study highlighted the need for the production and dissemination of patient-oriented educational material on VR technology to help in guiding and informing patients. Additionally, the integration of storytelling elements and techniques in VR tasks to enrich user experience might increase patient engagement and enjoyment. Finally, findings of this study emphasised the importance of patient involvement before and during VR scenario and task designs to ensure the development of patient-focused VR tools. Future studies should focus on exploring ways in which patients' ideas and feedback are pursued from the early stages of development. This can be acquired through online surveys and interviews or recruiting a control group of stroke patients for scenario and task development.

Introduction

Stroke is the fourth largest cause of death in the UK, and the third leading cause of disability globally (Feigin et al. 2014; Stroke Association 2018; Wang 2020). In 2018, the Stroke Association reported that over 1.2 million stroke survivors reside in the UK – the cost of care for whom is a staggering £26 billion per year. There are approximately 100,000 stroke events in the UK every year. Around two-thirds of survivors have a stroke-related disability upon discharge from hospital. The statistics are on the rise, and the stroke population in the UK is expected to approach the 2 million mark by 2035 (Stroke Association 2018).

Post-stroke impairments and deficits – whether cognitive, sensory, motor or psychological – are multifarious and pose several challenges to survivors, especially upon returning to the home/community environment (Buscherhof 2015; Sun, Tan, and Yu 2014). In many cases these deficits are likely to have negative long-term impact on daily life and functioning, thus leading to reduced quality of life among survivors (Clarke and Black 2016; Dai et al. 2014).

The hemispheric specialisation, also known as lateralisation of brain function, means that lesions in either of the cerebral hemispheres lead to characteristic impairments depending on the side, size and specific location of these lesions within the brain (Allegri 2000; Corbetta and Shulman 2011). For example, language and speech impairments are more frequent following left hemisphere lesions, perhaps because one of dominant functions of the left hemisphere is language processing (Suchan and Karnath 2011). On the other hand, visuospatial deficits such as unilateral spatial neglect (USN) are more common following right hemisphere strokes (Heilman and Van Den Abell 1980; Karnath and Rorden 2012).

USN is a common post-stroke visuospatial impairment, characterised by reduced responsiveness to sensory stimuli presented on the contralesional side of brain damage (Swan 2001). This disorder is often described as heterogenous due to the wide variability of symptoms seen among USN patients. Patients can experience motor deficits (e.g., difficulty or failure to

use the limbs contralateral to brain damage) or sensory impairments (e.g., miss stimuli or bump into objects in the neglected side) (Buxbaum et al. 2004; Laplane and Degost 1983; Zebhauser et al. 2019).

Traditionally, conventional assessments such as pencil and paper tests are used to screen for USN (Eschenbeck et al. 2010). However, studies report that conventional assessments have several limitations including low sensitivity to mild USN deficits and limited ecological validity (Grech et al. 2017; Pitteri et al. 2018; Rengachary et al. 2009). To address these limitations, more ecologically valid assessments such as the wheelchair test and Catherine Bergago Scale (CBS) were developed and used to assess USN symptoms and measure post-rehabilitation impartments (Azouvi 2017; Azouvi, Olivier, De Montety, et al. 2003). However, there are concerns around the inability to standardise the assessment/physical environment in different settings and discrepancies observed in test scoring/data collection for these ecologically valid tests (Azouvi 2017; Chen et al. 2012).

With significant advances in technology, novel methods such as virtual reality (VR) have been introduced to medical fields such as surgical training (Gallagher et al. 2005), psychological therapy (e.g., phobia treatment) (Botella et al. 2017), and post-stroke cognitive assessment and rehabilitation (e.g., USN rehabilitation) (Aravind and Lamontagne 2018; Perez-Marcos et al. 2018). It is theorised that VR can allow researchers to create enjoyable and engaging assessments and interventions that mimic real life scenarios and provide patient-oriented insights in a standardised and ecologically valid manner.

As part of this project, a VR prototype employing voice commands and immersive technology was developed. The VR prototype was designed for the assessment of USN and entailed a street crossing task in a virtual environment. The purpose of this thematic analysis was to evaluate USN patients' experience of the VR street crossing task and its usability.

Methods

Participants

This qualitative assessment was part of a project to develop and assess the accuracy and usability of a VR street crossing task for the assessment of stroke patients with USN. The quantitative analyses are presented and discussed in the pilot study (Chapter 7). This thematic analysis focuses on the user experience of the 24 stroke patients that participated in the pilot study. The demographic data for the study subjects of this qualitative study are presented in **Table 8.1**.

Table 8.1 Characteristics of patients included in the qualitative study

	Qualitative Study Subjects	
	Neglect (USN+) ***N=12***	**Non-Neglect (USN-)** ***N=12***
Gender (*n*, %)		
Male	7 (58%)	8 (67%)
Female	5 (42%)	4 (33%)
Age (years)	63.1 ± 10.0	60.7 ± 10.6
Education (years)	11.8 ± 2.7	11.5 ± 3.2
Chronicity (Days)	373.9 ± 366.3	207.4 ± 294.5

Data collection

This qualitative assessment is based on semi-structured interviews conducted with 24 stroke patients who completed the USN-VR assessment discussed in Chapter 7. The interview format was opened ended, allowing patients to give their honest feedback and share thoughts and suggestions. Patients were encouraged to identity and criticise flaws and limitations of the current task design to help inform any potential future modifications of the USN-VR prototype. The interviews were conducted following the completion of all USN assessments, including the USN-VR task. Each interview lasted from 15 to 35 minutes, depending on each patient's willingness to engage and answer questions as well as their levels of fatigue. As for interview

questions, participants were asked to comment on five thematic areas and were prompted with questions. The five themes and examples of questions were:

I. **Clarity of instructions**: Did you understand the instructions? / Were the instructions explained clearly?

II. **Degree of technology experience**: Did you have any experience with VR before? / Did you hear about VR before?

III. **Level of immersion and presence**: To what extent did you feel present inside the virtual environment? / To what extent did you feel immersed or engrossed while completing the VR task? / To what extent did you feel that you were in a computer-generated environment?

IV. **Experience of discomfort, dizziness, or motion sickness**: Did you feel general discomfort during the VR task? Did you feel nauseated or experience any motion sickness during the VR task?

V. **Enjoyment and engagement**: Did you enjoy the VR experience? / Did you find the VR task engaging? / Did you find the VR task user-friendly?

In addition to the five thematic areas, patients were encouraged to share any thoughts and suggest ideas for potential improvements to the VR task from their viewpoint.

During the interview process, patients' responses and suggestions were recorded on an interview form that included a section for each of the five thematic areas plus any additional comments and suggestions. These responses were later transcribed digitally for analysis. The researcher conducted the interviews. At least one other person (either a nurse or another independent member of the hospital staff) were present during the interview. Privacy of all patients was ensured and respected during the interview process.

Thematic analysis method

Braun and Clarke's six-stage approach (Braun and Clarke 2006) was employed to carry out this thematic analysis. The six stages used to generate this thematic analysis and report are presented in **Figure 8.1** below.

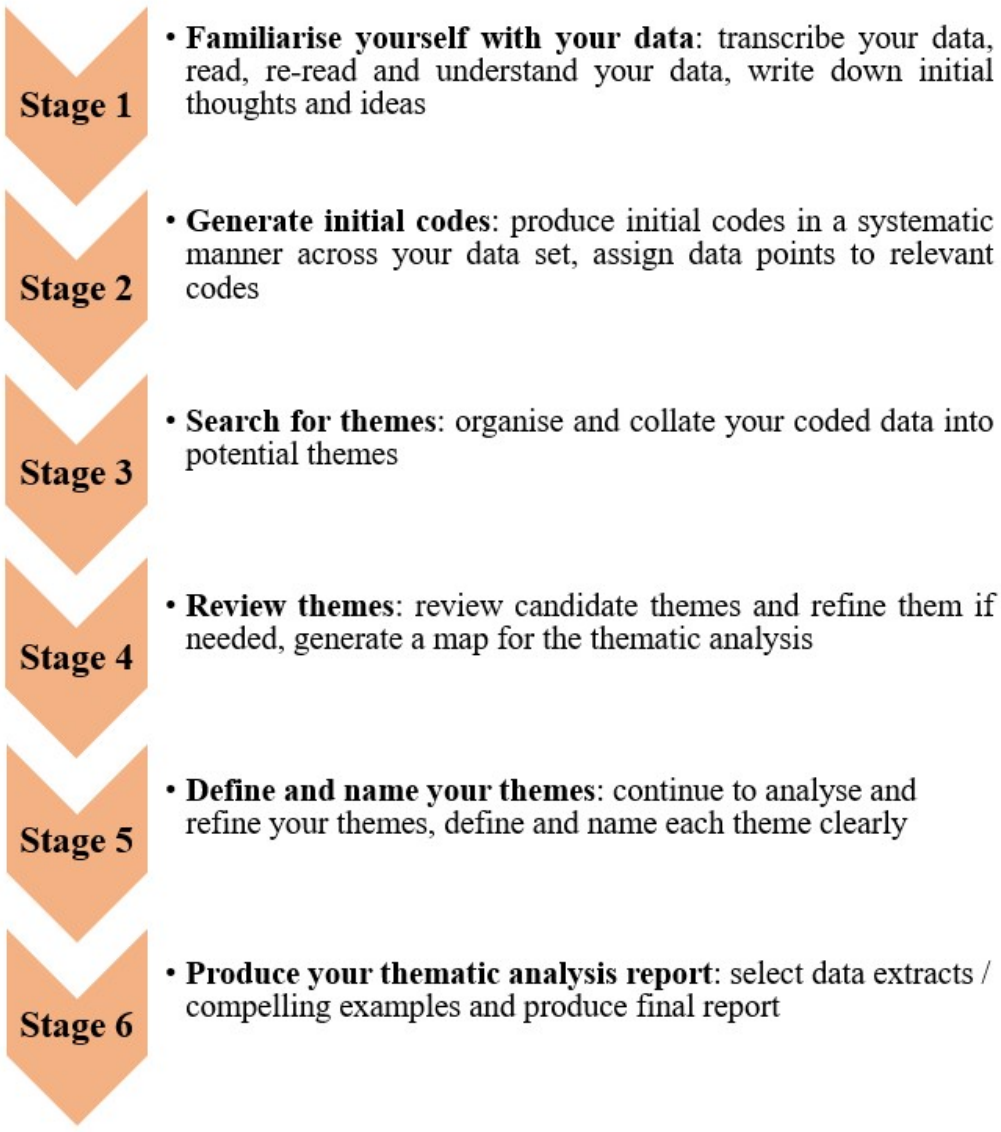

Figure 8.1 Braun & Clarke's six-stage approach to thematic analysis

Findings

Twenty-four stroke patients (15 men and 9 women) participated in this study. The mean age was 62 years. Twelve patients had USN confirmed on the line bisection and bells tests and 12 patients had no USN. After completing the USN-VR assessment, the patients responded to

prompt questions on the five thematic areas presented above. The responses of the patients are summarised in **Figure 8.2** below.

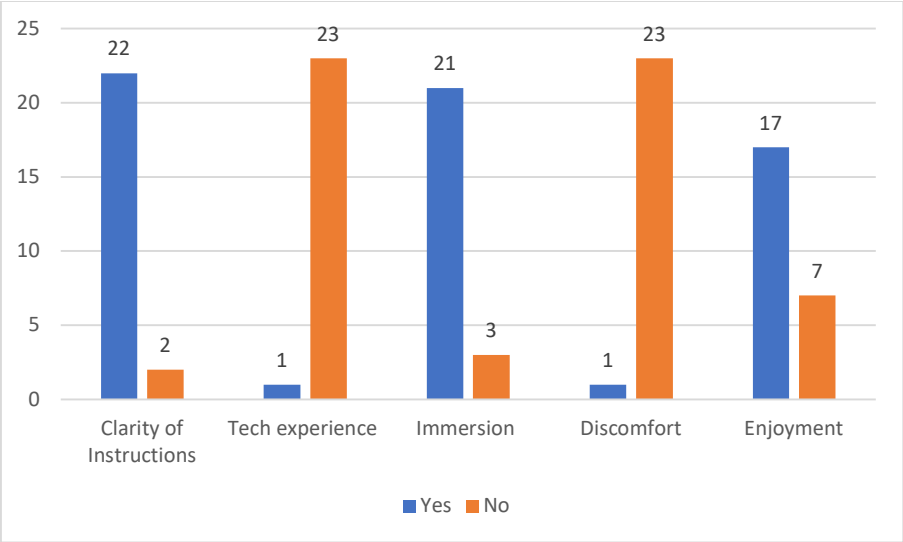

Figure 8.2 Patients' responses to interview questions

Regarding the clarity of instructions, most patients (n=22) found the instructions clear, whereas two patients felt that the instructions could have been explained better. As for prior VR/tech experience, only patient reported familiarity with VR and said they used it before. For immersion and presence, three patients said the virtual environment did not feel real and the graphics needed improvements. Only one patient felt some discomfort and nausea whilst completing the VR task. When asked whether the VR task was engaging and enjoyable, 17 patients reported positive feedback on their experience, whereas seven patients said they did not find the experience enjoyable. Overall, patients' feedback on the acceptance and usability of the VR task was positive.

Thematic analysis findings

The thematic analysis of the patients' responses uncovered three main themes:

1. **Unfamiliarity with VR technology**
2. **The need for more engaging scenarios**
3. **Importance of patient involvement before and during prototype design**

An example of the thematic analysis conducted using Braun & Clarke's six-stage approach is presented in **Figure 8.3** below.

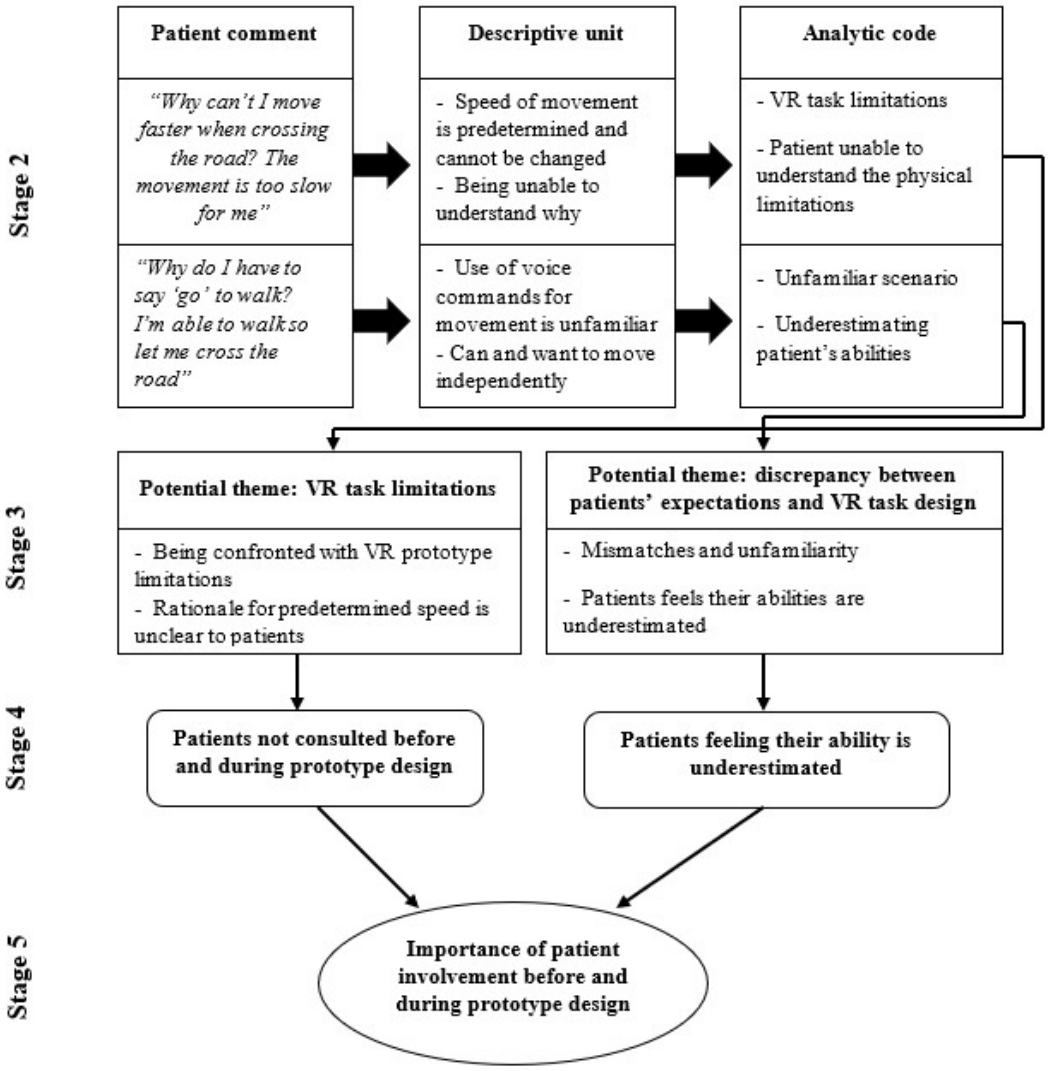

Figure 8.3 Example of the thematic analysis conducted

Theme 1: Unfamiliarity with VR technology

One of the main themes identified from the patients' discourses was their unfamiliarity with VR technology. Patients reiterated that the use of VR goggles to access a computer-generated

environment is an unfamiliar concept. Prior to the start of the USN-VR, patients were introduced to this technology and its components, including the safe use and removal of the VR headset. However, some patients suggested that more educational material were needed to ensure they fully understand this technology and why it is being used with stroke survivors. Some patients suggested making video tutorials on VR technology and sending educational material in advance or during the recruitment stage adding that these videos might help inform their decision on whether to participate or not.

Theme 2: The need for more engaging scenarios

Although over two thirds of the study subjects found the VR street crossing task enjoyable and provided positive feedback on their experience, a recurrent theme in their discourses was the need for more engaging scenarios. The task and scenarios were developed with simplicity in mind, instead of walking to cross the street patients had to use voice commands. Some patients felt the scenario could be made more engaging, enjoyable, and challenging by, for example, adding different levels of difficulty to the task. One way this can be achieved is by increasing the velocity of vehicles and therefore their frequency and having two or three levels of difficulty, rather than just one.

Separately, younger patients highlighted that the storytelling element is missing from the task. These patients suggested that, to achieve a higher degree of patient engagement and enjoyment, we should think of a storyline for the VR task.

Theme 3: Importance of patient involvement during prototype design

During the prototype design and evaluation stages (see Chapter 6), the views of stakeholders were considered through the recruitment of healthcare professional (e.g., stroke nurses) as controls to test and evaluate the VR prototypes developed. The recommendations of these individuals were considered and attempts to integrate their suggestions were made. However,

the thematic analysis highlighted a flaw in our design process, that is the absence of patient involvement before and during the design process.

Some patients repeatedly complained about the slow speed of the predetermined movement inside the virtual environment and asked why there were not able to control this movement. Further, these patients highlighted the physical limitations of the VR task and that felt their abilities were underestimated. These discourses highlighted the importance of patient involvement in the early stages of design and during prototype development.

Discussion

This qualitative study revealed three main themes that summarised the main learnings and captured the experiences and suggestions of 24 stroke patients who completed the USN-VR street crossing task. The literature on the use of VR for the assessment and rehabilitation USN patients is quite limited. Further, it is uncommon for studies to report on the stroke patients' experiences of VR and their involvement and suggestions in designing VR tasks assessments. Findings of this study might help developers and researchers to enhance the patients' VR knowledge and experience by highlighting the need for more patient-oriented training material, engaging scenarios that employ storytelling, and finally, the importance of consulting and involving patients before and during the VR task design, rather than during the VR assessment or training only. This was one of the main learnings of this project. The three themes identified during this study as well as lessons learned and recommendations for future studies are discussed below.

Unfamiliarity with VR technology

Patients' unfamiliarly with VR technology was hardly surprising. During the recruitment stage, it became clear that most of the eligible patients we contacted were unfamiliar with this technology and its uses for the assessment and rehabilitation of stroke-related deficits. While

we attempted to provide as much information and details on the VR technology and the street crossing task, it was evident that more educational and supplementary materials were needed. Patients who agreed to participate in this study were relatively younger than those who refused to. The majority of those who refused to participate cited their unfamiliarity with VR and its uses. From the 24 stroke subjects who participated in this study, only one patient said they were familiar with this technology. Therefore, designing and disseminating materials (e.g., video tutorials, infographics etc) that aim to educate stroke patients on the use of this technology and its application in stroke assessment and rehabilitation is of great importance. This will ensure that patients are well-informed and able to make the right decisions on whether they would like to take part in these studies or not. Further, younger individuals are generally more familiar with technology and tend to use it with more ease than older individuals. As technologies continue to advance, it is important to ensure that suitable educational and training materials are being produced and shared with the right audiences (in this case, stroke patients) prior to the start of the trials.

For example, none of the VR studies reviewed and discussed in Chapters 4 and 5 mentioned providing any educational or training materials aimed at educating and informing patients. The current study also failed to produce and disseminate educational materials on VR technology, partly due to budget constraints. Future studies should consider producing and disseminating such materials during the patient recruitment stages. These materials will not only enhance the patients' confidence and knowledge regarding this technology but will also inform their decision on participation in studies. Therefore, it is an ethical research requirement.

The need for more engaging scenarios

A second major theme in the patients' discourses was the need for more engaging VR scenarios. This pilot study employed a VR street crossing task for the assessment of USN. The task and its design were simple and did not have a storytelling element. When asked to comment on the

VR task and whether they found it enjoyable and engaging, patients highlighted the absence of a storyline in the task. The task was simple, patients had to cross the road and avoid accidents. However, patients suggested that developing a storyline or adding different layers of complexity or difficulty will make the task more engaging and enjoyable.

The one main advantage of VR over other USN assessment (e.g., simple paper tests) or rehabilitation methods (e.g., visual scanning training) is its potential to provide a high degree of ecological validity and realism. The absence of the storytelling element takes away from the VR experience. For example, people watch films and emotionally engage with them because of the ability of this film medium to transport them from the comfort of their seats to a world where the story of the film may control their emotions and reactions. VR tools can offer a similar medium, making the task more enjoyable and engaging if it was developed with a storyline in mind. Future studies should consider developing VR tasks for stroke patients that have a storytelling component to enhance the engagement and enjoyment of the VR experience.

Importance of patient involvement during prototype design

During the post-assessment interviews, it became clear that this project would have benefited hugely from patient involvement before and during the prototype design stage. Although the literature was reviwed and informed and the prototype design (see Chapter 6), and the stakeholders' views were considered through tests and evaluations with healthcare professionals (e.g., stroke nurses), stroke patients were not directly involved in the pre-design stages. This is a flaw and limitation of this project. The reason for the lack of patient involvement before and during prototype design was outside of our control. The project required the approval of an NHS ethics committee; thus we could not access stroke patients or their contact details prior to being granted this approval. Considering that this project was part of an academic degree and had specific timelines and budget constraints, we had to make a pragmatic decision and start the design phase whilst waiting for the ethics committee approval.

Despite this, it is important to acknowledge the lack of patient involvement in the early stages of scenario and prototype development as a limitation of this project and the protypes developed. This was a lesson learned for future studies.

It is important to employ a "from the audience to the audience" approach when developing VR protypes for stroke and other patients. The direct beneficiaries of these VR prototypes are stroke patients. Therefore, consulting stroke patients and receiving and analysing their feedback before and during scenario and task design is of great importance. Future studies should focus on exploring ways in which patients' ideas and feedback are pursued from the early stages of development. This can be acquired through online surveys and interviews or recruiting a control group of stroke patients for scenario and task development only, but not for participating in the trial that employs the task developed.

Limitations

This study had a small sample size. The patients recruited were relatively young and there was a dipropionate number of males and females in the sample. It is likely that there will be gender differences in terms of user experiences of VR tasks. Therefore, future studies should aim to recruit a more homogenous sample.

Additionally, the thematic analysis was based on semi-structured interviews that took place following the USN-VR assessment. To ensure standardisation of data collection and analysis, future studies should consider using standardised interview questions or questionnaires. Another option would be to employ a longitudinal design where each patient is interviewed twice to ensure the capture of all important insights to give patients the chance to reflect of their experiences with the VR technology.

Conclusion

This qualitative study presents the experiences of 24 stroke patients of a VR street crossing task. Overall, the VR street crossing task was well-accepted, relatively enjoyable, and did not

cause significant negative side effects. Findings of the thematic analysis showed the sample of stroke patients recruited was mostly unfamiliar with VR technology. This highlighted the need for the production and dissemination of patient-oriented educational material on VR technology to help in guiding and informing patients. Additionally, our findings further highlighted the need for integrating storytelling elements and techniques in VR tasks to enrich user experience and increase their engagement and enjoyment. Finally, findings of this study emphasised the importance of patient involvement before and during VR scenario and task designs to ensure the development of patient-focused VR tools.

Chapter 9

Conclusion

The purpose of this thesis was to review the literature on the use of virtual reality (VR) for the assessment and rehabilitation of unilateral spatial neglect (USN). This review would inform the design of VR prototypes to assess USN patients. The aim was to develop a mobile phone application involving fully immersive VR prototypes for the assessment of sensory (visual) and motor deficits associated with post-stroke USN. Another aim was to use open-source software during the development of these prototypes.

The systematic reviews conducted in Chapters 4 and 5 suggest that the literature on the use of VR for the assessment and rehabilitation is quite limited. The studies reviewed indicate that this novel technology might offer a higher degree of ecological validity than traditional assessments and scales. This theory is based on the ability of VR to recreate real life scenarios. However, the evidence presented across these studies is inconclusive and further research is needed.

During this project, we sought to develop simple VR tasks that can assess both sensory and motor USN deficits. Previous studies (e.g., Katz et al, 2005) developed a non-immersive street crossing task for the training of USN patients. We sought to build on previous studies and develop an immersive street crossing task, but for the assessment of USN. Further, most studies employing VR technology with stroke patients focus on one type or phenotype of USN only.

We attempted to develop prototypes that can assess both sensory (e.g., visual) and motor USN deficits. This was an attempt to create versatile systems that can assess a wide range of USN-related symptoms. However, although two prototypes were initially developed, the evaluation of these prototypes discussed in Chapter 6 showed that prototype one (street-crossing using Microsoft Kinect motion sensor) was somewhat unsafe for patients to use. To overcome this limitation, we modified prototype one and used Microsoft Cortona voice assistant to replace physical walking (Chapter 6 – prototype two was a street crossing task using voice commands). This prototype was evaluated across different sittings and its performance was better than

prototype one (see Chapter 6 – p xx for evaluation). Therefore, it was included in the pilot study.

The third protype aimed to provide an assessment for motor USN-deficits as well as visual impairments associated with this disorder. This prototype was an object detection and collection task in an immersive virtual environment. The protype was developed, but performed poorly in terms of ease of use, system responsiveness, and user experience across different sittings. Due to budget and time constraints, we had to make a pragmatic decision and stick to prototype two (street crossing with voice commands) only. Therefore, we only partially succeeded in achieving the original objectives of this project.

The use of mobile phones as a medium for a fully immersive VR app to assess USN patients is innovative. No study in the literature reported using mobile phones as a host for their immersive VR systems. We sought to experiment with the use of mobile phones due to their immense popularity and the emerging and developing interest in telediagnosis and telerehabilitation.

Lessons learned and recommendations

This project was the first project of this nature for the PhD student. There were inevitably several mistakes made and lessons learned throughout the project. The following section summarises the lessons learned during this project and provide some recommendations for future studies:

- We failed to capture the views of stakeholders/direct beneficiaries (i.e., stoke patients) in the early stages of the VR scenario and task design. The importance of capturing the views of direct beneficiaries was highlighted repeatedly during the interviews conducted with stroke patients following the completion of the USN-VR assessment. Although we considered and implemented the feedback on the VR prototypes provided by healthcare professionals (e.g., stroke nurses), this was not sufficient. Failure to

capture patients' views early on should be considered a major limitation of this project. The views and feedback of stroke patients is more important should have been captured from the early stages of this project. Future studies should aim to capture the views and feedback of stroke patients in the early stages of any VR task design.

- The absence of storytelling elements and techniques in the VR tasks designed. The tasks were simple, and we had a very small budget for this project. However, attempts should have been made to develop and integrate a storyline in the VR scenarios and tasks developed. Storytelling elements could enhance the patient experience of the task and future studies should aim to integrating these implements into the design.
- A better and more innovative study design should have been used. As with any pilot study, there were several limitations to the work completed during our pilot study. These were highlighted in Chapter 7. The study design could have been better and more innovative. For example, with the well-documented heterogeneity of USN and absence of consensus on gold standard assessments, this study could have employed a hybrid model of USN assessment, rather than just comparing VR with other modes of assessments. Upon reflection, the need to experiment with hybrid models of assessment became clear in the final stages of this project. None of the reviewed studies in Chapters 4 and 5 experimented with hybrid models of assessment and rehabilitation for USN. Studies, including the current pilot study, focused on comparing one method (e.g., paper tests) with another (e.g., VR). However, the heterogeneity of USN symptoms should encourage researchers to experiment with combining different methods, rather than proving one is better than the other. Future studies should consider experimenting with hybrid models of assessment as this might contribute to the development of a gold standard battery of assessments for USN.

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Appendix

Appendix 1: Prototypes videos

I) Prototype two: VR street crossing using voice commands (pilot Study)
II) Prototype three: Object detection and collection (not included in pilot study)

Appendix 2: Participant information sheet

Ashford and St. Peter's Hospitals NHS
NHS Foundation Trust

ROYAL HOLLOWAY UNIVERSITY OF LONDON

Information about the Research

Study Title: The Use of Virtual Reality for post-stroke unilateral spatial neglect

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve. **Someone will go through the information sheet with you and discuss the information provided and answer any questions you may have.** Please feel free to talk to others about the study if you wish.

Part 1 tells you the background/purpose of the study and what will happen to you if you take part.
Part 2 gives you more detailed information about the conduct of the study.

Ask us if anything is not clear.

Important Contacts

The site where the research is taking place:

- Ashford & St. Peter's Hospitals NHS Foundation Trust
  St. Peter's Hospital
  Guildford Road, Chertsey
  Surrey
  KT16 0PZ

Questions about the research can be directed to:

The Chief Investigator: Professor Pankaj Sharma

- Institute of Cardiovascular Research – Royal Holloway University of London, Egham, TW20 0EX
- Tel: 0178 444 38 07
- Email: Pankaj.Sharma@rhul.ac.uk

Complaint Procedure:

If you have a concern about any aspect of this study, you should ask to speak to the Chief Investigator mentioned above who will do his best to answer your questions (01784 443 807).

If you remain unhappy and wish to submit a formal complaint, you can do this by contacting
NHS England
PO Box 16738
Redditch
B97 9PT
Email: england.contactus@nhs.net
Tel: 0300 311 22 33

Part 1

Background to the project
People who have experienced a stroke may have subsequent visual deficits known as unilateral spatial neglect (USN). We need to collect information about stroke patients with and without unilateral spatial neglect to improve the assessment methods of USN.

Purpose of the research
The current study aims to validate a newly-developed virtual reality tool (USN-VR) for the assessment of unilateral spatial neglect which, if validated, could be used by a variety of healthcare professional as a brief screening tool for USN.

Traditionally, conventional paper-and-pencil tests have been used to detect and assess USN. Conventional tests use static targets to assess visual deficits. Studies suggest that these tests fail to detect milder forms of USN. Virtual reality (VR) is a developing technology that has been increasingly used to assess USN among stroke survivors. Unlike conventional tests, VR systems can recreate individualised 3-D environments where patients are trained to perform specific tasks to achieve a goal. As an assessment tool, VR systems can register and objectively measure the performance of patients within the virtual world and their behavioural responses. It is worth noting that the USN-VR tool may detect milder deficits that otherwise go undiagnosed on conventional paper-and-pencil assessments.

Who can take part?
You are eligible to take part if you are 18 years of age or older and have suffered a stroke. English does not necessarily have to be your first language. We will not include you if you have a severe speech or cognitive impairment or a significant psychiatric condition. We will also not be able to include you if you are currently abusing drugs or alcohol. **If you are unsure that any of these apply to you, please discuss it with the Chief Investigator or your direct care team.**

Do I have to take part?

No.

Your participation in this study is completely voluntary. We would like you to take part because we believe you can make a significant contribution to the research and healthcare of stroke patients with unilateral spatial neglect.

How do I take part?
If you agree to take part, someone from the hospital research team will go through the information sheet with you and you will be asked to sign a consent form after watching a short a video explaining how to safely use the VR goggles. **Please bear in mind that you are free to withdraw at any time, without giving a reason.**

What will I have to do I take part?
You will be asked to complete various tests, which measure your attention, memory, problem-solving and visual-spatial skills. Some use pencil and paper while other involve wearing virtual reality goggles to assess unilateral spatial neglect in a virtual environment that mimics a real-life street crossing. You may find some easy and others more challenging.

Where will I have to go and for how long?
The test session will take place at St. Peter's Hospital, Guildford Road, Chertsey, Surrey**,** KT16 0PZ. The tests will be administered by a trained researcher [Doctoral (PhD) student].

Participation will take about an hour and can be usually be completed in one test session with breaks if you need them.

Part 2

What are the potential benefits of taking part?
Whilst there may be no personal benefits to participating, the data collected during the study could contribute to improvements in the quality of visuospatial testing for patients with unilateral spatial neglect.

Are there possible disadvantages or risks involved in taking part?
It is possible that the tests may cause you to feel fatigued. If this happens, you can ask to take a break, or we can arrange another time to finish testing. Additionally, some people who use virtual reality headsets may experience dizziness (motion sickness) or headaches. If you experience any dizziness, pain or feel uncomfortable during any stage of the assessment, the headset will be safely removed, and the consultant neurologist will be informed.

Will my participation be kept confidential?
We will follow the ethical and legal practice to ensure that all data collected and the results from your tests will be kept strictly confidential. All data will be coded anonymously and stored securely.

The overall results of the study will be made public in a completely anonymous form ensuring that no participants can be identified.

What will happen to my results after the study?
All your information will be stored anonymously. Analysis of the anonymised data obtained will be completed on a password protected computer by the Chief Investigator based at the Institute of Cardiovascular Research – Royal Holloway University of London.

The broad findings of the study will be published in a scientific paper of peer-reviewed journal and used to compile the Doctoral student's PhD Thesis. They may also be presented at appropriate scientific conferences.

If you would like a summary of the study's findings, please indicate this on the consent form.

What will happen if I want to withdraw from the study?
You can decide you no longer wish to take part at any point. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. This will not affect the standard of care you receive or your legal rights.

Should you give consent and later lose the capacity to do so, we will include your data in the study unless you indicate otherwise on the consent form.

Who is organising the research?
The study is being organised and undertaken by a postgraduate student and is sponsored by the Institute of Cardiovascular Research – Royal Holloway University of London and Ashford & St. Peter's Hospitals NHS Foundation Trust.

Additional Information - General Data Protection Regulation (GDPR)
Ashford & St. Peter's Hospitals NHS Foundation Trust is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Ashford & St. Peter's Hospital will keep identifiable information about you for one year after the study has finished.
Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.
You can find out more about how we use your information by contacting

- Ms Freda Gomes
  Research & Development Support Manager
  Ashford & St. Peter's Hospitals NHS Foundation Trust
  St. Peter's Hospital
  Guildford Road, Chertsey, Surrey, KT16 0PZ¨
  Tel: 01932 723534
  Email: Freda.Gomes@asph.nhs.net

As an NHS organisation, we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Your rights to access, change or move your information are limited, as we need to

manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.
Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.
If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful, you can complain to the Information Commissioner's Office (ICO).
Our Data Protection Officer is **Dr Isaac John,** and you can contact them at Isaac.John@asph.nhs.uk
Ashford & St. Peter's Hospital will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Ashford & St. Peter's Hospital and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Ashford & St. Peter's Hospital will pass these details to sponsor organisation along with the information collected from you and your medical records. The only people in Ashford & St. Peter's Hospital who will have access to information that identifies you will be people who need to contact you to formally invite you to participate or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Ashford & St. Peter's Hospital will keep identifiable information about you from this study for one year after the study has finished.
Ashford & St. Peter's Hospital will collect information about you for this research study from your medical records. This information will include your name/ NHS number/ contact details and health information, which is regarded as a special category of information. We will use this information to determine whether your eligible to participate in this study.
When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.
This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

Appendix 3: Consent Form

Consent Form

Study Title: The Use of Virtual Reality for post-stroke Unilateral Spatial Neglect

Unique Identification Number:

Participant identification number for study:

	Please initial to confirm
1. I confirm that I have read the information sheet dated 01.11.2018 (version 3) for the above study.	☐
2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily	☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason.	☐
4. I give permission for data already collected to be retained for the purposes of the research if I lose capacity to consent to taking part after the completion of the test session.	☐
5. I would like to receive summary/feedback about the overall results of the study. I understand this will be sent once the study is complete in late 2019. I give permission for my email address to be held by the above-named researcher until the end of the research to facilitate this.	☐
6. I agree to take part in the above research study	☐

Additional

Original copy of the consent form to be kept by the participant; 1 copy for research site file.	☐

Date: _____ **Signature:** _____

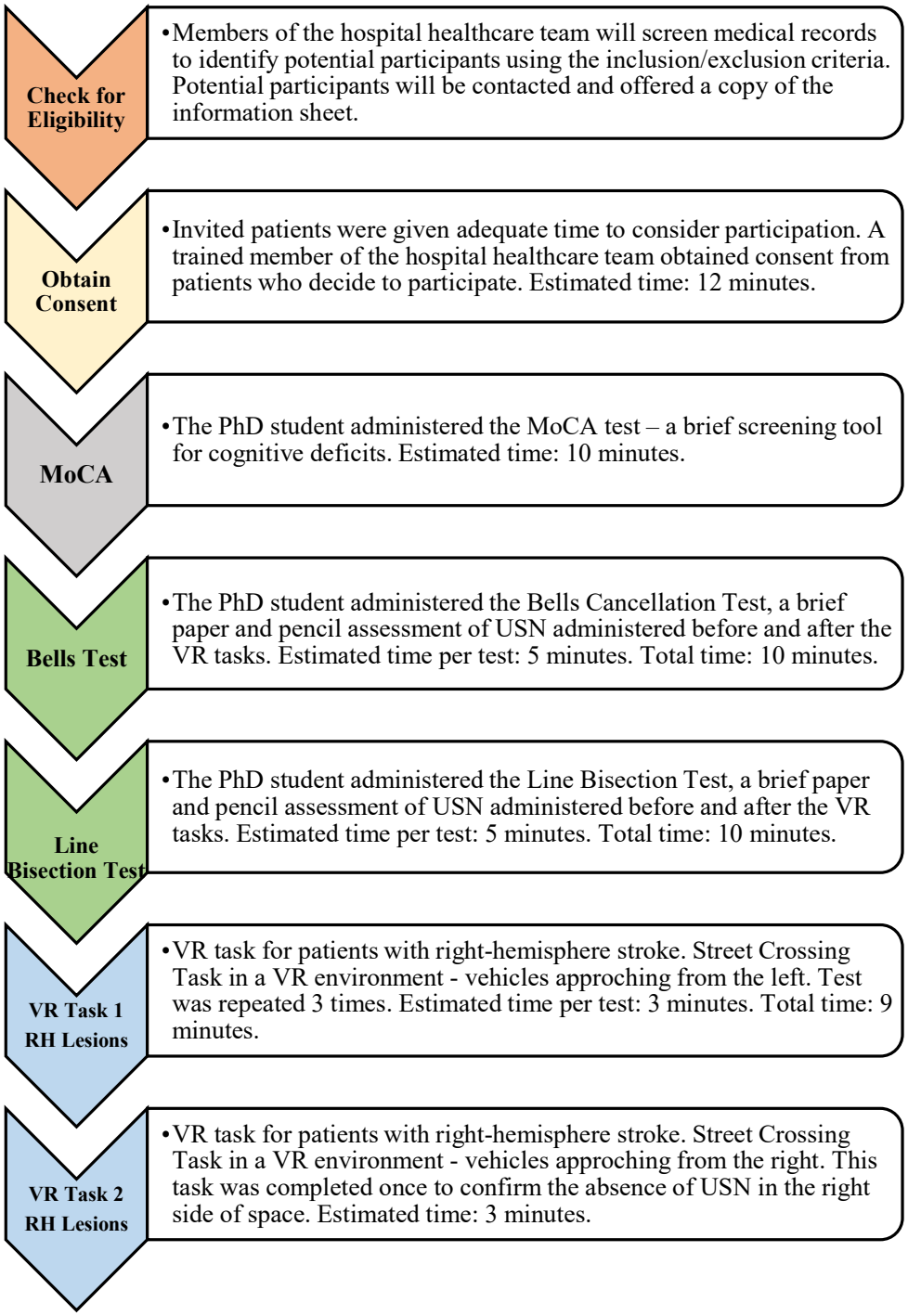
_____

Name of participant

Date: **Signature:**

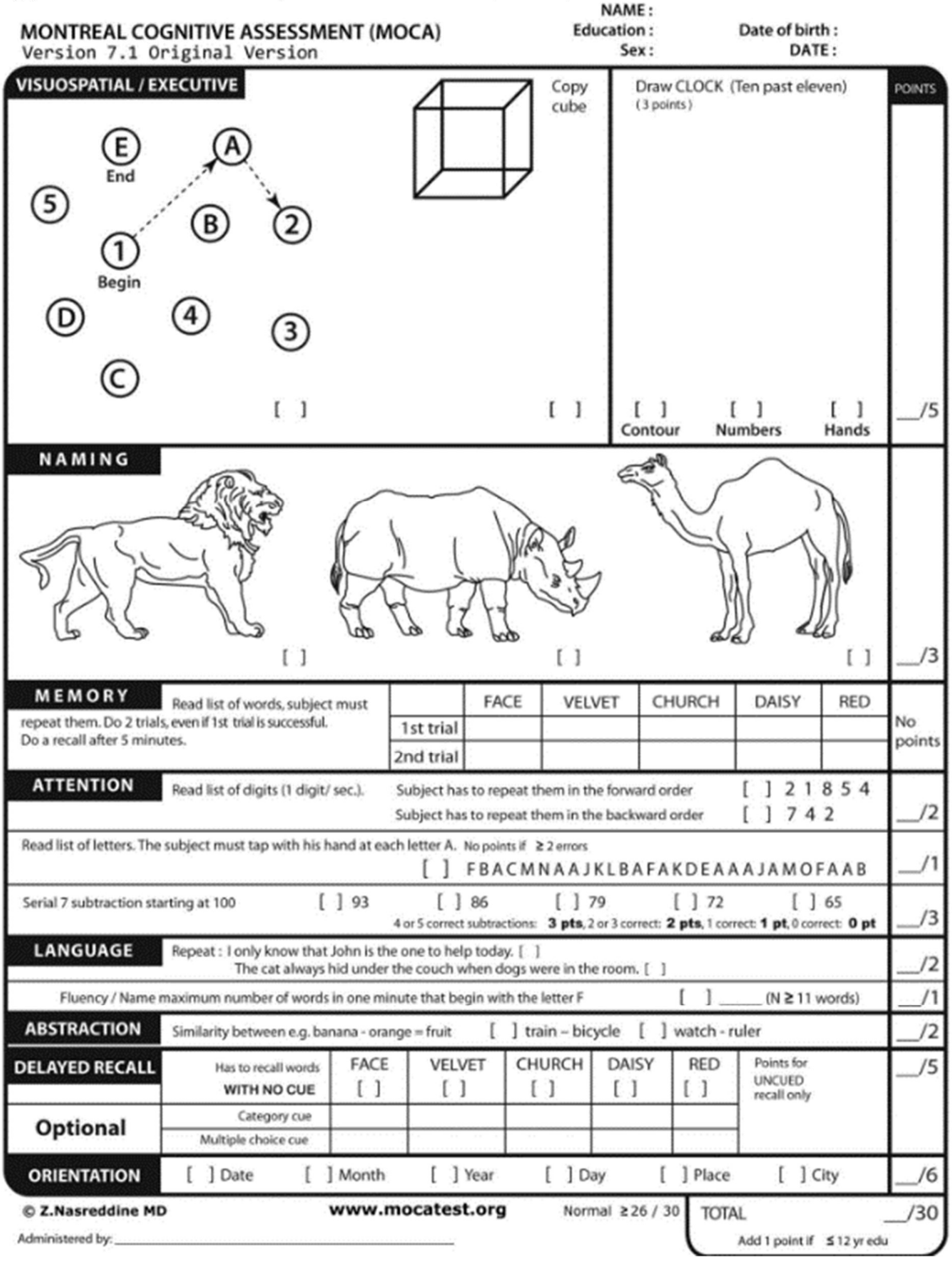
Name of person taking consent

Appendix 4: Study Protocol Flowchart



Estimated time per test session: 60 minutes

Appendix 5: Montreal Cognitive Assessment (MoCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands __/5

NAMING

[ ] [ ] [ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

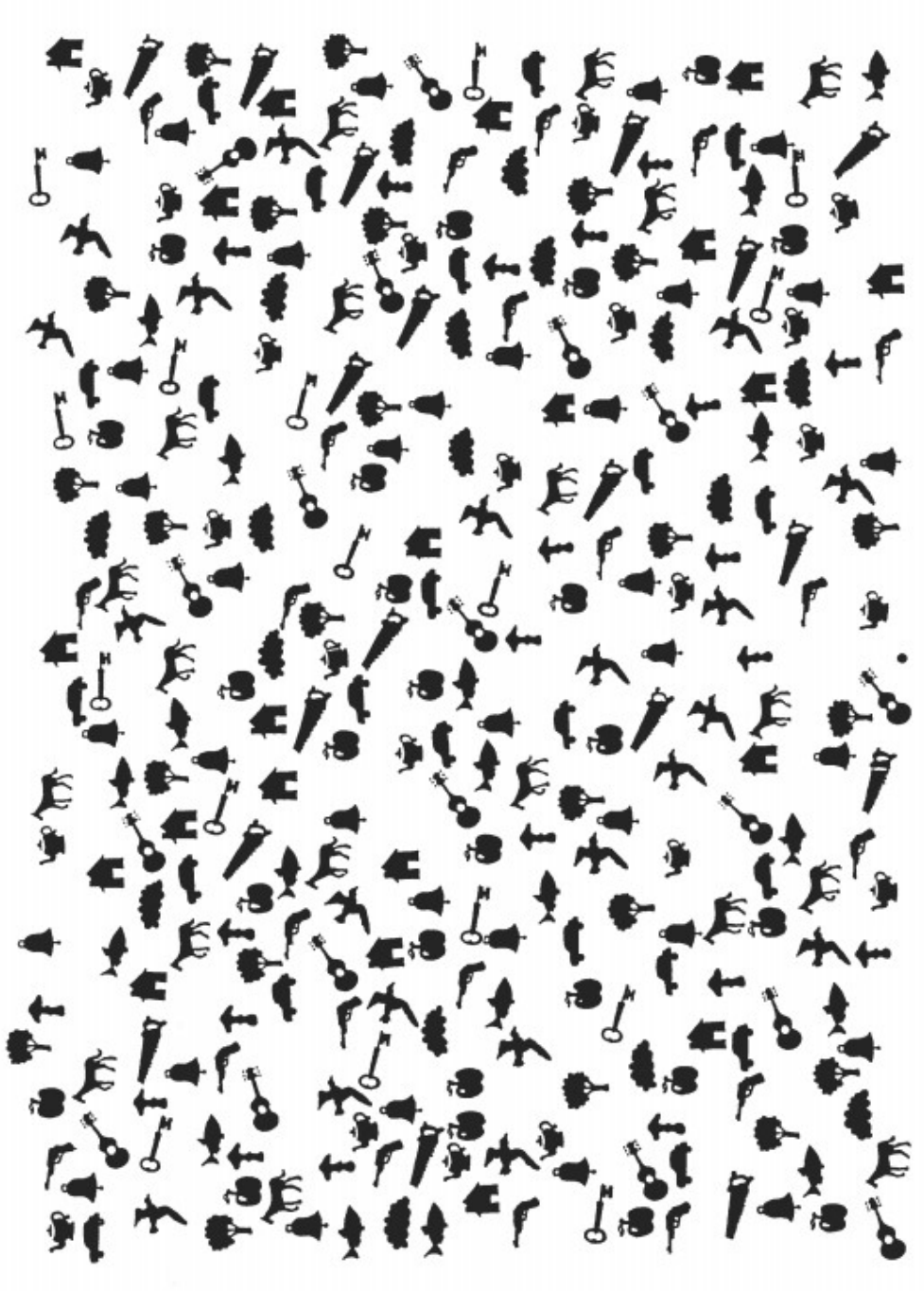
© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

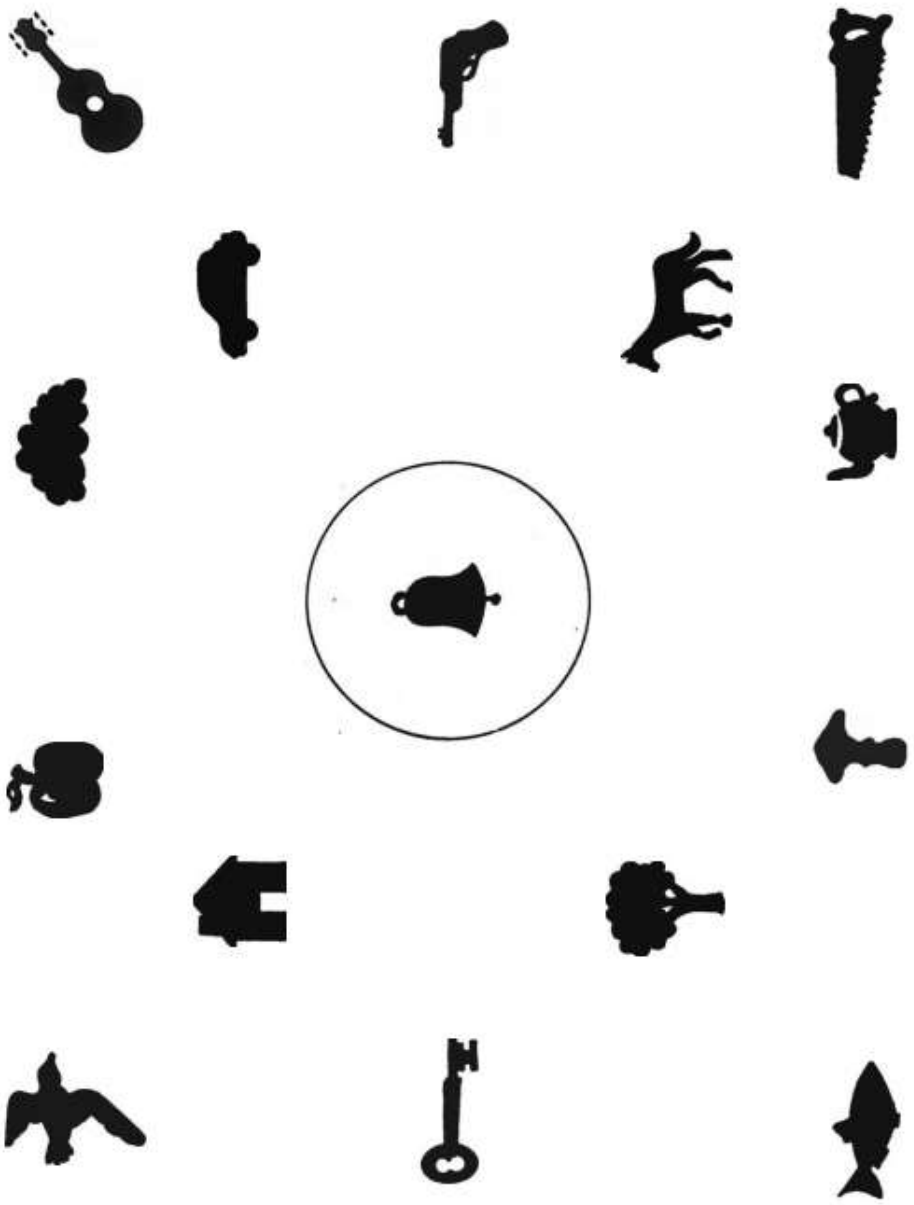
Administered by: _____

Appendix 6: Bells Cancellation Test



Bells Test - Demonstration

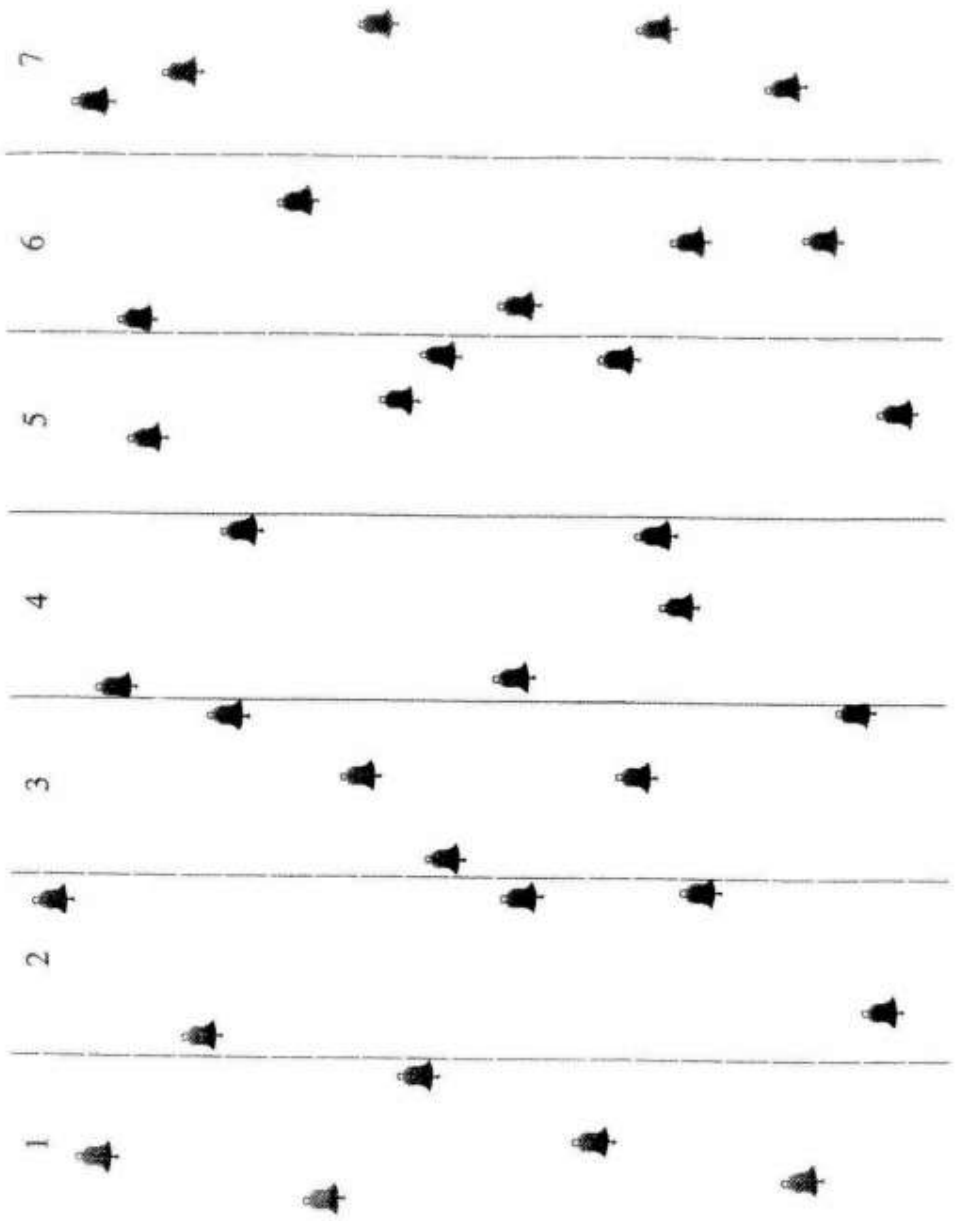
Bells Test-Demonstration



Bells Test – Scoring Sheet

Bells Test - Scoring sheet

Total number of bells circled:	/ 35	Number of Left omissions:	
Realisation time (minutes):		Number of Right omissions:	
Time taken to complete test (minutes):			



Appendix 7: Line Bisections Test