USE OF AN ENRICHED ENVIRONMENT POST-STROKE: TRANSLATING FROM BENCH TO BEDSIDE

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I Heidi Janssen hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968.

I Heidi Janssen hereby certify that this thesis is submitted in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author; and endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

In addition, ethical approval from the University of Newcastle Human Ethics Committee was granted for the clinical study presented in this thesis. Participants were required to read a participant information document and informed consent was gained prior to data collection.

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ABSTRACT

Despite evidence linking higher levels of activity with better outcomes, stroke patients undergoing rehabilitation in hospital settings spend the majority of their waking hours inactive and alone. Environmental enrichment, through the use of equipment and organisation of the environment to facilitate physical, cognitive and social activity, is an intervention which has been used extensively in animal models of stroke. Results from these models have demonstrated the sensorimotor and cognitive benefits of recovering in an enriched environment, however there is conflicting data suggesting no benefit. The purpose of this PhD was to determine the efficacy of environmental enrichment in animal models of stroke, and then develop and pilot test a model of enrichment in stroke survivors.

Systematic meta-analytic methods were used to determine the efficacy of an enriched environment in animal models of stroke. Exposure to an enriched environment in animal models of stroke was associated with significantly better sensorimotor function and a trend towards better learning. Recovering in an enriched environment was also associated with a small but significant increase in lesion size (larger damaged area). However, the importance of this finding at an experimental level requires further investigation.

To explore the feasibility of translating this paradigm from the bench to the bedside, a model of environmental enrichment incorporating both communal and individual enrichment was developed for use with stroke patients in the clinical setting. Behavioural observation was used to evaluate its effect on stroke patient activity. Patients exposed to individual and communal environmental enrichment were more

likely to be active and were less likely to spend time ‘inactive and alone’ or sleeping than those recovering in a non-enriched rehabilitation unit.

This thesis outlines the research undertaken in the first known attempt to translate the use of a model of environmental enrichment from the laboratory into a clinical stroke rehabilitation setting. Evidence presented demonstrates that this model of environmental enrichment can increase activity levels of stroke patients. This preliminary research sets the foundations for further exploration of the efficacy of environmental enrichment on post-stroke function, mood and quality of life.

CHAPTER 1
LITERATURE REVIEW

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1.1 INTRODUCTION

1.1.1 STROKE

1.1.1.1 Stroke in Australia

Stroke is defined as, “rapidly developing signs of focal (or global) disturbance of cerebral function, lasting longer than 24 h (unless interrupted by death) with no apparent non-vascular cause” (WHO MONICA Project Investigators, 1988, p. 108). It is caused by interruption of the blood supply by either occlusion (ischemic stroke) or rupture (haemorrhagic stroke) of a blood vessel [1]. A stroke is a major life changing event.

Stroke can cause serious disability and in some circumstances, death. Each year worldwide, 15 million individuals suffer strokes, from which 5 million die and 5 million survive but do so with impairments causing permanent disability [2]. In Australia in 2012, approximately 50 000 individuals[3] had their first ever stroke.

After coronary heart disease, stroke is the second leading cause of death in Australia [4]and is third on the list of most burdensome diseases, accounting for close to five per cent of the total burden of disease [5]. This burden is manifested through both death and disability, affecting the stroke victim, stroke survivor, their family and the community all to varying degrees [6]. Locally, approximately one quarter of the burden of disease associated with stroke arises from the years of healthy life lost due to disability and poor health [5]. Stroke has been estimated to cost Australia $5 billion each year [3] .

1.1.1.2 Risk factors: The importance of physical activity and age

Modifiable risk factors

Population attributable risk (PAR) describes the "…independent contribution of each risk factor to the burden of stroke worldwide" (O'Donnell et al., 2010, p112) [7]. The nine most attributable modifiable risk factors, by PAR are: hypertension, physical inactivity, abdominal obesity, unfavourable apolipoprotein ratio, smoking, poor diet, cardiac causes (ie. atrial fibrillation), diabetes mellitus, excessive alcohol intake and psychological stress/depression [7]. Other less established risk factors for stroke include: sleep disordered breathing, metabolic syndrome, lipoprotein (a), hyperhomocysteinemia, and coagulation disorders [8].

Primary stroke prevention at the individual level tailors management based on the individual's risk factors and overall risk [9]. Stroke prevention strategies at the population level focus predominantly on prevalent and modifiable risk factors. For example factors such as physical inactivity, abdominal obesity and smoking are targeted through health promotion programmes which advocate an active lifestyle, cessation of smoking and a healthy diet [10]. A significant reduction in stroke mortality over the last four decades has been attributed to better management of risk factors both at an individual and population level [11].

Physical activity: Its role in reducing stroke risk and enhancing functional outcome

Physical activity levels of Australians are low and the three most recent National Health Surveys reveal an increasing trend in the proportion of Australians not sufficiently physically active [5]. Over 70% of Australians aged between 25 and 65 years of age have

low or sedentary levels of physical activity and, not surprisingly, the highest proportion of people with sedentary or low levels of activity is in those aged 75 years or older [5].

Physical inactivity accounts for approximately 29% of the risk of stroke worldwide, second only to hypertension (PAR~35%) [7]. Relative to other risk factors, very little time and money is allocated to research on the role physical activity plays in reducing stroke risk. This is despite evidence from epidemiological studies which reveal a strong positive link between frequency of physical activity (of a low to moderate level of intensity) prior to stroke and stroke risk reduction [12,13]. Partaking in regular physical activity has been associated with better stroke outcomes, with a negative relationship between pre-stroke physical activity and stroke severity , as well as functional attainment, very early (eight days) [14] and short- (3 months) [15] and long-term (2 years) [13] after stroke. These statistics highlight the need to determine the efficacy of physical activity in preventing initial stroke, reducing stroke severity and facilitating functional recovery.

The mechanisms by which physical activity prevents stroke, reduces severity, and enhances function may vary. In terms of stroke risk reduction, evidence suggests physical activity assists with preventing and or minimising the severity of other modifiable risk factors (ie. obesity, hypertension, diabetes and dyslipidemia) [16]. Additionally, the sheer stresses placed on vasculature during high intensity physical activity (ie. exercise) has been shown to favourably alter vessel structure and function which is thought to reduce atherosclerotic sources of stroke [17].

The mechanisms by which exercise reduces the severity of brain injury are still yet to be confirmed, but results from animal models of stroke indicate pre-ischemic exercise induces better ischemic tolerance. Pre-ischemic exercise is thought to achieve this by (i)

augmenting nitric oxide mediated vasodilation, (ii) promoting angiogenesis (iii) inhibiting both reperfusion related inflammatory responses and glutamate over-activation (iv) preventing blood brain barrier dysfunction (common after brain injury) (v) reducing apoptosis, (vi) improving cerebral blood flow and (vii) reducing post ischemic oedema [18-20].

Undertaking regular exercise prior to stroke is associated with less severe post-stroke neurological deficits in both human and animal observational studies [20] . Again, the actual mechanisms by which this occurs requires further research but is likely related to the smaller lesions which result from the neuroprotective chemical and structural changes explained above. The proposed mechanisms by which pre-stroke exercise improves post-stroke function include: (i) the development of greater cardiovascular reserve (which additionally may minimise the loss of ischemic penumbra in the brain), (ii) better collaterisation of blood after arterial occlusions, (iii) through extracting oxygen more effectively from circulating blood, and lastly (iv) the development of greater functional neuromuscular reserves which enables the stroke patient to perform compensatory movements more easily [15].

Non-modifiable risk factors

Age, gender, race, ethnicity, low birth weight and genetic predisposition are all accepted non-modifiable risk factors for stroke [21,22]. Of these and the previously listed modifiable risk factors, age is the single most important risk factor for stroke [22]. The incidence of stroke increases with age [23-25], affecting: 5% of women and 8% of men aged 65-74 years, 11% of women and 15% of men aged 75-84 years and 15% of women and 17% of men aged 85 and older [5]. For every decade after 65 years of age, there is a 10% increased risk of having a stroke [26].

It is probable that an ageing population will have an impact on the allocation of resources for both the prevention and rehabilitation of stroke. Due to the predicted ageing of the population, even if age-specific incidence decreases somewhat, the incidence of stroke overall has been predicted to rise [27]. There are concerns that the current model of health service delivery will be unable to cater for the increase in demand which will result [28]. Complicating this further, it has been shown that elderly stroke survivors : (i) present with more severe strokes [29], (ii) experience greater disability [30], (iii) require a longer time to recover (and rehabilitate) from their stroke [31], (iv) are less likely to be discharged to their own home and, (v) are more likely to require institutionalised care [31,32].

1.1.1.3 Mortality and morbidity

Based on the most recent local epidemiological research, one in five Australians suffering their first-ever stroke die within the first month, and one third die within the first year [33]. In the majority of instances a stroke victim survives but is left with significant neurological impairments [28]. Depending on the extent and location of the initial brain damage, sensorimotor and cognitive impairments present in the first few days can persist for weeks, months and for some, years. The majority of survivors experience significant and persistent disability as a result of post-stroke impairments [34].

Stroke affects a wide array of body functions and structures, which can limit a stroke survivor's capacity to engage in many tasks and possibly restrict their participation in activities of daily living (see Figure 1). Impairments sustained can include: swallowing deficits (dysphagia), loss of motor control (strength and or mobility), loss of sensation, visual field deficits, communication difficulties and cognitive dysfunction [35]. Further to this, stroke related deficits can be compounded by secondary complications (ie.

contractures, incontinence, mood disturbance), pre-existing health conditions and social circumstances.

Stroke recovery is heterogeneous [35]. Two in three stroke Australian survivors depend on others to perform their activities of daily living [3]. Furthermore, the proportion of survivors capable of functioning independently after their stroke decreases with time [36]. This dependency places strain on both a stroke survivor's family and health infrastructure.

Stroke patients who are depressed following stroke struggle to actively participate in the rehabilitation process [37]. The negative effects of reduced mood extend beyond the immediate post-stroke phase. Experienced by approximately 40% of survivors [38], post-stroke depression is associated with greater dependence [39], poorer socialisation [40], reduced participation and reduced health related quality of life (HRQoL) [41,42]. Furthermore, at least one in two carers of stroke survivors report depressive symptoms, significant strain and to be dissatisfied with his or her life [43].

The majority of stroke survivors report to have a poor HRQoL [41]. Survey of Australian stroke survivors revealed that their perceived HRQoL was approximately 40% lower than healthy aged matched individuals living in the community (ie. stroke survivors utility score of 0.5 and healthy aged matched individuals 0.86). A utility score of 0.5 means individuals in the community would rather give up half of their remaining years of life in full health than continue living with the health of the average stroke survivor [44]. Disability adjusted life years (DALYs) is a combined measure of the years of life lost due to premature death and years of life lived with disability. Globally, stroke ranks as the seventh leading cause of lost DALYs [28]. In 2012 in Australia, stroke caused 285 158 DALYs, equating to $49.3 billion [3].

In 2012 there were over 420 000 Australian stroke survivors. There is predicted to be 77 million worldwide survivors of stroke by 2030 [28], 709 000 of which will be Australian stroke survivors [3]. Stroke related burden takes on many forms - personal, financial, physical, emotional, psychological and social. There is evidence to suggest that the impact of this burden is greatest during the later stages of recovery, once the stroke survivor is back living in the community [45]. Reducing stroke related burden requires the development and implementation of cost effective stroke rehabilitation therapies.

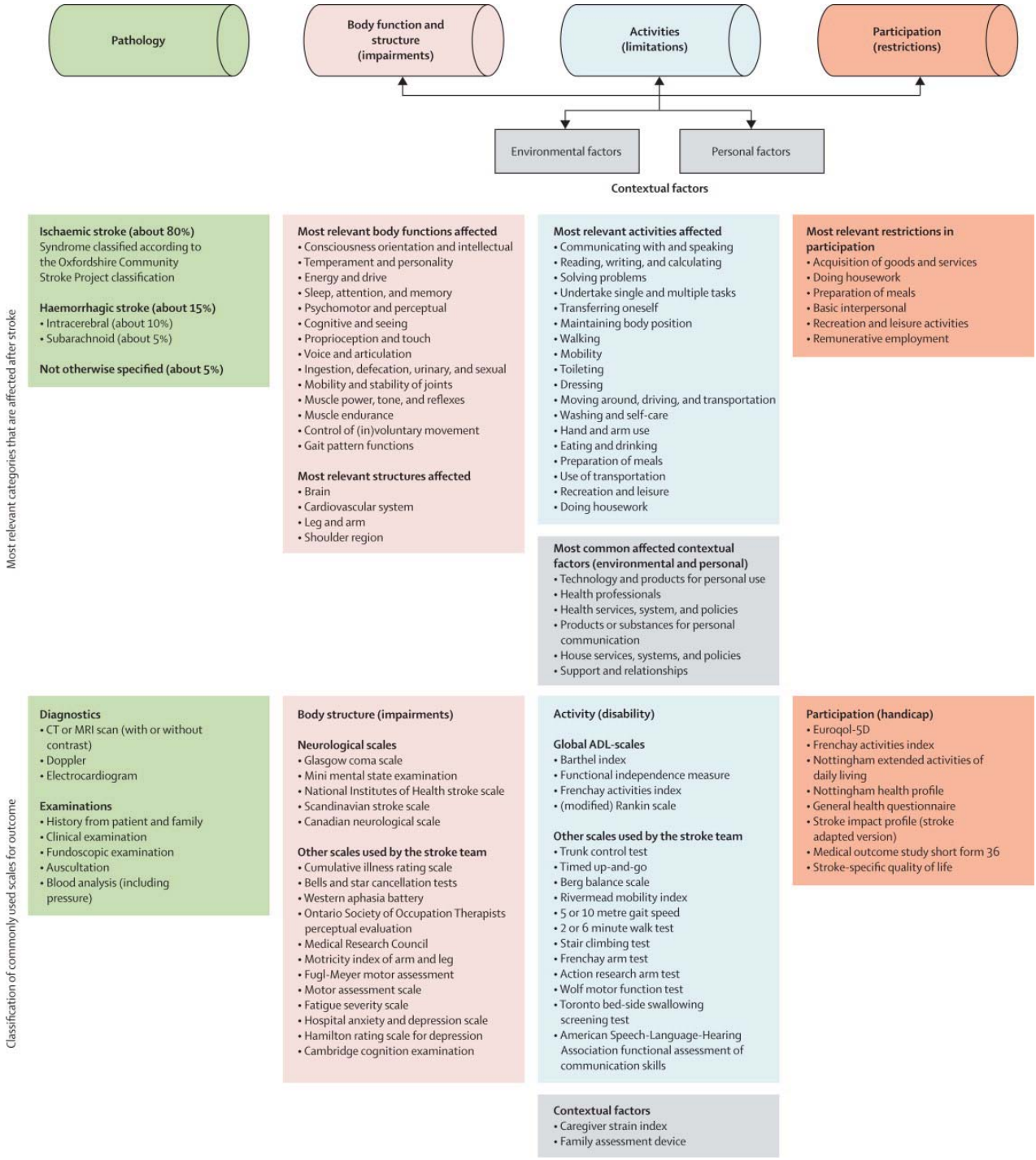

Figure 1. WHO Impairment, Activity and Participation boxes (reproduced with permission from Langhorne, Bernhardt and Kwakkel 2011 [35])

1.1.1.4 Acute management of the stroke survivor

Acute

At the individual level, advances in the acute and recently the hyper-acute [46] management of stroke have been shown to be highly effective in reducing the incidence and impact of stroke-related deaths and disability. One of the most influential interventions has been the use of thrombolysis in ischemic stroke. Recombinant tissue plasminogen activator (r tPA) [47,48], which is an anti-clotting agent used to re-establish blood flow in an clot occluded blood vessel, is the most cost effective acute intervention for stroke. However the window of effectiveness (time post-stroke) is very narrow [49,50]. Furthermore, access to this therapy is less than ideal, with only 7% of Australians presenting with ischemic stroke receiving r-tPA[51].

When administered within the first 4.5 hours post-stroke, tPA has been found to reduce the level of death and disability at three to six months post-stroke [52,53]. However, despite the fact that thrombolytic therapy may reverse the symptoms of stroke in some stroke patients, close to half of those survivors receiving it remain dependent on others in normal activities of daily living [54,55].

Stroke units [56], aspirin [57] and hemicraniectomies [58,59] have also been shown to be effective stroke therapies. The number needed to treat for benefit is 79 for aspirin [60], 2 for a hemicraniectomy [61], and compared to general medical wards, only 20 stroke patients need to be treated in a stroke unit in order to prevent one survivor from failing to regain independence [62].

Despite access to these effective therapies during the acute phase of their stroke recovery, the majority of stroke survivors will still require ongoing input from health

professionals to maximise their functional recovery. If health services are available, their post-stroke disability is mild to moderate and social support is adequate, they will often return home and receive their ongoing rehabilitation as an outpatient. Inadequate social supports and or high levels of dependency due to severe physical and or cognitive impairments require a large number of these survivors to be transferred to a rehabilitation unit to undergo inpatient stroke rehabilitation.

1.1.1.5 Rehabilitating the stroke survivor

Rehabilitation directed by the multi-disciplinary team, comprised of medical, nursing and allied health professional skill, aims to provide those with loss of function or ability due to injury or disease with the greatest possible level of functional independence. This is achieved through management and treatment based on individual assessment and regular review [63]. Stroke rehabilitation has been shown to reduce the likelihood of death and long term dependency of stroke survivors[64].

Stroke rehabilitation provides the opportunity for: strengthening, improvement of co-ordination, retraining of speech and cognitive functions, prevention of secondary complications (contractures, learnt non-use, chest infections), retraining of activities of daily living and personal care such as cooking, dressing, bathing and continence and other self-care behaviours. When reacquisition of such skills is unsuccessful, compensatory strategies are taught [65]. It is recommended that rehabilitation should commence as soon as the stroke survivor is medically stable [62]. For some it can continue formally in the following months in an inpatient and outpatient setting, or informally for many years after stroke onset in the home environment.

The health professionals involved in the formal process of stroke rehabilitation may include: rehabilitation physicians, nurses, physiotherapists, occupational therapists, social workers, speech therapists, dieticians and in some cases psychologists. This multi-disciplinary team works in conjunction with the stroke survivor and family in the formulation of goals aimed at facilitating independence [35].

Approximately one third of those admitted to Australian hospitals for acute management of their stroke receive formal inpatient rehabilitation in either a stroke specific or mixed rehabilitation unit [51]. The median age of a stroke survivor undergoing rehabilitation in these units is 76 years, and the majority are moderately to severely impaired and dependent on others to mobilise at the time of admission [66].

Neurological and functional recovery peaks in the majority of stroke patients between six and twelve weeks post-stroke [67]. However, most survivors have completed their inpatient rehabilitation within the first four to five weeks of this critical period of recovery. For example, the median number of days post-stroke that survivors are admitted to inpatient rehabilitation is ten days **,** and finishes 24 days later (inter quartile range (IQR) 14-42) [66]. Recent audits indicate that Australian stroke patients undergoing inpatient rehabilitation on average receive 56 minutes per weekday of allied health therapies [68]. As outlined further in Section 1.2, stroke patients spend over half of their day inactive. There is scope therefore to increase activity levels of stroke survivors during this critical time of recovery. It could be argued that inactivity during the first six to twelve weeks after stroke (when functional recovery peaks) may be preventing a survivor from reaching their functional potential.

1.1.1.6 Evidence for stroke rehabilitation

Compared to general medical wards where multi-disciplinary stroke care is not available, for every 100 stroke patients who undergo inpatient (subacute) stroke rehabilitation an extra five return home, most of whom are independent [64]. However despite the established benefits of rehabilitation, the list of therapies supported by high level evidence during the subacute phase of stroke rehabilitation is small. The majority of activity based therapeutic interventions routinely used by clinicians on stroke patients have yet to be proven to be effective [69]. For those few which have been proven efficacious at either the impairment and or functional level, uncertainty remains regarding the ideal dosage (ie. frequency and intensity) and time to commence.

Results from Cochrane Collaboration reviews and the few high quality RCTs conducted in this population indicate there are few effective interventions for use during the recovery phase. *Mirror therapy* as an adjunct to 'standard' therapy-has been shown to assist in the recovery of motor functions, and reduce dependency and pain[70]. *Repetitive task training* involving (a) the *lower limb* (i.e. walking and standing up) appears to enhance the ability to mobilise and perform activities of daily living following stroke [71] and (b) the *upper limb* improves function short term, and these gains remain evident up to 5 months post-stroke [72]. Evidence is emerging that *robotically assisted gait training* (including body weight support treadmill training) has benefits for both those very mobile early after stroke [73], and those unable to mobilise or heavily dependent on others to move whilst within hospital [74-76]. Lastly, *robotically assisted upper limb training* has been shown to improve stroke survivor participation in activities of daily living [77]. Although evidence for these interventions is favourable, clinical practice has been slow

to change. Repetitive task training is used in the majority of rehabilitation units in Australia, mirror therapy and robotics are used very infrequently [69].

Additional high quality stroke rehabilitation research is required. Recommendations from a recently held Synergium involving basic scientists, clinicians and researchers of stroke, expressed the sentiment that much time, effort and money could be gained by discontinuing practices which are driven by factors other than robust clinical evidence[78]. This is pertinent to the field of stroke rehabilitation considering only a small number of the therapies used routinely in the clinical setting have been proven to be effective from systematic review of all relevant randomised controlled trials [66] .

Health system costs for stroke comprising hospital costs, general practitioner and specialist services, pharmaceutical costs and allied health service costs, amounted to $881 million in 2012 [3]. These health costs are high, predominantly due to the substantial burden of disability in many survivors. Any intervention which can reduce inpatient length of stay and additionally the amount of services required following discharge, and in doing so maximise functional independence, is likely to be cost saving.

1.1.2 EFFECTIVE STROKE REHABILITATION

1.1.2.1 Plasticity: What we have learnt from animals.

Results from animal research conducted in the last 30 years have disproved the long held belief that the adult or injured brain is unable to be 'remoulded' or simply, changed. The brain in fact is capable of significant structural remodelling and functional adaption. The ability of the brain to alter its functional organisation as a result of experience [79] and the surrounding environment [80] is referred to as 'plasticity'. Plasticity

can be either adaptive or maladaptive [81] and the distinction between the two has yet to be clearly determined. What is clearly accepted now, is that the behaviour of an animal (human or non-human primate), is one of the most powerful modulators of post-stroke recovery [79]

Correlates of plasticity in animals with healthy and injured brains include: altered cortical maps, change in the morphology of synapses and dendrites, change in the trajectory of axons, modulation of certain neurotransmitters and the survival and differentiation of new neurons [79]. These physiological and anatomical changes of the brain have been shown to be driven by various factors including: skilled motor training [82], sensory stimulation [83], peripheral [84] or central [85] injury, exogenous growth promoting agents (eg. brain derived neurotrophic factor (BDNF) [86]), exogenous neuromodulating drugs (eg. fluoxetine [87]), electrical [88] and magnetic [89] stimulation and recovering in an environment which stimulates physical, cognitive and social activity [90]. Although definitive proof is lacking, this structural remodelling and functional reorganisation is thought to underlie the functional (ie. motor, speech and cognitive) gains made following stroke. For example, alterations in the cortical maps have been shown to occur both very close to the infarcted area, as well as in remote areas; evidence of cortical remapping has been found in the contralesional hemisphere of stroke survivors regaining hand function during the two weeks following stroke [91].

1.1.2.2 Effective interventions

Animal models of stroke

It is important to correlate anatomical re-organisation and structural remodelling of the brain with functional improvements. Testing rehabilitation interventions on animals

recovering from stroke provides us with an opportunity to explore the extent of this relationship. A causal relationship has yet to be established but interventions including treadmill [92] and running wheel training [93] and skilled reach training [94] have been found to enhance motor recovery and trigger structural and behavioural changes indicative of neuroplasticity.

Findings from animal research indicate that more activity post-stroke is beneficial [82]. The specific mechanism by which activity contributes to better post-stroke motor function is yet to be completely understood. However, animal data suggests that the time to commencement [95] of and dosage [82] of activity based rehabilitation (ie. intensity) are likely to play an important role .

Clinical stroke

Those interventions for which there is strongest evidence of benefit include: constraint induced movement therapy [96],mirror therapy as an adjunct to 'standard' therapy [70], repetitive task training for both the upper [72] and lower limb [97] and robotically assisted gait [76] and arm [77] training. Most importantly, these interventions have been shown to result in better post-stroke function. Like the interventions in animal studies, exactly how long after stroke (ie. days) and the specific dosage at which these therapies need to be delivered has yet to be determined.

Engaging in physical activity based therapy of any type may be more advantageous than doing nothing. In a meta-analysis which included inpatient, outpatient and home based interventions, physiotherapy of any single or mixed approach (eg. orthopaedic, neurophysiological and or motor relearning principle) for post-stroke postural stability and lower limb function, was better than no treatment or placebo in terms of improving

functional capacity, walking speed, leg strengthening or balance [98]. The level of therapy required to provide maximal benefits is yet to be quantified. Some researchers have suggested more energy should be dedicated to understanding this better - knowing *how much* rehabilitation is needed (ie. the number of repetitions required) rather than the specific *type* of therapy [99].

There is an absence of high level evidence for the interventions used to address post-stroke impairments including communication (aphasia) [100], sensory [101], visual [102] and cognitive [103] (eg. perceptual [104] and attention issues [105]) deficits and post-stroke urinary incontinence [106]. Most recommendations in current stroke guidelines on how to manage these impairments are based on expert opinion [97]. Absence of evidence does not necessarily mean that the interventions used to address these post-stroke impairments do not work. They may in fact be efficacious. Testing these interventions and strategies in randomised controlled trials would help grow the evidence base.

1.2 ACTIVITY AFTER STROKE

Pooling data from individual clinical studies indicates higher levels of post-stroke activity, in particular therapeutic activity, results in improved function [107]. The meta-analysis from which this is based included over 20 clinical studies (n=2686) which tested various types of movement based interventions and concluded that post-stroke function, in particular walking and activities of daily living, is enhanced after receiving an average of 16 hours of additional therapy [107]. This amount of supplemental therapy during the first six months was associated with a 1 point change on the Barthel Index. Although the clinical significance of this approximate 4-5% increase at the individual level may be questionable, it could be argued that this gain in function could have a significant impact at the population level. The studies pooled for meta-analysis were highly heterogeneous. There was great variability in the characteristics of participating stroke survivors, the type and intensity of interventions used in both the control (comparative) and experimental groups, and in the outcomes of interest. The mean treatment effect was calculated using a standardised mean difference approach. Whilst this choice of statistical method was appropriate and addresses the variability associated with the use of different measurement tools, it does not overcome the heterogeneity which arises from the other aforementioned features of study design. Despite having this point estimate of efficacy, it remains unclear: which stroke survivors (eg. of a particular severity and or time post-stroke) benefit most, what is the ideal dosage of therapy (ie. intensity and frequency), and of great importantly, which type of intervention should be used.

What is known though, is that better post-stroke function enhances independence. This is important considering the ability to care for oneself is associated with better health

related quality of life (HQoL) [108] and mood after stroke [109]. Furthermore, a stroke survivor able to care for oneself is likely to be able to return home, which is a beneficial outcome for both the individual and community.

The growing evidence for a positive relationship between higher volumes of therapeutic activity and better motor recovery in both clinical and animal studies has fuelled the sentiment that more 'active' (physical based) rehabilitation is better. For example, most major national stroke bodies advocate that activities related to recovery of function should be commenced as soon as possible and performed as frequently as tolerated by the stroke survivor [97,110-113]. This recommendation is mainly based on evidence from animal models of stroke and a small amount of clinical data which supports higher levels of activity in human stroke survivors. Locally, in the National Stroke Foundation of Australia Clinical Guidelines for Stroke Management it is recommended that stroke survivors, within the first six months, receive structured rehabilitation and be provided with as much opportunity to practice as possible. Specifically, physical therapies including physiotherapy and occupational therapy should be provided, with a minimum of one hour per five day week allocated to active practice, circuit and or group classes and video self-modelling. It is also recommended that assistance from family members should be sought to ensure as much practice as possible is achieved [97].

Despite these recommendations, observation of stroke patients consistently reveals that patients are receiving much less than the 'recommended level of therapy' during therapy hours, let alone additional activity or training outside of this time [68]. This is concerning given that recently published data indicating that adherence to the National Stroke Foundation Guidelines (of which one hour per day of activity training is included) is associated with better stroke outcome [114].

In most units, locally and internationally, stroke survivors rehabilitating in hospital units do very little; both during and outside of therapy hours [115]. This section outlines the importance of activity to functional recovery, the current evidence regarding stroke patient inactivity and highlights how non-physical based activities are often neglected.

1.2.1 ACTIVITY

Research into activity levels of stroke survivors to date has focused predominantly on behaviours and interventions of a physical nature, for example ambulation, exercise and physical therapies. There is a limited amount of work quantifying levels of cognitive activity and virtually none regarding social activity. The World Health Organisation (WHO) framework for rehabilitation, the *International Classification of Functioning Disability and Health* (ICF), defines activity as "the execution of a task or action by an individual" (WHO, 2002, p. 10) [116]. This implies that in addition to physical behaviours, non-physical cognitive and social behaviours are included in the WHO definition of activity. There is a shortage of research investigating the frequency of behaviour, and training of activities which are not necessarily dependent on motor function, such as communication, socialising, memory and attention. Stroke patients consistently identify these non- physically based activities to be very important [117]. Furthermore, restriction in these activities (and the contributing stroke impairments themselves) can at times persist up to 12 months post-stroke [117]. Being able to communicate [118], participate in leisure activities of interest [119] and re-integrate easily back into social life [42], have all been shown to correlate with better post-stroke health related quality of life . This is supported by qualitative data in which stroke survivors reported many of these factors had a significant impact on post-stroke quality of life

[120,121]. There is very little data concerning how frequently stroke survivors engage in cognitive and social activity during inpatient stroke rehabilitation.

1.2.2 DEFINING AND DESCRIBING ACTIVITY AFTER STROKE: CURRENT EVIDENCE

1.2.2.1 Physical activity

For the purposes of this thesis, ***physical activity*** is defined as

any every day, personal, athletic, recreational or occupational activities that require physical skills and utilize strength, power, endurance, speed, flexibility, range of motion or agility. This encompasses virtually any purposeful physical movement and as such includes activities such as eating or drinking using utensils etc, all personal activities of daily living and active participation in transfers, ambulation and physical, occupational and speech therapies (adapted from McGraw-Hill Companies, 2013 [122]).

Efficacy of physical activity after stroke and the underlying biology of change

Research on the relationship between physical activity (ie. training of a skilled motor task or endurance exercise) and sensorimotor function indicates that physical activity facilitates, and in some cases triggers, processes involved in both physiological and anatomical plasticity [86,123]. These alterations may contribute to cortical reorganisation, which in some circumstances results in healthy brain regions assuming functional roles once governed by the infarcted areas.

As detailed in Section 1.1 and briefly in the opening paragraph of this section, participation in physical activity after stroke is advantageous; in particular, being more

physically active is associated with greater functional recovery. Engaging in higher levels of physical activity (ie. an additional 16 hours of physiotherapy or occupational therapy than typically received during the first 6 months post-stroke) has been shown to reduce dependency [107], improve walking ability and walking speed, and significantly improve the performance of activities of daily living (ADLs) [124]. Furthermore, the meta-analysis from which these results were obtained showed no ceiling effect for activity [107], suggesting that further increase in activity may yield added benefit.

Physical activity levels of patients after stroke

Robert Keith [125] was the first to highlight how inactive stroke patients in hospital are and alarmingly, similar work conducted over the 30 years since indicates that this is still the case [126-132]. A recent systematic review and meta-analysis of the amount and type of physical activity undertaken by stroke patients in stroke units or general rehabilitation unit settings revealed that moderate or greater intensity activity (eg. unsupported sitting, active participation in transfers, standing and or walking) was performed for less than a quarter of their waking hours [115]. Although behavioural categories of interest and methodology used in observational studies conducted on stroke patients differs slightly, the data show that patients spend very little time engaged in therapeutic behaviours or activities (i.e. tasks advantageous to functional recovery) [115,132]. The majority of activity is undertaken by stroke patients when they are with therapists [129,133]. It appears that the remainder of the day (non-therapy times) is most often spent doing nothing, and either sitting or resting in bed [128,134]. In the most recent work conducted locally in a comprehensive care stroke unit (acute and post-acute rehabilitation services within the one site), only 10% of the day was spent in therapeutic activities [134].

Stroke survivors are significantly more active in their own home environment then they are when undertaking inpatient rehabilitation. Manns et al. (2009) [135] measured the difference in number of steps taken and bouts of activity at one week prior to, and two and six weeks post discharge. One week prior to discharge, ten stroke patients spent an average of 183 (+/-39) minutes per day in ambulatory activities. On average, this approximate 3 hours of activity was comprised of 5541 steps, of which there were 58 episodes of activity (ie. activity bouts). Six weeks following discharge, stroke survivors performed 30 minutes more activity per day than they did whilst within the rehabilitation unit [135]. On average, patients in this cohort were able to walk with minimal assistance (performed >75% of the task), and only 'incidental' hands on help was required. Hence, these results may not be generalizable to all rehabilitation units.

The reasons why these survivors moved more once at home would have varied. Some hypothesised reasons may be that: (i) there is more opportunity to ambulate (fewer barriers), (ii) the environment may be more stimulating, inciting movement and encouraging the survivor to engage in their surrounds (iii) survivor motivation levels and mood may have improved once back in a familiar environment, and (iv) survivors were 'forced' to be more independent as there were relatively less people (or none) at home to assist them.

There are many other patient specific factors which may have influenced activity levels on discharge, but additionally, it could be argued that the surrounding rehabilitation environment has a role to play as well. For example, despite evidence indicating that inpatient activity is driven by therapists , these stroke survivors, who were relatively mobile on admission (and highly functioning), became more active once they went home (and without access to therapists). This raises another important question - *how*

physically active are stroke survivors in the home environment relative to healthy non stroke affected individuals living in the community?

Stroke survivors living in the community spend similar amounts of time on their feet performing physical activities (up-time) as their healthy aged matched counterparts, whether the intensity of this activity is comparable remains unknown. For example, the frequency of physical activity (measured via activity counts on an accelerometer) was significantly less in the 42 stroke survivors under observation [136]. Similar 'up-time' with fewer activity counts over a similar period of time suggest movements of stroke survivors were slower, which is conceivable considering the many motor impairments prevalent after stroke [136].

It is unclear whether the physical activity undertaken by stroke survivors is of an intensity level sufficient to exert the protective effects observed in the healthy population in regards to stroke risk reduction and event prevention. There is very little research concerning the energy expenditure of stroke patients performing physical activity during inpatient rehabilitation or even survivors in the community. Evidence for the effectiveness of regular physical activity in the prevention of recurrent stroke is less clear [16] and furthermore, has yet to be explored comprehensively in either animal models of stroke or human stroke survivors.

Given stroke survivors appear to spend (i) more time in physical activity once discharged from rehabilitation and (ii) as much time up on their feet as healthy aged matched individuals when in the home environment, it could be argued that rehabilitation unit environments restrict physical activity more than they do encourage it. Critical analysis of rehabilitation unit environment is warranted. This process may prove to be very beneficial given the accepted time frame of the critical period of stroke

recovery (best functional recovery is achieved within the first six to 12 weeks [67] following stroke) and that the majority of this time is spent within a hospital (ie. approximately four to five weeks [51,66]).

1.2.2.2 Cognitive activity

For the purposes of this thesis, ***cognitive activity*** refers to *any non-physical leisure activity which involves the participant actively engaging in a mental task. Examples include: reading a book or newspaper, listening to music or the radio, crosswords, puzzles, games, speech therapist prescribed language exercises, occupational therapy prescribed cognitive exercises, video games, writing, computer use and playing a musical instrument.*

This definition of cognitive activity is derived from the work exploring the link between the cognitive health of individuals without dementia and their participation in mentally stimulating activities [137]. These are in general non-physically based 'leisure activities' which require mental engagement. Examples include but are not limited to reading, participating in board or card games, doing word puzzles/crosswords, attending the theatre or listening to music. Grouped collectively as 'leisure' or 'recreational' activities, these are often included in population based studies which have explored the link between participation in cognitive activities and cognitive function (ie. onset of dementia or Alzheimer's disease) [137-140].

Efficacy of cognitive activity and the underlying biology of change

Research into the use of music and other cognitively stimulating leisure activities following stroke has only recently begun. For example, listening to music or audio books daily for one to two hours over eight weeks saw stroke patients in a pilot study report lower scores of depression – half as high - as those without access to such cognitive stimulation. Furthermore, this cognitively stimulated group had significantly larger increases in change scores indicative of better focused attention and verbal memory [141]. The understanding of how music alters the stroke-affected brain is in its infancy, but suggested mechanisms include: (i) activation of the dopaminergic mesolimbic system (enhancing arousal and improving mood) [142] ; (ii) reduction of cortisol levels (reduced stress) [143]; (iii) higher glutamatergic neurotransmission (augmenting learning and memory)[144]; and more generally (iv) enhanced molecular and structural plasticity associated with the 'enriching' nature of the musical stimulation[145].

Review of research which has explored the importance of the 'use it or lose it' principle in the prevention of dementia [146,147] suggests that frequent participation (3 times weekly over 12 weeks) in board gaming (Mahjong) which is cognitively challenging has been found to reduce cognitive decline (an average of 5 points on the Mini-Mental State Examination) [148] and symptoms of depression [149] in individuals with mild dementia. Cognitively challenging board games may also hold promise for people with stroke.

Furthermore, results from research investigating activities which incorporate physical, cognitive and social stimulation (multi-modal stimulation), such as interactive gaming and the Nintendo Wii[150] [151,152] in the stroke population suggests that there may be other cognitive based 'leisure' activities beyond reading and crossword puzzles which may be useful to employ as a compliment to conventional rehabilitation therapies. As will be

outlined in the following sections (Section 1.3), relatively more research in investigating the use of multi-modal stimulation (ie. that which promotes physical, cognitive and social activity) has been conducted in animal models of stroke.

Cognitive activity levels of stroke patients undergoing inpatient stroke rehabilitation

The majority of observational studies involving stroke survivors undergoing rehabilitation have been focused on measuring physical activity and as such have not classified other behaviours that may have therapeutic value. In many studies, activity classification is limited to physical or exercise related 'activity', or if not physically related, as 'inactive'[127,153,154] or 'unrelated'[128]. Such a description of 'inactive' behaviour has at times included tasks such as reading or doing crosswords, both examples of activities that require significant cognitive engagement, and as such could be classed as cognitive activities. Few list behaviours considered to be of a leisure, recreational or 'inactive' nature. Only one study made a distinction between such tasks, with 'active leisure' (reading) analysed separately to the leisure tasks of watching television and listening to music [130]. In this observational study, stroke survivors within two different rehabilitation units, spent approximately 3.5% reading, and 0.5% of the day (8.30am to 5.10pm) either watching TV or listening to music.

Two studies have found that participation in leisure [130] or recreational [155] activities comprise only a small part of a stroke survivor's total day (4% and 9% respectively). Further observational research specifically designed to assess this aspect of activity is required given not only the importance stroke survivors place on returning to pre-morbid leisure activities [156], but the possibility that frequent participation in such activities may contribute to better cognitive health longer term.

1.2.2.3 Social Activity

For the purpose of this thesis, ***social activity*** refers to *any interaction which involves verbal communication with people present or through telecommunication devices, and other nonverbal interactions such as touching, kissing or holding. Examples include: talking, laughing, touching, telephone/mobile phone/email/internet forum use and being present within a group of people engaged in 'group therapies/activities'.*

Efficacy of social activity and the underlying biology of change

The benefits of engaging in social activity after stroke have yet to be determined but research in animals where aspects of socialisation have been associated with better stroke recovery suggests this is an area of stroke research which warrants closer attention. Physical contact between animals[157] and recovering under relatively stable housing conditions [158] or just generally amongst other animals [159] has been shown to augment functional recovery and in some cases even reduce lesion size [157].

Stroke survivors undertaking inpatient rehabilitation value social interactions, both with their therapists and fellow patients [160]. Despite this, the importance of social activity in stroke recovery is yet to be completely understood. Data available from the few studies which have been conducted with stroke survivors suggests there is a positive relationship between the frequency of social interactions and mood and quality of life. Stroke survivors in the community reporting infrequent engagement in social activities are more likely to experience post-stroke depression [161], be more dependent in ADL [162] and score low on surveys of HRQoL[42] . For example, simply talking to people or engaging in structured leisure activities both early (< 2 months) [42] and much later (> 2 - 7+ years) [163] following stroke is associated with better HRQoL. Socially active stroke

survivors score higher in HRQoL domains which incorporate both physical and cognitive functioning (emotional role and mental health). Although this association exists, many larger studies are required before we can conclude that social activity plays an important role in stroke recovery, and to establish if there is a causal link between the two.

How social interaction may cause these effects is poorly understood, but factors such as alterations in inflammatory, neuroendocrine (ie. level of oxytocin [164]) and plasticity processes are believed to play a role. Levels of anxiety and aggression, basal metabolism, heart rate and core body temperature have been found to differ between those animals housed in isolation and those in social conditions [157], so these variables may be involved as well.

Social activity levels of stroke patients undergoing inpatient stroke rehabilitation

Nearly every major observational study involving stroke patients in this setting has revealed that a significant proportion of a stroke patient's day is spent alone [128,129,131,132] or in solitary activities [125,154,165]. Research to date has estimated how much of the day is spent with and without a particular group of people (eg. relatives, staff or patients). Types of social interactions, such as: talking, holding, touching, laughing or even phone conversations, have rarely been studied. Furthermore, only King et al. (2011) [134] have attempted to categorise the social activity of communication into receptive and expressive communication. The 11 stroke patients in this rehabilitation unit were observed in receptive communication 26% of the day and in expressive communication 16% of the day. Unlike studies of physical activity, it can be challenging to classify subtle activities using observation. King et al. found the inter-rater reliability of this

classification was low (k=0.4, for expressive communication), despite the use of trained observers.

Studies using observation often measure people present with a stroke patient, with the underlying assumption that when someone is with a patient an interaction is occurring. While whether someone is there or not can be reliably measured, this simple classification does not truly measure social interactions. Furthermore, data from animal models of stroke suggests that the physical contact component of socialisation, may have beneficial effects on sensorimotor recovery [157]. Hence, more research is required which specifically quantifies social activity, both verbal and non-verbal social interactions, and to understand the role both types may play in brain recovery.

Achieving maximal activity levels of stroke patients within a busy rehabilitation unit may require new approaches. Current observational data indicates onsite access to and management by an experienced multi-disciplinary rehabilitation team does not foster an active rehabilitation environment. The patient's rehabilitation environment should be one which encourages them to be as active as much as possible, throughout the entire waking day. One which entices them to practice the functional skills learnt during therapy, and from what we know is important in animal data, practice them a lot. The ideal arrangement would be a unit in which stroke patient activity was facilitated, not by the therapists, but by the surroundings itself. A rehabilitation environment in which the distinction between 'therapy' time and 'non-therapy' time need not even exist; an environment where most of the day was spent in activity, not inactivity.

1.2.3 CONCLUSION

Engaging in higher levels of physical activity after stroke has been found to be beneficial in both animal and human models of stroke. There is growing evidence that non- physical based activities offer value as well. The evidence presented in the preceding section suggests that human stroke survivors are recovering in environments that do very little to promote activity. There is a strong relationship between independence (in both physical and non-physical functional tasks), mood and health related quality of life. Hence it would prove useful to encompass all types of purposeful behaviour (physical, cognitive and social) when observing the stroke survivor in the clinical setting. This will be done in the first stage of the clinical trial associated with this PhD **[Chapter 4: Publication 2]**. One intervention derived from the laboratory setting which has been used extensively in animal models of stroke, and by design facilitates activity, is an enriched environment.

1.3 ENRICHED ENVIRONMENT: IN ANIMALS

An enriched environment was conceived and has been thoroughly explored in the laboratory setting. It describes conditions which encourage all types of activity. Organisation of the environment and provision of equipment within an enriched environment facilitates sensorimotor (physical), cognitive and social stimulation, and therefore activity in general [90]. This section outlines the origins, features of and evidence relating to the use of an enriched environment in animal models of stroke.

1.3.1 ORIGINS

Results from Canadian neuropsychologist Donald Hebb's work in 1947 investigating the influence of environment on memory and learning, generated much interest around the concept that brain function and organisation may be experience dependent. Hebb found that rats set free to roam throughout his house, had better learning and problem solving skills than those caged in standard housing conditions in his laboratory [166]. Rosenzweig and his colleagues developed the principle of environmental enrichment further, creating the treatment paradigm and model known as an 'enriched environment [167].

1.3.2 DEFINITION

Originally, environmental enrichment was a term used to describe housing conditions which provided the opportunity for inanimate and social stimulation [168]. Compared to deprived (one animal in one cage) or standard (two to three animals per cage) conditions, which most often involve small cages without contents but free access to food, water and nesting; enriched cages are larger in size, contain on average eight to

twelve animals and are filled with objects and toys which are frequently changed and or rearranged (see Figure 2a and 2b). Animals in such an enriched environment are free to voluntarily explore and engage in challenge-free interaction with each other and the cage contents [169]. Animals are not forced to do any particular task [170]. It remains the most popular model for exploring the effect a stimulating environment has on brain development, recovery from injury and response to degenerative disease.

Current models of environmental enrichment aim to enhance an animal's opportunity for sensorimotor, social and cognitive activity. Sensorimotor (or physical) stimulation in an animal model of enrichment is provided via the cage contents which may include but are not limited to such items as novel inanimate objects (balls and toys), horizontal boards, ladders, chains, tunnels and ropes. Additional voluntary 'exercise' is available due to the increased space available in the larger enriched cages, and in some cases through the presence of a running wheel [90]. The main source of cognitive stimulation within the enriched cage occurs through frequent removal and addition and/or rearrangement of cage contents as this requires enriched animals to formulate and continually update spatial maps associated with their environmental surrounds [90]. Although not commonly employed, cognitive activity has also been encouraged in environment enrichment models where access to food, treats or water is dependent on successful completion of mazes or tunnels within the enriched cage [171]. Social activity is enhanced by increasing the number of animals per cage [90].

(a)

(b)

Figure 2. Laboratory rats housed in (a) standard environment [172] and (b) an enriched environment (reproduced with permission from Mora, Segovia, & del Arco 2007 [173]).

1.3.3 EFFECTS OF AN ENRICHED ENVIRONMENT

1.3.3.1 Cellular and behavioural effects

The healthy brain

Healthy animals exposed to an enriched environment have been shown to have heavier and larger brains with thicker cortices, greater dendritic branching, and have greater spine length and density [174]. Exposure to an enriched environment has been associated with enhanced synaptogenesis [175] and neurogenesis [176] . Behavioural effects found to occur in normal healthy animals exposed to an enriched environment include: improvements in learning and memory, a reduction in anxiety related behaviour, and conversely an increase in exploratory behaviours (for a detailed review see [90]). Recently, work has been published which revealed significantly lower rates of death in aged and ageing animals exposed to an enriched environment [177].

Neurodegenerative disease

Exposure to an enriched environment has been associated with a delay in the onset and progression of Huntington's disease in mice expressing a human Huntington transgene [178,179] and the augmentation of learning and memory in transgenic mouse models of Alzheimer's disease [90]. Environmental enrichment in rat models of Parkinson's disease enhances motor recovery [180]. Additionally, there is a small amount of data to suggest that both the motor and cognitive deficits associated with traumatic brain injury can be reduced, and exploratory activity increased in animals with epilepsy (kainic acid induced seizures)[181,90].

Stroke

Cellular effects

There is evidence that the structural changes occurring in the injured brain of enriched animals after experimental stroke are related to the process of cortical re-organisation [80,182]. These changes within the neural circuitry are thought to be instrumental in the recovery of functional skills and or in the acquisition of compensatory strategies (ie. successful performance of a motor task but with different limb kinematics to that used prior to the brain injury) [79]. The structural alterations seen post-stroke in an enriched environment are similar to those found in healthy animals raised in an enriched environment, and include: a greater number of dendritic spines [175] (see Figure 3), normalised astrocyte-neuron ratios [183] and an increase in the level of neurotrophic factors such as brain derived neurotrophic factor (BDNF) [184].

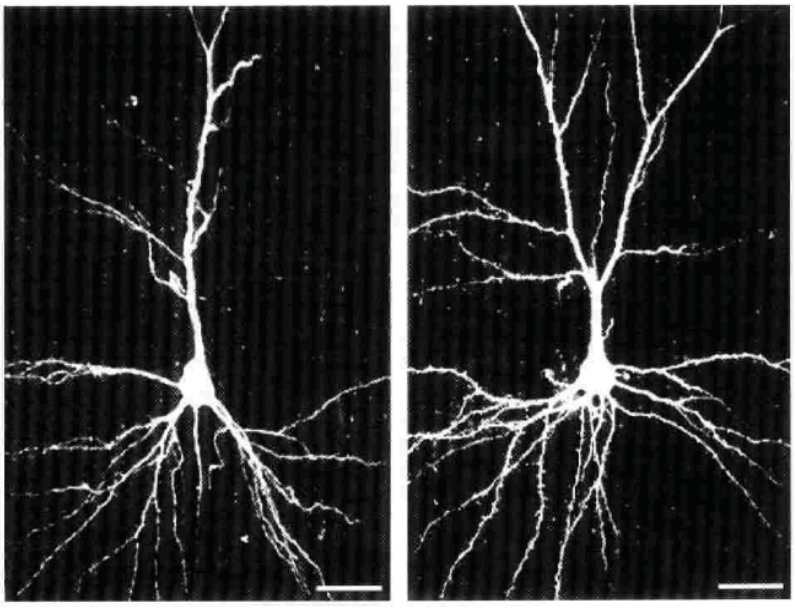

Figure 3. Dendritic branching of pyramidal neurons from the somatosensory cortex of a rat following housing in (a) non-enriched and (b) enriched conditions for 3 weeks (reproduced with permission from Johansson and Belichenko 2002 [175]).

Behavioural effects

Sensorimotor function

All but a few [185-187] studies in which environmental enrichment has been tested in animal models of stroke have found that enriched animals recover sensorimotor function significantly better than animals housed in either standard or deprived conditions. These results are obtained from studies which have used small sample sizes. Debate continues regarding whether such improvements in function are due to the restoration of motor skills or as shown recently in an experimental model of environmental enrichment after stroke, through the development of compensatory movements [171]. Additionally, as a measure of disability has yet to be developed for use in animal models of stroke, it remains unclear how much of an impact these functional gains have on their ability to perform tasks required in daily life. Regardless of this, the majority of studies on environmental enrichment reveal functional benefits without a significant increase in infarct size [170,186,188-191]. Furthermore, one study has revealed that animals housed in an enriched environment prior to and following stroke recovered at a significantly quicker rate and to a greater extent than animals housed in standard conditions prior to stroke and then housed in enriched or deprived conditions [188].

Cognitive function

There are some conflicting results about the effects of environmental enrichment on post-stroke cognitive function. Most studies have detected improvements in those exposed to an enriched environment [94,187,192-197] , however some have not shown any improvements [193,198,199]. Housing conditions of the control animals and contents and protocols of the enriched cages varied greatly amongst these studies. Although the

majority of data indicates an enriched environment improves cognition, in particular spatial memory, heterogeneity in study design makes it difficult to make any firm conclusion on the effect of enrichment on cognition.

Stress and mood

There is very limited evidence currently available concerning the effect that exposure to an enriched environment has on indicators of stress or mood in animals recovering from stroke. The data concerning whether an enriched environment is stressful for *healthy* animals is again conflicting [200]. Many researchers use higher levels of corticosteroids as a marker of stress, however higher levels may not necessarily indicate an animal is negatively affected by being stressed. The most recent data indicates that other measures of stress, such as body weight gain and adrenal gland weight, were comparable in healthy animals housed in an enriched environment for six weeks and those housed in standard conditions [201]. Furthermore, when subjected to a stressful act, although peak levels of corticosteroids were similar in both the enriched and non-enriched animals, corticosteroid levels of enriched animals returned to baseline much quicker. Taken together these results suggest that the stress experienced by animals housed in enriched conditions, and the physiological changes which occur as a result, may in fact prove to be beneficial.

One hypothesis proposed for this rapid return to baseline levels of corticosteroid is that the constant novelty and accumulative effect of constant sensory and cognitive stimulation equips the animal to be a little more resilient in the face of future stressful events. That is, they may adapt more readily to new situations, which other non-enriched animals may find stressful [201].

1.3.3.2 Mortality and infarct size

Rates of death are one of the main outcomes used to evaluate the risk of harm associated with an intervention in animal models of stroke. However relatively few studies present mortality rates. Results which have been published have failed to demonstrate any significant difference between the number of deaths with either housing condition [170,190,198,199,202].

Another outcome commonly used to evaluate the adverse effects of stroke therapies in animals is infarct size. It's inclusion in research involving non-pharmacological therapies stems from the small amount of animal data using constraint induced movement therapy following stroke which suggests excessively early activity may result in larger lesions (ie. greater brain damage) [203]. The majority of enrichment studies to date have revealed there to be no significant difference in the size of lesions in animals housed in standard (or deprived) conditions and those exposed to an enriched environment [188,189,204,205].

For outcomes that are rare (mortality), or where the effect size is anticipated to be relatively small (infarct volume), small studies are not adequately powered to detect differences. However, it is possible to pool data from these small individual studies and conduct a systematic review and meta-analysis to help determine the effectiveness of environmental enrichment after stroke. **[Chapter 3: Publication 1]**.

1.3.4 PROPOSED MECHANISMS

The underlying mechanism by which an enriched environment affects the animal brain is unknown. Two theories discussed in a reputable review of the neural consequences of

environmental enrichment are based on the hypotheses of arousal and of learning and memory [206]. Briefly, the arousal theory proposes that the cerebral and behavioural alterations following environmental enrichment stem from biochemical changes that are triggered by a "…transient increase in the electrical activity…" of the animal's brain (Walsh and Cummins, 1975, p.989) [207]. It is thought that this 'arousal reactivity' relies on the stimulating objects to be novel or have a special significance to the animal [207]. The learning and memory hypothesis stipulates that the biochemical processes associated with learning are responsible for the anatomical and functional changes seen in the brains of enriched animals [208]. Whatever the means are by which experience in a stimulating environment evokes its effects, there is good evidence that it augments plasticity of the brain [80,90,182].

1.3.5 MANY UNKNOWNS

1.3.5.1 Is there a critical time period in which to commence environmental enrichment?

This important question remains unanswered. The majority of studies have found significant improvements in sensorimotor function can be achieved when starting as early as one to two days post-stroke [170,192,196,199,205,209,210]. There is evidence as well indicating gains are obtained when environmental enrichment is commenced as late as two weeks after stroke [95,204]. This is contradicted by a small amount of data suggesting that as time to commencement increases, sensorimotor gains decrease [95]. Furthermore, there may be a certain time point after which enrichment fails to exert any effect [211].

1.3.5.2 Is there an optimal dose?

There is still a shortage of evidence surrounding the ideal dosage of environmental enrichment. A small amount of data indicates both three and 24 hours a day of enrichment contributes to better sensorimotor function [190]. A similar relationship has also been shown in healthy animal models, where exposure two hours a day enhanced learning and memory as effectively as exposure 24 hours a day [212]. As is very common in animal research, the sample size calculation in both of these studies was not included with the published results. Hence there is a possibility that a Type II statistical error is present in both, whereby the studies were not adequately powered to detect a significant difference between these groups receiving different a dosage of enrichment. The dose response effect of environmental enrichment is yet to be determined. Lastly, better maintenance of functional recovery has been associated with a longer period of exposure (in days) [190,211]. Overall the evidence surrounding dose is insufficient to draw any firm conclusions.

1.3.5.3 Which component (physical, cognitive or social) contributes most to the improvements observed?

Discussion continues around the importance of the individual components to the change in neural, sensorimotor and cognitive function observed in post-stroke enriched animals[206-208]. Physical activity (ie. voluntary running on running wheel) in isolation, is not as effective in improving functional recovery as exposure to all the components together [170,198], and one study indicates it may even be harmful [198]. Animals in this latter study had unrestricted access to a running wheel in singly housed cages. Unlike humans in a similar circumstance (ie. exclusive and easy access to exercise equipment), rats will

run for very long periods of the day, hence interpreting these findings with respect to humans is difficult. Environmental enrichment promotes the survival of newly generated neurons, but physical activity by itself has been shown to impede their survival [209]. Additionally there is a small amount of evidence which indicates social features of enrichment may be more influential than physical features following stroke [170], however this area is much less studied than the influence of physical activity. The importance of the cognitive component of enrichment is still yet to be investigated. To date, comprehensively enriched animals have always out performed those housed in conditions reflecting the individual components [170,198,209].

The interaction of all components (physical, social and cognitive), rather than each in isolation may be responsible for the favourable effects seen in animals recovering from stroke [206]. Cleverly designed studies are required to tease out whether, if at all, one component is more influential than the others. However, the inherent complexity of these enriched environments may ultimately limit the success with which this question can be answered.

1.3.5.4 Does environmental enrichment exert its effect differently on an aged brain?

The majority of work has used animals of adolescent age, but there is some data from enrichment work involving aged animals. Despite older animals (20 months) recovering motor function at a slower rate and to a lower level than adolescent animals, enriched conditions are still more advantageous to this group than are deprived conditions [196].

Results also suggest that there may be an age dependent relationship between environmental enrichment and infarct size. [213]. Very young rats (ten days post natal)

exposed to environmental enrichment following stroke have been found to have significantly less cortical damage than relatively older rats (nine and 25 week old rats) raised in the same conditions. Additionally, exposing aged rats to enriched conditions following stroke appeared to increase lesion volume (compared to those recovering in standard housing). It is important not to over interpret these results which are derived from work involving a very small number of animals. Considering the large proportion of elderly stroke survivors clinically, more animal work investigating the effects of enrichment on lesion size of the aged brain is warranted.

1.3.5.5 Does environmental enrichment prior to stroke make a difference?

There is scarce evidence regarding the effectiveness of pre-stroke enrichment. Data indicates animals housed in enriched environments both prior to and following stroke have a slight advantage over those exposed post-stroke only [188]. In particular, these animals appear to regain function a little sooner and to a slightly higher degree than those exposed after stroke. Higher levels of physical activity prior to stroke in humans has been shown to be associated with better functional recovery. There may be a similar trend with environmental enrichment in humans whereby 'enriched activity' prior to stroke may prove to be just as beneficial. There is a small amount of clinical data indicating that greater participation in physical, cognitive and social activity prior to stroke is associated with better functional recovery [214].

The effects of an enriched life prior to stroke may be similar to the hypotheses provided by researchers in the field of Alzhiemer's Disease; that living an 'enriched life' may enhance the brain's cognitive reserve [215]. That living a life filled with physically,

cognitively and socially stimulation equips your brain with the capacity to compensate for degenerative disorders or in relation to brain injury, stroke.

1.3.6 CONCLUSION

In summary, further work is required before we can be confident that environmental enrichment may be a promising intervention in improving post-stroke outcomes. Inconsistent results, coupled with the fact that the majority of studies have only used relatively small numbers of animals, highlights the need for a systematic review and meta- analysis of the work investigating the use of an enriched environment in animal models of stroke. It has been suggested that joint systematic reviews and meta analyses aid researchers to better select the most promising interventions for investigation in clinical trials[216]. Hence, conducting a review and applying meta-analytic methods to the literature concerning the use of an enriched environment in animal models of stroke was an important initial step in this PhD **[Chapter 3: Publication 1]**.

Data presented in the preceding section suggest that current rehabilitation units may be more representative of the 'standard' or 'deprived' housing conditions modelled in animal models of stroke. Hence, testing the efficacy of an enriched environment in the clinical setting is not only possible (ie. an enriched rehabilitation unit environment compared to a rehabilitation unit delivering standard care), but when we reflect on the impact of stroke now and the burden it has been predicted to cause in the future, this investigation is very much needed. Despite the clinical data obtained over the last 30 years suggesting patients are inactive and the favourable results from individual studies of the use of environmental enrichment in animal models of stroke, this paradigm has yet to be utilised as a strategy to promote activity and functional recovery in the clinical

setting. Components of environmental enrichment have been used with stroke patients in the inpatient rehabilitation units. Most of the studies discussed in the following section, have either lacked the statistical power (ie. small sample sizes) or have failed to include the necessary outcome measures to determine functional efficacy.

1.4 ENRICHED ENVIRONMENT: IN THE CLINICAL SETTING

Components of environmental enrichment have been investigated for use in the human stroke population, but a model of environmental enrichment as used in animal models, has not. This section outlines work which has been performed in humans regarding the 'enrichment' of human environments and is then followed by a discussion of results obtained from clinical stroke trials which have examined individual components of the model of environmental enrichment akin to that used in animals.

1.4.1 USE IN NON-STROKE POPULATIONS

Studies investigating the use of 'enrichment' in humans have revealed beneficial effects. However the term enrichment encompasses a broad scope of interventions in both non-clinical and clinical settings. Environmental enrichment, as applied in humans can be divided in to two main categories. The first method of environmental enrichment produces a stimulating environment by altering the organisation or delivery of services (organisational enrichment). For example, delivering teacher/therapist led educational or leisure classes or providing more nutritious food, would be considered organisational enrichment. Here individuals within the environment have little choice whether they accept the enrichment: they are a 'passive' participant within their changed environment. The second which is similar to that which occurs in animal models, creates an enriched environment by changing the participant's surrounds and or adding objects which are designed to promote activity or a change in an individual's behaviour (geographical enrichment). In this approach to environmental enrichment, individuals in

these conditions have greater choice in whether they will interact with the enrichment activities within their surroundings. Examples of geographical enrichment designed to promote voluntary engagement in activity includes changes to the ward layout of a hospital and or the provision of activities and equipment within a ward environment which are of interest to the participant (i.e. music and or games).

Enriched environments in clinical studies have been associated with improvements in: the behaviour and intelligence quotient (IQ) of institutionalised children with intellectual disabilities when exposed to enrichment in the form of education and social interaction [217,218], and the weight and height, academic achievement and IQ of orphans following removal from a deprived environment (an orphanage) [219]. Enrichment of the environment of children growing up in impoverished villages in a developing country, in the form of better education and nutrition, has resulted in an increase in arousal and attention [220] . Significant improvements were found in the neuropsychological functioning of elderly residents in a deprived institutional environment that were given greater access to social and leisure stimulation, planned activities and motivation through the use of a token system [221]. Lastly, the term environmental enrichment has been used by reviewers discussing the general therapies and use of virtual environments in paediatric brain injury rehabilitation[222,223] .

In almost all of this work, environmental enrichment participants are compared against relatively 'impoverished' conditions. Just as in experimental models, it is possible that the results of such studies highlight the harmful effects of environmental deprivation rather than the beneficial effects of enrichment.

Human enrichment research has placed very little emphasis on the importance of free exploration of or choice within the individual's environment. In experimental research

the animals ultimately determine the level of the environment induced activity. The majority of examples of human enrichment research provided above involve the investigators or service providers controlling the provision of services (ie. the enrichment). As such, their presence and or involvement in the delivery of services is likely to have a significant effect on the uptake of participation and any associated behaviours; the subjects exposed to the enrichment play a less passive role than do the animals in experimental models of this paradigm.

Implementation of enrichment type research in the clinical setting indicates that changing behaviour of both patients and health professionals is very difficult to achieve and maintain [224] [225]. The type of enrichment employed in this clinical work has involved increasing or adding new services. Delivering these additional services is reliant on the capacity to employ more staff or increase existing staff workload. Furthermore, these interventions are likely to be staff, not patient, driven and as such incur greater costs through the need for more labour and staff time.

In contrast, the paradigm of environmental enrichment as defined and researched in the laboratory, if applied into the clinical setting has the potential to be very cost effective. After the initial purchase of equipment, there is unlikely to be many additional expenses for the activity is participant, not clinican driven. Engagement in the enriched environment, which is better access to physical, cognitive and social activity, is voluntary. The participant decides how much they actively participate.

1.4.2 NOVEL ENRICHMENT ACTIVITIES USED IN THE STROKE POPULATION

1.4.2.1 Music

As is often used in Parkinson's Disease [226], music as rhythmic auditory feedback has been incorporated into stroke patient therapy sessions to facilitate better gait [227,228]. Post-stroke exposure to music within a rehabilitation unit, either formally as individualised 'music therapy' or informally in group sessions has been investigated as well. Most of this work has involved small underpowered studies and based on the study design and methods presented, held considerable bias in favour of the intervention groups. One of the earliest studies, a pragmatic randomised controlled trial, reported that chronic stroke survivors receiving group music sessions once a week over 12 weeks, demonstrated improved emotional stability and greater spontaneous social interaction [229]. Music therapy groups within a rehabilitation unit have been shown to enhance social interaction, mood and stroke patient participation in therapy [230,231]

There is only one clinical randomised controlled trial to date which has explored the effect that musical enrichment (ie. a form of cognitive stimulation) has on post-stroke outcomes. Sarkamo and colleagues found that the provision of self-selected music to acute stroke patients, in conjunction with encouragement to listen to this music for a minimum of one hour a day, resulted in significant improvements in verbal memory, focused attention and mood relative to those simply listening to audio books or receiving standard care (i.e. no additional stimulation) [232]. The study (n=60) had several limitations, the most important being the inclusion of multiple outcomes (ie. >20).There were no pre-specified (primary or secondary) outcomes and the alpha level for this

study was set at 0.05. Additionally, although there was no statistically significant difference between the groups in terms of the proportion using mood altering medication, the clinical effect of these absolute differences warrants discussion (ie. 50% in the intervention group and 30% in the control group). Specifically, it is difficult to attribute the significant difference between the depression scores of patients in the music group and control group (favouring the music group) to the use of music alone when we consider nearly three times as many patients were on anti-depressants in the music group than in the lower performing control group. Furthermore, the effect of this disparity in medication use may extend to the cognitive measures which were found to be better in the music group (ie. verbal memory and focused attention were better in the music group which could have improved as a result of better mood through use of anti-depressants).

The use of anti-depressants is especially important to consider given the link between music, mood and cognition (discussed in the following paragraphs). Hence, this study should be considered more an exploratory study, one which can inform a much larger randomised controlled trial. One which is adequately powered based on pre-specified outcomes.

Although there appears to be a positive link between the use of music and post-stroke recovery of cognitive function and mood, there is no certainty regarding how simply listening to music results in such favourable outcomes. There are many issues to consider. For example, certain factors, including the music's tempo, complexity or key signature may play a role. It could simply be how much the stroke survivor enjoys a particular piece of music [233], or even more difficult to study, the role it may play in evoking memories and emotions.

Hypotheses concerning how music alters the behaviour of a stroke patient and most importantly their brain are derived from both animal and human research. Music exerts it's effects: (i) through greater arousal and improved mood which results from activation of the dopaminergic mesolimbic system (and perhaps also involvement of noradrenaline system), (ii) reduced levels of stress and the prevention of depression through lowering cortisol levels, (iii) improved learning and memory arising from increased glutamate-based neurotransmissions, and lastly as is most relevant to this thesis (iv) enhanced molecular and structural plasticity associated with the 'enriching' nature of the musical stimulation [144].

Work involving the use of music in animal models is difficult to interpret and extrapolate into the clinical setting, since the meaning and effect of music may be very different to animals than to humans. For example, the effect of familiar music on a human brain which is injured and belonging to a person who is most probably in shock and or depressed, is likely to be very different to a laboratory rat which is hearing this music for the first time (and of which there is unlikely to be any emotional significance). Hence understanding whether and how music contributes to better post-stroke outcomes is very complex and will most probably require many (large) studies in both healthy and stroke affected populations.

1.4.2.2 Interactive gaming

The commercially available gaming console, Nintendo Wii incorporates the three main components of environmental enrichment. It could therefore be considered 'multi-modal stimulation'. Depending on the game selected, use of the Nintendo Wii requires: (i) some form of physical activity, involving at a minimum, the upper limb, head and or trunk, (ii) cognitive involvement through problem solving, visuospatial memory and short term memory, and (iii) social interaction between players of the game. Add on to this the competitive nature of the gaming (between players or with the computer), the provision of immediate feedback, the enjoyment factor and to most, especially in an aged stroke population, it's novelty, and the Nintendo Wii appears to be an ideal tool by which to 'enrich' conventional therapy.

Results from the few individual randomised controlled studies of the use of Nintendo Wii conducted to date indicate this intervention may be not only feasible to include in stroke rehabilitation, but may contribute to better post-stroke function. Used in conjunction with conventional therapies in the first three months post-stroke, Nintendo Wii has been shown to reduce the severity of stroke induced motor impairment. Although deemed feasible, these results are based on a small number of patients (n=16) [151]. Excitingly, a small study (n=12) of the Nintendo Wii later on in in the stroke recovery phase (ie. an average 12 months post-stroke) showed improvements in motor performance and functional use of the affected limbs (as perceived by the stroke survivor) [150]. No effects were observed on measures of balance, dexterity or spasticity. Similarly to the Sarkamo et al. (2008) study discussed previously (pg 53), alpha levels were not adjusted to accommodate the multiple outcomes included. In this case over 25 outcomes were measured and analysed. It is appropriate to the design of a preliminary,

hypothesis generating study to use multiple outcomes. These preliminary findings need to be confirmed in larger randomised controlled trials which are powered to reflect the number of outcome measures under investigation.

This uncertainty though does not prevent discussion around how these gains in function, both during the subacute and chronic phase of stroke recovery may result. Is it for example, simply a result of using or training the affected limb, body part, or body system (balance, cognition) more? Or does the pleasurable nature of this activity trigger release of neurotransmitters which are important in learning (ie. dopamine) [234,235]?

As with music use in this patient population, the mechanisms by which interactive gaming such as Nintendo Wii contributes to better stroke outcomes are complex and yet to be clearly defined. Although it is not known how music and interactive gaming contribute to these effects, both are positive additions to an environment in which patients have been repeatedly shown to do much more than sit inactive by their bed all day.

1.4.2.3 Reading, visual arts and dancing

Presently the strength of evidence regarding the efficacy of reading, art (visual) and dancing in stroke rehabilitation is weak. There are several case reports which indicate their inclusion in conventional rehabilitation has been of value [236-238]. Furthermore, there is some work outlining the benefits of art based activities delivered in groups, but data is predominantly qualitative, with only a small sample of quantitative data from underpowered pilot studies. As outlined below, the majority of research has focused on the emotional effects of exposure to art based activities alongside inpatient stroke rehabilitation.

In the only study which has examined the use of reading (groups) with patients recovering from stroke, employed actors read to individual patients or small groups of patients (n=21) [237]. Reading material was chosen by the patients from the unit's library of books or from their own personal collections. Again, patient experience was overall positive. They reported that the reading provided them with stimulation; it stimulated their mind and conversation, improving their motivation to socialise with others. There were also signs that participation in the reading groups facilitated patients interest in rehabilitation therapy sessions, and in one participant encouraged physical activity outside of therapy hours (ie. the reading group reignited his interest in reading and he wanted to walk to the library to read independently). Furthermore, patients perceived that the reading groups were a 'distraction in a setting which provoked anxiety and boredom'. Unfortunately, as in similar research involving the arts, staff did not consider the reading groups as important as conventional therapy, that it was entertainment and were concerned that it would increase their workload [237]. The patients were not forced to attend the reading sessions and this intervention was driven by the actors paid to read. Hence, the sustainability of this approach is questionable as it is likely to rely on passionate staff or adequate funds to employ readers. These results though do indicate that patients enjoyed this type of stimulation.

Visual art and other artist modalities (ie. clay and painting) have been investigated in stroke rehabilitation to a lesser degree than music [238 239]. Results from this work suggest that stroke patients enjoy participating in these types of activity whilst they are receiving stroke rehabilitation. As this work does not extend beyond a single case study or a qualitative analysis of a group of patients, of which three were survivors of stroke, this conclusion cannot be assumed to be representative of the stroke population in general.

The most recent research incorporating art into stroke rehabilitation may have the most informative data to date. Again outcomes on cognitive or physical function were not collected, but rigorous and accepted qualitative methods were employed. Bauman et al. (2012) explored patient experience of an arts programme (group based) designed for use in long stay stroke rehabilitation [240]. Four to six sessions were delivered to the patients by professional artists who specialised in a variety of activities including creative writing, dance/movement, visual arts and music. Art activities varied between sessions and the guidelines of the programme were underpinned by a patient-centred philosophy.

Again, qualitative interviews revealed that the patients enjoyed this activity and believed it allowed them to engage in purposeful occupation. Interestingly, other benefits reported by the patients suggest that the addition of these artistic activities to standard rehabilitation was enriching For example, the art sessions provided them relief from boredom and they valued the mental stimulation, learning and creativity which it brought. As detailed in Section 1.3, these themes echo the aims of an enriched environment in animal models of stroke. Frequency of use was not quantified formally, but the artists involved in the groups did note the various ways patients engaged in each art form, both passively and actively. Overall, patient experience was positive, but there were a few isolated negative experiences. For example one patient had difficulty in choosing what activity to undertake, whilst another was saddened by her inability to perform an activity she enjoyed prior to stroke.

Dancing has yet to be formally examined as a strategy to enhance functional recovery after stroke. As does interactive gaming (ie. the Nintendo Wii), dance incorporates all facets of environmental enrichment-physical, cognitive and social activity. The benefits of rhythm and music, which are aspects of dancing, is currently being investigated in

the chronic stroke population. Data for outcomes including participation, mood, physical and cognitive function, quality of life and blood biomarkers are being gathered. These results, which are expected by early 2014, will help us gain a better understanding of the role music can play in stroke recovery [241].

1.4.3 CONCLUSION

In summary, a model of environmental enrichment, through simultaneous provision of physical, social and cognitive stimulation, as defined in experimental research, has yet to be explored in humans. A few small studies that have explored aspects of environmental enrichment in stroke patients suggest that extra stimulation may improve patient experience of rehabilitation through better mood and increased motivation levels, and there is a small amount of pilot data suggesting it may augment recovery of post-stroke cognition. Much more adequately powered and well-designed randomised controlled trials are required if we are to understand the benefits of such interventions following stroke.

The overall goal is to conduct a clinical trial to determine the efficacy of enriching the environment of stroke patients within rehabilitation units. An important initial step (and the purpose of the clinical trial associated with this thesis) is to establish the feasibility of an enrichment strategy akin to that used in animal studies. In particular, we sought to determine whether it increases activity levels of stroke patients.

1.5 ENRICHED ENVIRONMENT: BENCH TO BEDSIDE

1.5.1 PROPOSED MODEL

To be considered enriched in animal models, the environment must: (i) enable socialisation (large numbers of animals) (ii) contain inanimate objects which can be easily accessed and interacted with and lastly, (iii) the contents or structural arrangement of the environment must be changed or rearranged frequently so as to ensure novelty [242]. The main feature lacking in the majority of attempts at 'enrichment' in human populations is the participant's freedom to participate voluntarily in any of the enrichment activities.

Two of these three criterion are achievable within the workings of a busy mixed rehabilitation ward. Patients recovering from stroke in a hospital ward setting can be provided with an environment which:

(i) facilitates greater socialisation and,

(ii) contains objects and activities which they can access and use.

The enriched environment model developed in the clinical trial associated with this PhD was largely influenced by what was feasible, safe and easily integrated into a busy rehabilitation unit. This required consultation with the nursing unit manager and staff working in this unit. The layout of the unit and certain processes in place (ie. storage of equipment and unit routines) prevented a model in which patients could sleep and eat within an enriched environment (as is done in animal models of stroke). Importantly as well, the environmental enrichment developed for this typical rehabilitation unit, sought to minimise staff involvement. That is, as is the case in animal models of environmental

enrichment, we sought to arrange items and activities within the stroke patient's unit which were easily accessed (by the patient themselves, not staff). Ideally, we sought to designate a section of the unit as a 'patient area', and arrange the furniture and activities within this environment which was (i) novel and (ii) increased the opportunity for physical, cognitive and social activity.

Hence, a pragmatic approach was adopted and the model of enrichment developed for this unit encompassed (i) individual enrichment and (ii) communal enrichment. Individual enrichment involved access to objects and items of interest to the patient at their bedside. These items were portable so could be taken around the rehabilitation unit if so desired by the stroke patient. Communal enrichment describes an area within the rehabilitation unit where all stroke patients (and other rehabilitation patients) had free and easy access to interesting activities and objects. This was set up in the dining area of the unit, and furniture was arranged to encourage socialisation, especially during meal times. Greater detail of the enriched environment used is given in the published protocol presented in **Chapter 4: Publication 2**.

1.5.2 ACTIVITY LEVELS AS A MEASURE OF FEASIBILITY.

The feature of enrichment believed to be responsible for these gains is the increased animal activity, a behavioural response resulting from recovering in an environment which is stimulating – one which provides greater physical, cognitive and social stimulation.

The efficacy of environmental enrichment in humans, specifically after stroke, has yet to be determined in the clinical setting. Important steps must be taken before we undertake a large (adequately powered) study to determine efficacy of this intervention

in the clinical setting. It is important to firstly determine if a model of environmental enrichment similar to that used in animal models but developed specifically for the clinical setting, can facilitate physical, cognitive and social activity. Hence, the specific research question under investigation in the pilot study was: does a human equivalent model of environmental enrichment promote activity, specifically physical, cognitive and social activity? This required an understanding of how these three types of activity can be measured in stroke survivors undergoing inpatient rehabilitation.

1.6 MEASURING ACTIVITY LEVELS IN STROKE SURVIVORS

1.6.1 TOOLS USED TO MEASURE ACTIVITY

1.6.1.1 Physical activity

Physical activity levels of stroke survivors have been measured in many studies in different settings and at different stages in the stroke recovery phase. Many methods have been used to quantify this physical activity data, the accuracy of which is dependent on the measurement tool used and the setting in which it is applied. Choice of tool may also be dependent on feasibility and price, particularly in larger studies.

There is a variety of measurement tools available to measure levels of physical activity. These include: direct behavioural observation, questionnaires, interview, physiological markers (ie. heart rate, calorimetry-doubly labelled water method) and motion sensors (ie. accelerometry) [243]. *Behavioural observation* and the use of *doubly labelled water* to measure total energy expenditure, are both considered to be the 'gold standard'; that is, these methods are considered to be the most reliable and valid measures, the measures which all other methods of quantifying activity should be compared against [244]. As will be explained further, behavioural observation has been used extensively with stroke survivors.

Doubly labelled water as a method of estimating total energy expenditure (ie. physical activity) involves an individual consuming water labelled with heavy, non-radioactive isotopes (ie. ^{2}H and ^{18}O). The rate at which these isotopes are eliminated is used to

estimate the mean metabolic rate of the individual [245]. Even though the elimination of doubly labelled water is the criterion method for determining overall activity expenditure, this method does not capture the duration, frequency or intensity of activity [246]. This method has not been used in the stroke population directly, but has been used to validate motion sensors, such as accelerometers and other whole body based accelerometry devices, which are frequently used and have been validated for use in the stroke population.

Cheap and easy to administer *questionnaires* and *self-activity reports* are considered a less desirable choice of instrument for use in observational research given that weaknesses surrounding their reliability and validity in both healthy and diseased populations have been highlighted [243]. *Pedometers*, a relatively inexpensive tool designed to count the number of steps taken, have been shown to underestimate step counts, as the speed and stride of gait performed by individuals with neurological conditions is often too slow and lack the required force to be accurately detected [247]. More sophisticated instruments such as *accelerometers* are the more preferred tool of choice to quantify movement based activity [248].

Accelerometers measure movement in one, two or three directions (uni-, bi- or triaxial accelerometers) and are a reliable way to both measure the quantity and intensity of an individual's movement [246]. Accelerometers such as the Step Activity Monitor (SAM) and the Intelligence Device for Energy Expenditure and Activity (IDEEA) are used frequently in stroke research. The IDEEA is capable of capturing a wide spectrum of gait parameters and transfers (i.e. standing up from sitting), whereas the SAM is limited to use in research concerned with bidirectional ambulatory activity. Another popular electronic device used to estimate the frequency of a wide spectrum of physically based

behaviours is an automated positional sensor referred to as the Positional Activity Monitor (PAL) 2. The PAL 2 is an activity monitor which records human movement and position from time periods as little as ten minutes to as long as five days [249].

The majority of researchers which have used accelerometers to collect activity data on stroke patients have sampled survivors living at home in the community (ie. the chronic phase of stroke) [250-252]. Accelerometers have been used with stroke patients in the hospital setting [135,253] (see Section 1.2.2.1) but this method of quantifying 'activity' has several limitations.

None of these devices have yet been validated for use with stroke patients in the inpatient setting. This may be because all are quite expensive, prone to failure and require a significant amount of time and expertise to ensure correct application and functioning. These devices are particularly problematic to use to quantify the ambulatory activity of stroke survivors within the inpatient rehabilitation setting, since these patients mobilise infrequently and do so with slow and uncoordinated gait. Importantly though, this accelerometers fails to capture the other two types of activity which comprise environmental enrichment- cognitive and social activity.

1.6.2.2 Cognitive activity

Measuring participation in cognitive activities has not yet been attempted with stroke survivors in the hospital setting. The closest researchers have come to quantifying this type of activity is time spent in recreational activities. Definitions of these have often included activities which require very little cognition (ie. watching television). Methods used to quantify the frequency engaged in such activities rely on direct observation, in particular, behavioural mapping.

1.6.2.3 Social activity

The thoroughness with which this type of activity has been explored in stroke patients undergoing rehabilitation does not extend past whether or not somebody (person) is nearby the patient. Similar to cognitive activity, estimation of social activity has relied on direct observation using behavioural mapping. There is ample evidence concerning how 'alone' stroke survivors are in hospital settings, but there is no data concerning how frequently they participate in verbal and non-verbal social behaviours or activities.

Participation in community, leisure or recreational activities and the health related quality of life of stroke survivors incorporates a combination of the three types of activity discussed in this thesis. Administering questionnaires for completion by either the stroke survivor and or their carer is the most popular means for quantifying time spent in multi-modal activities such as these. Furthermore, this research has previously always been conducted once the survivor has returned home and is often many months if not years post-stroke [119,254-256]. Although these aspects of function and well-being are extremely important, attempts to measure these concepts or use these measurement tools to estimate multi-modal activity in a rehabilitation unit are not only unlikely to be reliable, but are not appropriate. For example, many popular questionnaires focus on recreational activities and community participation, both of which are neither available nor actively encouraged in current rehabilitation ward environments.

1.6.2.4 All types of activity: Behavioural observation

As outlined earlier, engaging in higher levels of activity within the first few months after stroke has been associated with better functional recovery [107]. It makes sense then to determine activity levels of stroke survivors whilst they are receiving post-acute

stroke therapies. The most commonly used and reliable tool used to estimate physical, cognitive and social activity levels of stroke patients during inpatient rehabilitation is behavioural mapping. Behavioural mapping is an observational method which is considered the 'gold standard' for quantifying not only physical activity levels of patients, but cognitive and social activity as well. It has been used in health for over 30 years, with application in the fields of psychiatry [257], dementia [258], general [224] and stroke rehabilitation [131,165]. It refers to the process of studying behaviour as it relates to the physical surroundings [257]. Trained researchers observe and record participant behaviours using checklists containing predetermined categories that reflect the topics under investigation. Observational categories most often used are activities (what they are doing), location of the participant (where they are) and people present (who they are with). Studies in stroke have often also sought to demarcate therapeutic from non-therapeutic activities.

Behavioural mapping enables the capture of the many forms of physical and non-physical behaviour observed in stroke patients. This is a feature which makes it ideal for the measurement of change in the frequency of physical, social and cognitive activities. Even though the presence of an observer may influence subject behaviour and the methods of activity collection are labour intensive [243], these disadvantages of behavioural mapping are overshadowed by its unique ability to add a contextual dimension to activity measurement. Regular observations and documentation of participant behaviour gives a more detailed description of where and what kinds of activities are being performed. Unlike the other popular measurement tools presented already, behavioural mapping captures more than ambulatory activity. Direct observation and description of behaviour enables estimations of the frequency of sleeping, social interaction, sitting, lying, standing and walking to be made.

Patient behaviour is dependent on many factors including their environment. Behaviour streaming is recommended as a preliminary process by which the categories used in behavioural maps are determined. It involves minute by minute observation of participant behaviour. Data are then analysed and grouped by behavioural and other relevant themes. These groups then form the checklists and associated categories used in the behavioural maps [259]. Use of this technique permits the definitions of activity to be purposively developed for this project, and ensures they are relevant to the current era and culture of stroke survivors under investigation [**Chapter 4**].

1.6.2 CONCLUSION

Past observational research of stroke survivors in the inpatient rehabilitation setting has concentrated on physical behaviours, and more specifically, ambulatory activity. The instruments typically used for measuring physical activity in this patient population are unsuitable to measure the much broader definition of activity of interest in this translational study (ie. they cannot measure cognitive and social activity). Hence methods that utilise direct observational techniques appear to be the best way to measure all three accurately and simultaneously.

1.7 CHAPTER CONCLUSION

Stroke is a life changing event that has serious financial and emotional consequences for the individual stroke survivor, their carer and their community. The incidence of stroke and the burden which results is predicted to rise sharply as the world's population ages over the next 20 years. There is therefore a crucial need to develop, test and implement effective rehabilitation therapies for stroke survivors. Evidence in both animal and human studies of the use of activity based therapies after stroke indicates that starting early and doing more is beneficial. Better functional recovery is associated with performing as little as an additional 16 hours within the first six months post-stroke. The majority of data in both animal and human stroke rehabilitation research indicates that increasing activity should be the prime focus of hospital based stroke rehabilitation.

However, stroke patients currently spend the majority of their waking hours 'inactive and alone'. They spend a very small proportion of the day engaged in physical activity, and although there is virtually no data in relation to cognitive and social activity levels, it is likely that these are low too. An enriched environment is an intervention which promotes physical, cognitive and social activity, and has been consistently associated with improving physical, and to a lesser degree, cognitive function in animal models of stroke. Somewhat surprisingly, considering the positive effects achieved in the laboratory, a model of environmental enrichment has not been tested in stroke patients, or indeed in any disease population.

CHAPTER 2

RESEARCH AIMS AND HYPOTHESES

2.1 RESEARCH AIMS

The overarching aim of this thesis was to systematically examine the use of an enriched environment in both animals and humans, and undertake pilot work to determine whether an enrichment model based on animal evidence could feasibly be translated to stroke patients undergoing rehabilitation, and result in increased activity. The aims of the studies in this thesis were to:

(i) determine the efficacy of the use of an enriched environment in animal models of stroke,

(ii) determine how much a stroke patient's day is spent engaged in physical, cognitive and social activity,

(iii) develop a human equivalent model of environmental enrichment , and then

(iv) determine the feasibility of using this model to increase activity levels of stroke patients undergoing inpatient rehabilitation.

2.2 HYPOTHESES

There were three hypotheses associated with the work arising from this thesis.

Hypothesis One

"The use of an enriched environment in animal models of stroke results in better sensorimotor and cognitive function and does so without a significant increase in infarct volume or higher incidence of death" **[Chapter 3: Publication 1]**,

Hypothesis Two

"Stroke patients undergoing inpatient rehabilitation spend a small proportion of their day engaged in activity-physical, cognitive and or social activity" **[Chapter 5: Publication 3]**, and

Hypothesis Three

"The use of an enriched environment in a mixed rehabilitation unit increases activity levels of stroke patients undergoing stroke rehabilitation" **[Chapter 6: Publication 4]**.

2.3 BRINGING IT ALL TOGETHER

The first goal of this PhD was to determine the efficacy of an enriched environment in animal models of stroke **[Chapter 3: Publication 1]**. Once determined, a human equivalent model of environmental enrichment for use in the clinical stroke setting was developed. Before designing and undertaking a large scale trial to look at the difference in functional gains made by survivors undertaking stroke rehabilitation whilst exposed to this model of enrichment and those rehabilitated in in a standard rehabilitation unit environment, feasibility of this model had to be determined. We sought to determine if the human equivalent model of environmental enrichment increased activity.

This required:

(i) development of a tool designed to record patient activity levels of the three components of enrichment (ie. physical, cognitive and social activity), **[Chapter 4]**,

(ii) measurement of baseline activity – to establish the potential to increase activity levels of patients undergoing stroke rehabilitation in a standard (non-enriched) rehabilitation unit **[Chapter 5: Publication 3]**, and then

(iii) measurement of stroke survivor activity during exposure to an enriched environment to answer the question - are stroke survivors undertaking inpatient rehabilitation in a rehabilitation unit with environmental enrichment more active than survivors rehabilitating in a standard rehabilitation unit? **[Chapter 6: Publication 4].**

During the conduct of this pilot study other aspects of environmental enrichment within a clinical setting were also explored. I collaborated with a number of researchers to explore environmental enrichment during stroke rehabilitation. These included:

(i) the relationship between stroke patient activity levels and

a. cognitive function [Buckley et al. 2010] [260]

b. physical function [Raad et al. 2010] [261].

(ii) preliminary investigations were undertaken to investigate the effect exposure to an enriched environment had on cognitive function [Hooke et al. 2011] [262], and

(iii) qualitative methods were used to describe the experience of patients [Bartley et al. 2012 [263], **Appendix B**] and staff [Alborough et al. 2012 [264], **Appendix B**] rehabilitating and working within an enriched rehabilitation environment respectively.

As these studies did not form part of the studies of the thesis driven and executed by me, they are not included in the body of work for this PhD and are only included for completeness.

CHAPTER 3

SYSTEMATIC REVIEW AND META-ANALYSIS OF THE USE OF AN ENRICHED ENVIRONMENT IN ANIMAL MODELS OF STROKE

PUBLICATION 1

Janssen H, Bernhardt J, Collier JM, Sena ES, McElduff P, Attia J, Pollack M, Howells DW, Nilsson M, Calford MB, Spratt NJ. An enriched environment improves sensorimotor function post-ischemic stroke. *Neurorehabil Neural Repair*. 2010;24:802-813.

Results from individual studies on the use of an enriched environment in animal models of stroke suggest that this paradigm favours the recovery of sensorimotor function and achieves such without significant adverse events. For example, animals given strokes and then exposed to an enriched environment have been found to make both small [189] or large [170] gains in sensorimotor function compared to animals recovering from stroke in non-enriched conditions. This systematic review and meta-analysis sought to determine the quality of work and efficacy of this environmentally based intervention when used in animal models of stroke.

"As co-authors of the paper Janssen H, Bernhardt J, Collier JM, Sena ES, McElduff P, Attia J, Pollack M, Howells DW, Nilsson M, Calford MB, Spratt NJ. An enriched environment improves sensorimotor function post-ischemic stroke. *Neurorehabil and Neural Repair*. 2010;24:802-813, we confirm that Heidi Janssen has made the following contributions:

•50% conception and design of the research

•65% analysis and interpretation of the findings

•70% writing the paper and critical appraisal of content."

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An Enriched Environment Improves Sensorimotor Function Post–Ischemic Stroke

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Abstract

Objective. An enriched environment (EE) refers to conditions that facilitate or enhance sensory, cognitive, motor, and social stimulation relative to standard (laboratory) conditions. Despite numerous published studies investigating this concept in animal stroke models, there is still debate around its efficacy. The authors performed a systematic review and meta-analysis to determine the efficacy of an EE on neurobehavioral scores, learning, infarct size, and mortality in animal models of ischemic stroke. *Methods*. Systematic review of controlled studies of the use of an EE in experimental stroke was conducted. Data extracted were analyzed using weighted mean difference meta-analysis. For pooled tests of neurobehavioral scores, a random effects standardized method was used. *Results*. Animals recovering in an EE poststroke had mean neurobehavioral scores 0.9 standard deviations (95% confidence interval [CI] = 0.5-1.3; $P < .001$) above the mean scores of animals recovering in standard conditions and showed a trend toward improvement in learning (25.1% improvement; 95% CI = 3.7-46.6; $P = .02$). There was no significant increase in death. Animals exposed to an EE had 8.0% larger infarcts than control animals (95% CI = 1.8-14.1; $P = .015$). *Conclusions*. The results indicate significant improvements in sensorimotor function with EE poststroke but suggest a small increase in infarct volume. Clarification of the underlying mechanisms requires further study but should not overshadow the observed functional improvements and their application to clinical trials during stroke rehabilitation.

Keywords

animal model of stroke, enriched environment, functional recovery

Introduction

In 1947, neuropsychologist Donald Hebb compared rats housed in standard laboratory conditions to those he set free to roam and live in his house and found that the latter had better learning and problem-solving skills.[1] These results prompted further research into the concept of an enriched environment (EE). An EE refers to conditions that facilitate or enhance sensory, cognitive, and social stimulation relative to standard (laboratory) conditions.[2]

Even though there are no standardized protocols, an EE most often involves social housing (8 to 12 animals) in large cages that are filled with inanimate objects, for the purpose of increasing sensory, physical, and social stimulation. Such objects include but are not limited to ladders, ropes, tubes, balls, horizontal boards, swing boards, chains, toys, and on occasions, running wheels. Participation in activities within the EE is voluntary. Training of skilled motor tasks or other sensorimotor therapies is not included within this environment. Environmental novelty and cognitive stimulation is maintained through the rearrangement and changing of cage contents at varied intervals, depending on the laboratory.[2]

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EE has shown benefit for brain development and recovery from injury in a number of animal models.[3] Unlike other rehabilitation techniques investigated in animals such as constraint and specific limb training, use of an EE differs, in that it facilitates voluntary and challenge-free activity in stimulating surrounds.[4] Application of this concept in animal stroke models has yielded inconsistent results. The majority of published studies report efficacy for enhancement of function and learning; however, some have had neutral or negative results.[5,6] Most have used relatively small numbers of animals, and estimates of effectiveness have varied.

The method of meta-analysis is well established in clinical trials. It enables increased precision in the determination of effectiveness of therapy by pooling data from a number of studies in an unbiased manner. Recently, this method has also been applied to animal studies and has made a significant contribution to the evaluation of effectiveness of therapies and to understanding how aspects of experimental design may affect study outcome.[7-9]

Our aim was to conduct a systematic review and meta-analysis to establish the quality of studies examining the use of an EE in animal stroke models and determine the effect an EE has on neurobehavioral scores, learning, infarct size, and mortality in these models. Determining the quality and efficacy of this environmental intervention is a necessary step before any attempts are made to translate this concept into the clinical setting.

Methods

This meta-analysis was based on previously published methods.[8] Searches were performed on October 2, 2008, from the electronic databases PubMed, MEDLINE, BIOSIS, and EMBASE using the following search strategy: (recovery of function OR behavior OR treatment outcome OR motor activity) AND (stroke OR cerebral infarct OR cerebrovascular accident OR CVA OR brain ischemia OR focal cortical ischemia OR cortical infarct OR cerebral ischemia OR MCA occlusion OR middle cerebral artery occlusion OR brain hypoxia) AND (animal OR mice OR rat OR animal model) AND (enrich* AND environment*). Manual search of the cited references from retrieved publications was also performed to identify any additional studies.

Inclusion Criteria and Outcome Measures

All controlled studies of therapeutic EE in animal models of focal cerebral ischemia that presented data for any of our nominated outcomes were considered for inclusion. Intracerebral hemorrhage models were excluded, as were models of global ischemia (primarily a model of cardiac arrest). Neurobehavioral score (for performance on a neurobehavioral test examining sensorimotor function) was the primary outcome. Secondary outcomes were learning, infarct size (volume or area), and death. Animals housed in standard laboratory conditions were designated as the control group.

Data Extraction

For each comparison, and for each control and treatment group, investigators (HJ and NJS) identified and extracted the number of animals per group, mean outcome, and standard error (SE) or standard deviation (SD). Where an outcome measure was measured serially, only the last measure was used because methodological limitations prevented pooling of data, and the last measure was considered most representative of the clinically relevant outcome of long-term functional recovery. When data were only presented graphically, attempts were made to obtain data from authors; if these were not available, values were measured from the published graphs. When animals were exposed to a physical or cognitive intervention in addition to exposure to an EE (cotreatment), this was noted. Cohorts receiving cotreatments with pharmacological or cell-based therapies were not included; however, where such studies presented data on both EE and standard-housed controls, data from these cohorts were included. Multiple publications (repeat publications) from the same study were noted, and all relevant data were allocated to the original group of animals studied. When a single control group served multiple treatment groups, the size of the control group entered into the meta-analysis was adjusted by dividing by the number of treatment groups served. Only animals that had died after allocation to the various housing conditions were used in the estimates for mortality, and animals that died during surgery or in the immediate postsurgical period were excluded from all calculations.

Housing density was a factor considered important in control conditions; hence, distinctions were made a priori between standard small-group housing (2-4 rats per cage) and social housing ($n \geq 5$). Prospective and retrospective exclusion of animals was noted. For example, use of a neurobehavioral score as an inclusion criterion before assignment to an EE was classed as prospective, whereas exclusion on the basis of small histological lesion (postintervention) was classed as retrospective exclusion. Studies that excluded animals retrospectively were not included in the meta-analysis for infarct size because of the possibility of confounding. To minimize the loss of statistical power that results from the analysis of multiple outcomes, a single measure of the Morris Water Maze test was chosen for the outcome of learning. The distance swum (path length) to reach the target (in meters) was used. The authors considered the 3 parameters commonly reported: path length, latency, and speed. Path length would be the least affected by residual motor impairments and hence would be more representative of the animal's cognitive abilities.

Quality was assessed against the Collaborative Approach to Meta Analysis and Review of Animal Data from Experimental Stroke (CAMARADES) study quality checklist,[10] which comprises (1) publication in a peer-reviewed journal, (2) statement of control of temperature, (3) randomization to treatment group, (4) blinded induction of ischemia, (5) blinded assessment of outcome, (6) avoidance of anesthetics with marked intrinsic neuroprotective properties, (7) use of animals with hypertension or diabetes, (8) sample size calculation, (9) statement of compliance with regulatory requirements, and (10) statement regarding possible conflicts of interest. Statements of randomization to treatment group were taken at face value. Absence of such a statement was interpreted as an indication that randomization did not occur.

Other pertinent data, including species, time of commencement of the EE relative to stroke, time of assessment, housing conditions of control animals, type of ischemia, duration of ischemia (for temporary occlusions), method of ventilation, method of anesthetic induction, dose (hours/day) and length (days) of the EE, and inclusion of a running wheel (yes/no), were also extracted for the purpose of exploring the effect such variables had on each outcome via stratified analyses.

Statistical Analysis

All meta-analyses were performed using a random effects model. For the primary outcome, neurobehavioral scores, data were pooled using a standardized mean difference (SMD) meta-analysis. In the case of the use of multiple tests of sensorimotor function, only 1 pooled outcome measure was entered into the analysis for each experimental animal. Weighted mean difference (WMD) was considered inappropriate for this pooled analysis, given the differences in neurobehavioral tests' measurement scales. Where specific neurobehavioral tests were performed in at least 3 individual publications, results were pooled. These data and that for infarct volume and learning were analyzed using WMD. Odds ratios and confidence intervals (CIs) were estimated for mortality. Significance level was set at $P < .05$ for the primary outcome (neurobehavioral score) and the associated exploratory analyses. For ease of comparison, data are presented with 95% CIs. To account for multiple secondary comparisons, significance level was set at $P < .017$ for the outcomes of learning, infarct size, and death. Stratified analyses to determine potential sources of heterogeneity were performed on aspects of study quality and design for the pooled and the individual neurobehavioral score data sets, infarct size, and learning. The significance of differences between n groups was assessed by portioning heterogeneity and by using the χ^2 distribution with $(n - 1)$ degrees of freedom, with the significance level set at $P < .01$. Overall heterogeneity was examined using the I^2 statistic.[11]

Results

In all, 21 studies both met the inclusion criteria and presented complete data sets (Figure 1 and Table 1). The median quality score was 5 of a possible total of 10 (interquartile range 5-6), with all but 1 study (with a score of 8)[12] scoring between 4 and 6 of a possible 10. Nine (43%) of the included publications reported randomization and 7 (33%) reported blinded assessment of outcome. Nearly all studies that reported randomization failed to specify details of this process. No study reported sample size calculations or whether surgeons were blinded to group allocation. The small number of experiments that contributed to each outcome resulted in insufficient power to statistically assess publication bias.

Efficacy

Neurobehavioral scores. We found that 13 studies (contributing 17 individual experiments) had complete data sets for the outcome of neurobehavioral scores. Exposure to an EE poststroke significantly improved function, with mean neurobehavioral scores that were 0.9 SDs greater than those of control animals (95% CI = 0.5-1.3; $P < .001$; Figure 2A). The most frequently used tests were rotating pole (7 experiments), limb placement (5 experiments), horizontal beam (4 experiments), and ladder test (4 experiments). An EE significantly improved neurobehavioral scores in the rotating pole, horizontal beam, and limb placement tests (Figure 2B). The ladder test point estimate of effect was in the direction of benefit but was not statistically significant ($P = .408$).

Stratification of the pooled neurobehavioral data revealed that 2 outlying studies[6,23] were the major contributors to heterogeneity (Figure 2A). Removal of associated data improved homogeneity ($I^2 = 65\%$ to $I^2 = 0$).

Exploratory analyses of the rotating pole test did not reveal any significant contributors to heterogeneity. Both time to administration ($P = .008$) and length of exposure ($P = .008$) to EE were significant sources of heterogeneity in the ladder test. The stratification according to these 2 variables separated out identical studies, so the major contributor to the observed heterogeneity could not be identified.

Learning. Only one[14] of the 8 studies used the labyrinth and radial arm test to assess learning. All others used the Morris Water Maze. Therefore, to improve homogeneity and enable use of WMD analysis, labyrinth and radial arm test results were excluded from further analysis.

Animals housed in an EE poststroke had a 25.1% improvement in learning relative to controls (95% CI = 3.7-46.6; $P = .022$; Figure 3), although this estimate showed moderate heterogeneity. Exploratory analyses revealed a 51.1% (95% CI = 30.9-71.4) improvement in randomized animals (3 experiments), compared with only 8.6% (95% CI = −13.1 to 30.3) in those that were not randomized (5 experiments; $P = .004$).

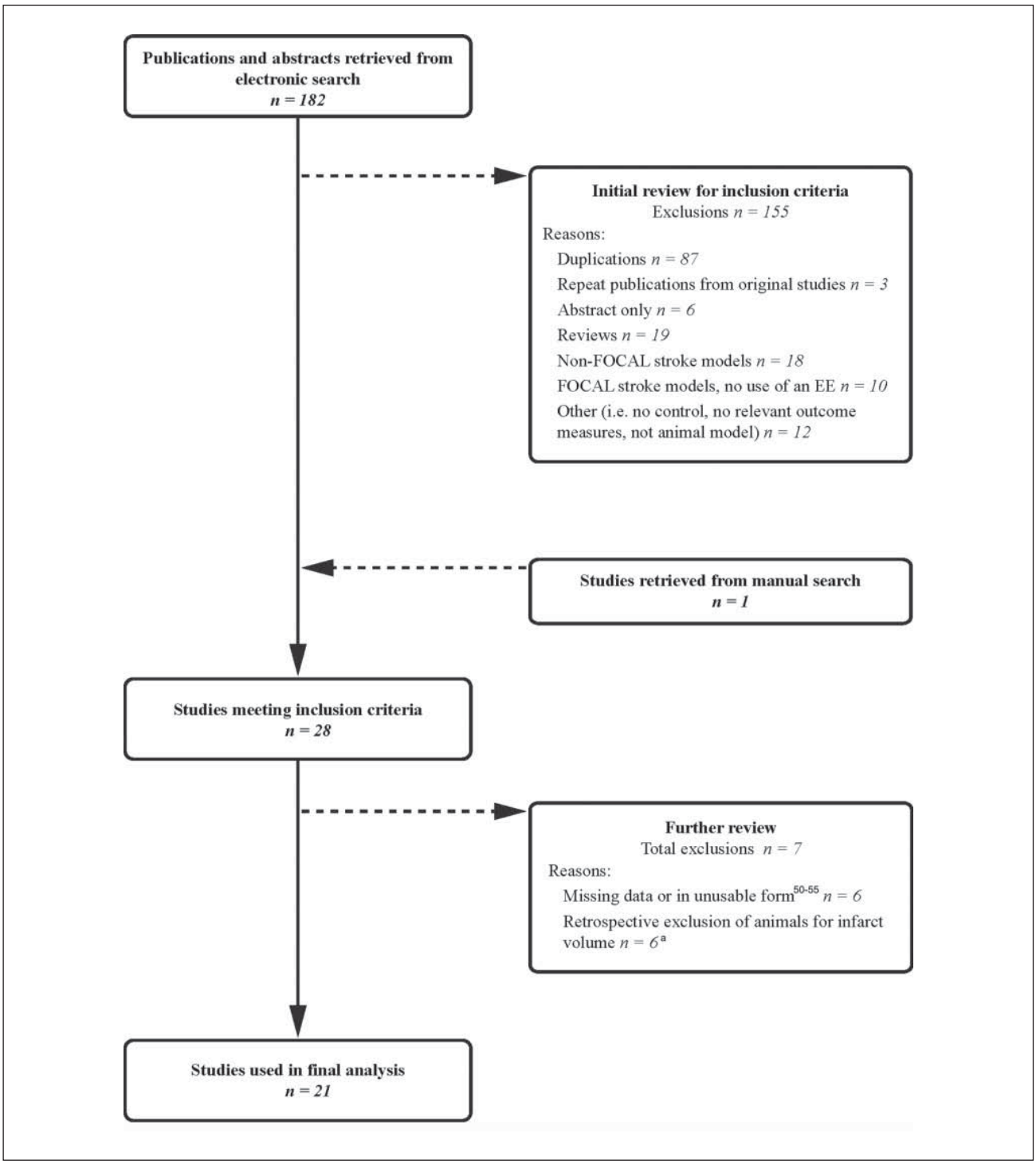

Figure 1. Schematic of study selection
[a]Only 1 of 6 was completely excluded from the analysis as the remaining 5 presented data for other outcome measures

Infarct size and mortality. Animals recovering in an EE had an 8.0% larger infarct postintervention than control animals (95% CI = 1.6-14.5; $P = .015$; Figure 4). There was low heterogeneity for this outcome ($I^2 = 0$), and exploratory analyses did not reveal anything of significance. A total of 7 studies (15 experiments) presented appropriate data for statistical

Table 1. Number of Individual Experiments Per Publication Contributing to Each Outcome Analysis

			Neurobehavioral Score							
				Individual Test Analyses						
Study	Year	Quality Score	Pooled Analysis	Rotating Pole	Limb Placement	Traverse Horizontal Beam	Ladder (Horizontal)	Infarct Volume	Learning	Mortality
Biernaskie et al[13]	2004	5	3				2			
Buchhold et al[14]	2007	5	2	1						
Dahlqvist et al[15]	1999	5						6		
Dahlqvist et al[16]	2004	6	1					2	1	
Hicks et al[6]	2008	5	1					3		
Johansson[17]	1996	4	1	1	1			1		
Johansson and Ohlsson[18]	1996	6	1	1	1	1				1
Komitova et al[19]	2005	5								1
Matsumori et al[20]	2006	4						1		
Nygren and Wieloch[21]	2005	5								7
Nygren et al[22]	2006	5	1	1						1
Ohlsson and Johansson[23]	1995	6	2	2	2	2		1		2
Puurunen et al[24]	2001	5	1		1	1			1	
Puurunen et al[5]	2001	5	1					1	1	
Risedal et al[25]	1999	4							2	2
Risedal et al[26]	2002	6								1
Ronnback et al[27]	2005	6							1	
Sonninen et al[28]	2006	4							1	
Wang et al[29]	2008	7	1					1		
Windle et al[30]	2007	5	1				1			
Wurm et al[31]	2007	5	1				1	2	1	

analysis. Recovering in an EE poststroke did not have any significant effect on mortality (OR = 1.0; 95% CI = 0.5-1.9; I^2 = 7%).

Exploratory Analyses

Experimental design between studies varied significantly (see Table 2). The a priori distinctions made regarding housing conditions of control animals became redundant as only 1 of the included studies used social conditions (n = 10 animals). The majority used standard housing, and 6 housed animals individually. Only one included an experimental paradigm in which animals received enriched housing both prior to and following stroke,[23] and just more than half of the included studies incorporated a running wheel into the EEs. Other parameters that varied included the time of commencement of environmental enrichment, ranging from 1 to 30 days; length of exposure to enrichment from 1 to 90 days; and changes in cage contents and frequency of exchange or rearrangement of contents from once a week to daily. Exploratory analyses to determine the contribution of these aspects and the effect of previously listed pertinent variables (see Data Extraction section) were performed, but insufficient data and many sources of variability prevented any meaningful conclusions.

Discussion

Our aim was to determine the efficacy of an EE poststroke using systematic review and meta-analysis. We are the first to attempt to analyze systematically all EE-based studies in animal models of ischemic stroke. The results demonstrate the significant beneficial effects of EE on neurobehavioral scores, overall, and on 3 of the 4 most frequently used individual tests. There was a strong trend for improvement in learning and a small but statistically significant increase in infarct size. There was no increased likelihood of death.

Moderate levels of heterogeneity were present in results for pooled neurobehavioral scores, the rotating pole and ladder tests, and learning. This was anticipated given the variability of study designs and small numbers of comparisons. Pooling of data revealed favorable effects on sensorimotor

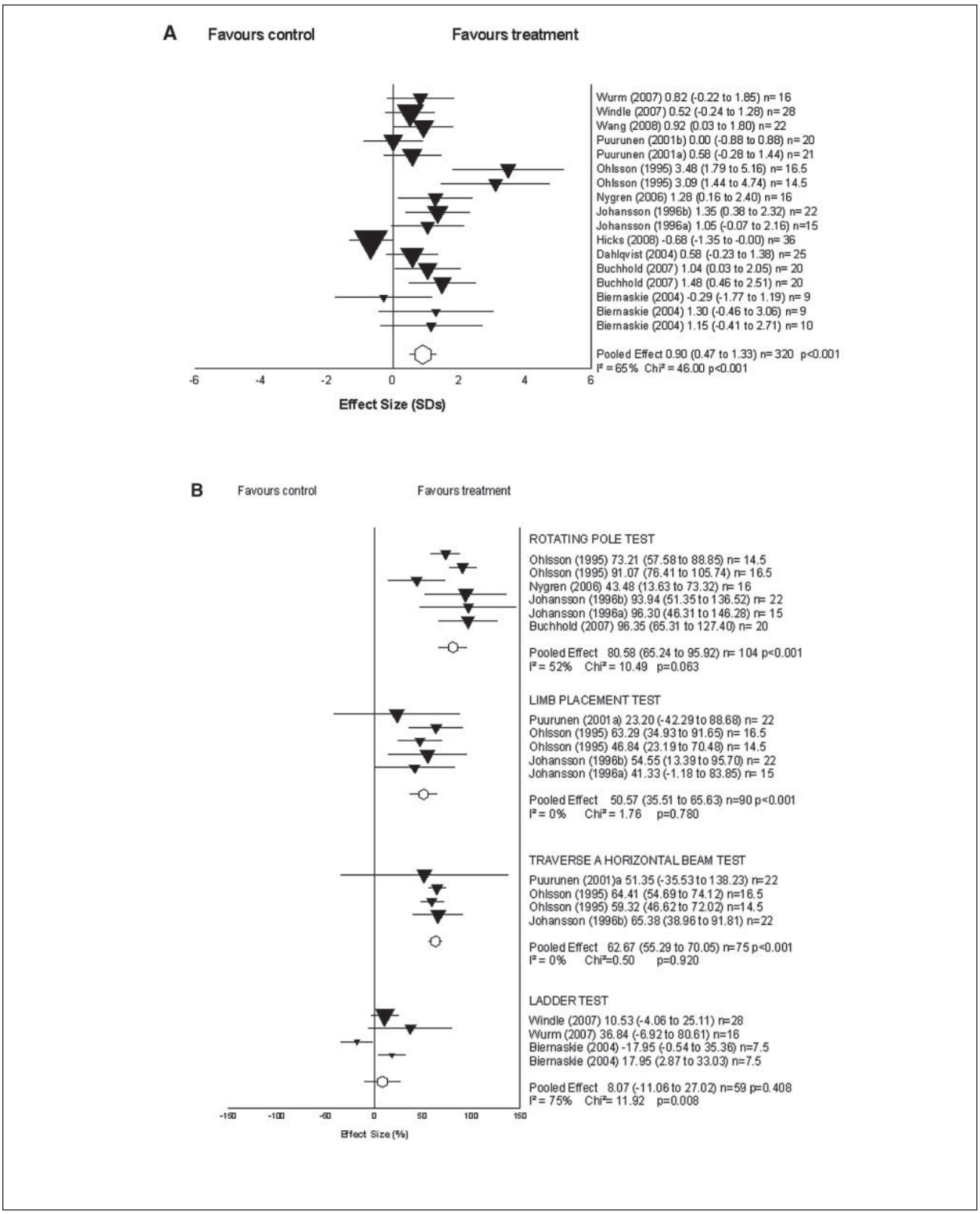

Figure 2. A. Estimates and 95% confidence intervals of effect size for an enriched environment (EE) on pooled neurobehavioral score. B. Estimates and 95% confidence intervals of effect size for an EE on neurobehavioral score by individual test

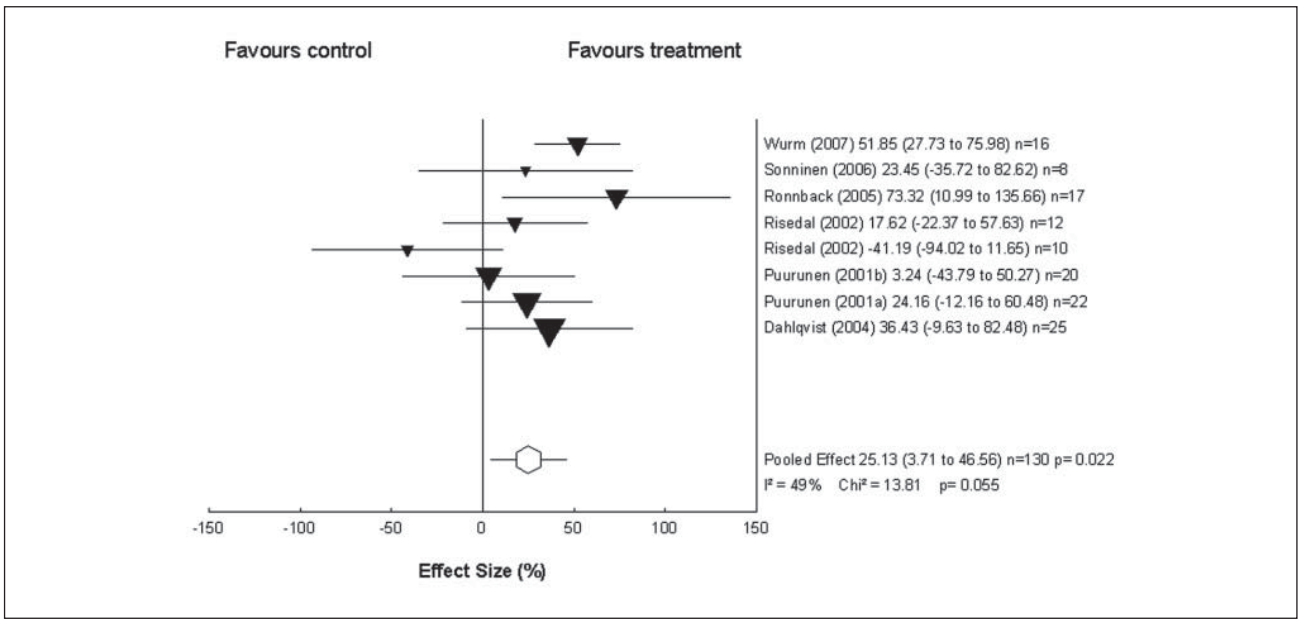

Figure 3. Estimates and 95% confidence intervals of effect size for an enriched environment (EE) on learning

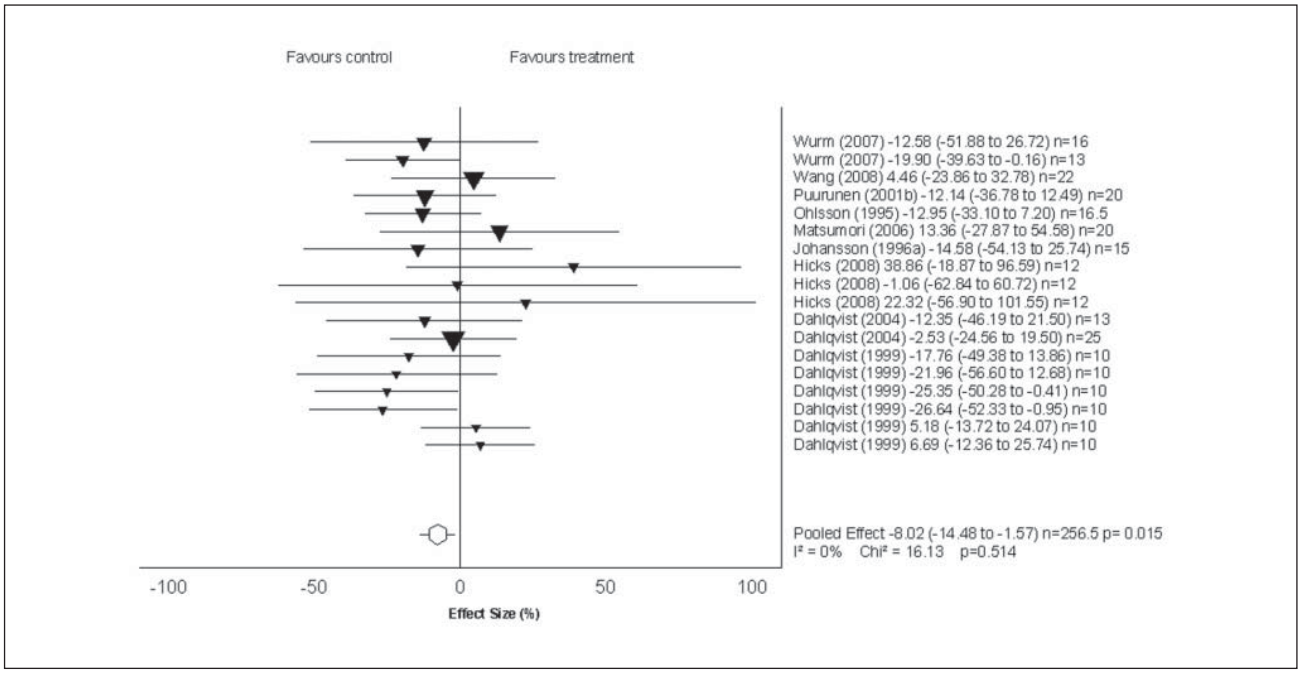

Figure 4. Estimates and 95% confidence intervals of effect size for an enriched environment (EE) on infarct size

function of animals recovering in an EE, even despite the largest experiment (n = 36) showing a trend favoring control. Small numbers and study heterogeneity prevented meaningful analysis of the contribution of individual components of the EE, such as exercise (running wheel), to outcome. Data from studies of intracerebral hemorrhage and global ischemia were not included in the meta-analysis in order to limit heterogeneity, and anticipated numbers of studies in these models were far too small to conduct separate analyses. Nevertheless, published studies on the effect of an EE on functional outcomes in such models are generally consistent with those found in focal ischemic models.[32-36]

Table 2. Summary of Variation in Study Design

Study	Year	Control Conditions	EE Commenced (days post stroke)	Hours Per Day	Length of EE (days)	EE			
						Size of Cage (mm)	N/ cage	Changes (Per week)	Contents
Biernaskie et al[13a]	2004	ST	5 and 30	24	35 and 10	NS	4-6	2	Ropes, beams, platforms, and various toys
Buchhold et al[14]	2007	D	1	24	27	NS (large)	8	NS	Catwalk, playing toys, hiding tunnel, and running wheel
Dahlqvist et al[15]	1999	ST	1	24	1, 2, 6, 11, 19, and 29	815 × 610 × 450	NS	NS	Chain, swing, horizontal boards, inclined boards, wooden blocks
Dahlqvist et al[16]	2004	D	2	24	29 and 34	820 × 610 × 450	12	7	Wooden tunnels, ladders, chain, swing, elevated horizontal boards, inclined boards, running wheel
Hicks et al[6]	2008	ST	8	24	27, 55, 83	NS (large)	8	1	Tubes, beams, shelves, ropes and ladders, and access to running wheel one 6-hour session per week
Johansson[17]	1996	ST	15	24	20	815 × 610 × 450	7	1	Chain, swing, horizontal boards, connecting boards, wooden blocks, swing boards
Johansson and Ohlsson[18]	1996	SL	1	24	90	815 × 610 × 450	9	1	Chain, swing, horizontal boards, connecting boards, wooden blocks and metal objects, swing board
Komitova et al[19]	2005	ST	1	24	7	815 × 610 × 1280	10	2	Chains, swing, horizontal and vertical boards, wooden blocks, and objects of different sizes and materials
Matsumori et al[20]	2006	ST	7	24	56[a]	2-story, 760 × 560 × 770	10	1	3-Dimensional labyrinth maze, ladder, chains, hammock, running wheel, wooden blocks, and nylon bones
Nygren and Wieloch[21]	2005	ST	2	3 and 24	12-54	Multilevel cage, 880 × 650 × 1400	10-15	3	Plastic tubes, ladders, chains, robes, platforms, running wheel, toys
Nygren et al[22]	2006	ST	2	3	26	Multilevel cage, 880 × 650 × 1400	10-15	3	Plastic tubes, ladders, chains, ropes, platforms, ramps, running wheel, toys
Ohlsson and Johansson[23]	1995	D	1	24	83	815 × 610 × 450	12	1	Chain, swing, horizontal boards, connecting boards, wooden blocks, swing boards
Puurunen et al[24]	2001	ST	1	24	25	2 cages, 610 × 460 × 460, connected by tunnel	6	3	Shelves, running wheel, manipulative objects (glass balls, jars, wooden objects), one wall constructed of bars
Puurunen et al[5]	2001	ST	1	24	32	2 cages, 610 × 460 × 460, connected by tunnel	6	3	Shelves, running wheel, manipulative objects (glass balls, jars, wooden objects), one wall constructed of bars
Risedal et al[25a]	1999	ST	1 and 7	24	41 and 35	820 × 610 × 450	8	2	Chain, swing board, horizontal boards, inclined boards, wooden blocks
Risedal et al[26]	2002	D	2	24	26	820 × 610 × 450	8	2	Horizontal and vertical boards, chain, swing, and swing board
Ronnback et al[27]	2005	D	2	24	31	820 × 610 × 450	8-10	7	Wooden tunnels, ladders, chain, swing, elevated incline, running wheel
Sonninen et al[28]	2006	D	2	24	23	2 cages, 610 × 460 × 460, connected by tunnel	4	3	Ladders, shelves, running wheel, manipulative objects (glass balls, jars, wooden objects)
Wang et al[29]	2008	ST	7	24	28	2 story, 760 × 560 × 770	5-6	1	3-Dimensional labyrinth, ladder, running wheel, a house, chains, hammock, nylon bones, wooden blocks
Windle et al[30a]	2007	ST	8	24	63	NS (large)	6-8	2	Ropes, beams, platforms, and various toys
Wurm et al[31]	2007	ST	1	24	9 and 41	850 × 750 × 400	6-8	7	Tunnels, ladders, chains, seesaw, places of escape

Abbreviations: EE, enriched environment; NS, not specified; ST, standard; SL, social; D, deprived.
[a]Cotreatment used.

The finding that EE-exposed animals showed better learning in those studies in which treatment allocation was properly randomized was unexpected. Most previous studies have shown an inverse relationship between randomization and overall effect size,[8,37] consistent with the principle that the lower the quality of the study, the greater the apparent benefit of the intervention. However, this finding was from a single exploratory analysis, and the result should be interpreted cautiously.

Although there has been a previous report of increased infarct size associated with early training and EE,[25] this is the first study to show a small increase in infarct size with EE, even in the absence of early training. There were 4 studies included in the meta-analysis, which included an additional training component, but data from only one of these were suitable for inclusion in the estimate of infarct volume. This study did not commence training until the second week postsurgery and indeed showed a trend toward smaller infarcts in treatment animals[20] (see Figure 4). The overall effect of EE on infarct volume was small (8% increase) but statistically significant. Lending robustness to the finding, 12 of 18 studies reported increased infarct volume of some degree, although none of the individual studies reported a statistically significant effect. The result suggests the possibility of increased late tissue loss (because EE did not commence until at least 24 hours after stroke induction), possibly contributed to by the stress of a new environment and social housing. Interestingly, the 3 experiments (presented in a single publication from the 1 laboratory) using the endothelin model, in which cell death has been reported to mature more slowly, did not show an increase in infarct volume.[32] Other possibilities, such as a change in the rate of tissue repair, must also be considered as possible explanations for the apparent increase in infarct volume.

Unfortunately, great variability in experimental design across studies limited our ability to investigate any relationship between sensorimotor function or learning and infarct size. Results from observational and training animal models of stroke that have not included EEs indicate that larger lesions (measured during the chronic phase) are associated with more significant chronic neurological deficits, irrespective of method of stroke induction.[38-40] Although there are numerous studies indicating a moderate correlation between infarct size and functional outcome clinically,[41-44] a recent review argues that such findings may be confounded by weak methodological design and a disregard for importance of location.[45] Hence, given this evidence, the finding that exposure to an EE results in a small but significant increase in infarct volume raises the question of whether this finding is functionally significant and whether the apparent infarct expansion includes loss of any viable brain tissue. Regarding mortality, the point estimate for effect was 1.00, implying no effect; however, the wide CIs suggest some caution in interpretation.

Not all human poststroke functional outcomes can be assessed in animals (ie, speech, mood, and quality of life). However, these models are still of great value because the neurobehavioral tests used in the majority of studies include elements that address aspects of sensorimotor function and learning that are highly relevant to humans recovering from stroke (including coordination, proprioception, gait, skilled reach and accuracy, and spatial memory).

Most studies achieved a moderate quality score. These results are consistent with previous meta-analyses of studies using animal stroke models, with many published papers of low to moderate reported quality.[8,37,46] The small numbers of studies that reported randomization, blinded assessment of outcome, or a priori sample size calculations are concerning; however, for the first two, the results are substantially higher than those from studies of other disease models.[47] Nevertheless, these data suggest that several important aspects of experimental design are not yet routine in experimental studies. The CAMARADES quality scale was used in this analysis, not because it reflects commonly used factors in clinical trial design but because it reflects the likelihood of the experimental results being unbiased. It is hoped that the recent publication of good laboratory practice[48] will address many of the quality issues raised from this study and encourage inclusion of all pertinent information in future publications.

General limitations to the technique of meta-analysis have been previously reviewed.[7,37] Attempts were made in this meta-analysis to address a number of these issues by accounting for factors such as prospective and retrospective exclusion, the use of cotreatments, and consideration of the impact that interstudy and intrastudy heterogeneity had on both analysis design and interpretation. Additionally, considering that the experimental setup of an EE in animal models is by nature very complex, meaningful statistical analysis of the multitude of variations observed in the included studies was not possible. Finally, aspects such as negative publication bias and bias introduced from aspects of trial design were potential sources of falsely elevated benefits of intervention. Unfortunately, there were insufficient experiments to permit a formal assessment of the effect of publication bias using the Egger method.[49]

Overall, 6 publications[50-55] were excluded because data for the experimental outcomes were either missing or were presented in a form inappropriate for statistical analysis (ie, medians or means without a SE or SD). Where necessary, investigators were contacted in an effort to maximize animal numbers and clarify experimental methodology; however, for the 6 above-mentioned studies, we were unable to obtain usable data. A limitation to the WMD meta-analysis method prevented the inclusion of data from 1 experiment for the rotating pole analysis.[14] These data were included in the SMD meta-analysis used to estimate the pooled effect size for neurobehavioral scores.

The results from this study now give statistical support to the consensus that an EE aids in the recovery of motor functioning.[2,3] However, this reopens the debate about whether control conditions in animal models are more representative of environmental deprivation than a "normal" environment. Standard housing conditions have improved significantly over the last 30 years (the main change being an increase in cage size to allow animals to stand on their hind legs), so the argument that EEs really highlight the negative consequences of environmental deprivation may be less relevant than in the past. Complicating this further is the difficulty in determining what constitutes a normal or natural environment for animals that have been bred specifically for, and therefore are possibly behaviorally adapted to, laboratory conditions.[56] Clearly, the degree of stimulation is much less than in rats living in a natural environment. This could also be argued for current medical and rehabilitation wards, as evidence continues to emerge that suggests that patients in these settings are relatively "environmentally deprived" compared with "free-living" healthy people.[57]

The results of this meta-analysis provide strong evidence for the effectiveness of exposure to an EE in improving neurobehavioral score after experimental stroke. Future methodologically rigorous studies will be required to address the relative contribution of different components of the EE.

Implications

Results from this systematic review and meta-analysis give strong support to the conclusions drawn by multiple small studies conducted over the past 15 years, which have shown that exposure to an EE following focal stroke enhances sensorimotor function. Given that the outcome of most interest clinically is poststroke function, the results of this meta-analysis are encouraging. The observed small increase in infarct volume has many potential explanations that may be unique to the experimental setup. This requires further investigation, but we do not believe that this should overshadow the observed functional benefits. Additionally, these conclusions may prompt clinicians to consider how physically, socially, and cognitively stimulating the environments of current human stroke survivors are—past studies suggest that many rehabilitation settings may in fact be relatively environmentally deprived compared with a normal human environment.[57,58] Enrichment of these environments may require review of current policies, rearrangement of ward setups, rethinking of ward routines, and the provision of additional equipment. It seems unlikely that enrichment of the ward environment could do harm, and many may argue that an EE should be a standard rather than the comparison intervention in a clinical trial. We believe that it is reasonable to seek ways to translate this animal research to stroke rehabilitation.[59]

Declaration of Conflicting Interests

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CHAPTER 4

PILOT STUDY PROTOCOL

PUBLICATION 2

Janssen H, Ada L, Karayanidis F, Drysdale K, McElduff P, Pollack M, White J, Nilsson M, Bernhardt J, Spratt NJ. Translating the use of an enriched environment poststroke from bench to bedside: study design and protocol used to test the feasibility of environmental enrichment on stroke patients in rehabilitation. *Int J Stroke.* 2012;7:521-526.

Results from our meta-analysis on the use of an enriched environment in animal models of stroke motivated us to explore the feasibility of developing of a human equivalent model of environmental enrichment for use in the clinical setting. An important step in translating this unit based intervention from bench to bedside was to determine whether the human equivalent model of enrichment developed by our team increased stroke patient activity. As cognitive and social activity had yet to be extensively measured in stroke survivors within a rehabilitation setting (see Chapter 1, Section 1.6), we needed to develop a measurement tool which could capture levels of such activities, as well as physical activity levels, of stroke patients within a hospital setting.

As mentioned in Chapter 1 (Section 1.6) an important step in the development of the instrument chosen to capture activity was to undertake behavioural streaming. This process involved observing stroke patient behaviour and taking detailed descriptive notes at times throughout a 12 hour period during both a weekday and one weekend day. Three stroke survivors with varying levels of mobility were observed. One who was dependent on others to transfer and mobilise within the unit, one who was mobilising with the assistance of one, and lastly, one who was mobilising independently within the unit.

Once each of the two observation periods were completed for each participant, the catalogued 'units of behaviour' (data), were analysed so as to identify the major categories of participant behaviour (see **Appendix A-(i)** for an example of a behavioural streaming data collection sheet). These data informed the definitions of activity (physical, cognitive and social) presented in Chapter 1 (Section 1.2.2) and informed the definitions of activity used to code behaviour in the behavioural mapping tool used in the pilot study contained in this chapter (see **Appendix A-(ii)** for an example of the 'enrichment' behavioural mapping tool used in the pilot study).

After development of the 'enrichment' mapping tool, a pragmatic model of environmental enrichment which sought to facilitate activity through easier and better access to equipment and activities both the bedside (individual enrichment) and in common or shared areas (communal enrichment), was created.

In addition to detailing the design study and statistical methods employed in this pilot study, the following protocol briefly describes methods used in the three main collaborative projects arising from this study: (i) the experience of patients [see **Appendix B**] and (ii) staff involved in the use of an enriched environment in a ward

setting [see **Appendix B**], and (iii) the exploration of the effect of an enriched environment on post-stroke cognition [260,262].

This pilot study was registered with the Australian New Zealand Clinical Trial Registry. ACTRN12611000629932.

"As co-authors of the paper

Janssen H, Ada L, Karayanidis F, Drysdale K, McElduff P, Pollack M, White J, Nilsson M, Bernhardt J, Spratt NJ. Translating the use of an enriched environment poststroke from bench to bedside: study design and protocol used to test the feasibility of environmental enrichment on stroke patients in rehabilitation. *Int J Stroke.* 2012;7:521-526.

we confirm that Heidi Janssen has made the following contributions:

•**80%** conception and design of the research

•**80%** writing the paper and critical appraisal of content."

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Translating the use of an enriched environment poststroke from bench to bedside: study design and protocol used to test the feasibility of environmental enrichment on stroke patients in rehabilitation

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Rationale **Environmental enrichment, a paradigm investigated extensively in animal models, is an intervention, which by design facilitates motor, sensory, social, and cognitive activity. It has been shown to improve poststroke motor and cognitive function in animal models of stroke. This is the first study to attempt to translate this intervention from the laboratory to the clinical setting.**

Aims **The overall aim of this pilot study is to test the feasibility of using environmental enrichment with stroke patients in a rehabilitation setting. The aim is to enrich the environment of stroke survivors in a rehabilitation ward and measure changes in their activity (physical, cognitive, and social activity).**

Design **Prospective nonrandomized block design intervention study.**

Study **In the control phase we will determine the change in activity levels of patients treated in a usual rehabilitation environment over time. In the intervention phase structured observational techniques (behavioural mapping) will be used to quantify the change in activity levels of patients exposed to environmental enrichment.**

Outcomes **The primary outcome is change in activity level. Additional data collected on entry to and exit from the study will include: cognitive function using a battery of cognitive tests, general function using the Functional Independence Measure, mood using the Patient Health Questionnaire 9 and boredom using the Stroke Rehabilitation Boredom Survey. Quality of life will be assessed using the Assessment of Quality of Life 1 month postdischarge from rehabilitation. Australian New Zealand Clinical Trials Registry# ACTRN12611000629932.**

Key words: activity, function, enrichment, experience, plasticity, stroke

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Conflicts of interest: None.

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Introduction

Stroke rehabilitation has been shown to reduce the likelihood of death and long-term dependency of stroke survivors (1). Intensity of therapy (2) has been associated with better functional outcomes after stroke. However, there is a substantial amount of evidence, which indicates that patients recovering from a stroke in acute and subacute inpatient settings spend a large amount of the day inactive and alone (3–5). Environmental enrichment is an intervention designed to increase motor, sensory, cognitive, and social activity by provision of a stimulating environment (6). It is predicated on the concept that exposure to such an environment will encourage activity in these domains. As it is not therapist dependant, it may be a cost-effective method to increase activity and thereby improve stroke outcome. This paradigm has been investigated extensively in animal models. It has been shown to facilitate brain plasticity at both a cellular and functional level. Brains from animals exposed

to an enriched environment poststroke have shown: a greater number of dendritic spines (7), normalized astrocyte-neuron ratios (8), and higher levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (9). Functionally, some studies have shown that recovering in enriched conditions is associated with improvements in both physical and cognitive function (10).

Despite the long history of investigation of environmental enrichment in experimental studies, few if any attempts have been made to rigorously evaluate the effect of environmental enrichment in the clinical setting. The evidence from animal stroke models, and the knowledge that patients spend too much time being inactive, supports development of studies to apply similar enrichment principles to the environment of human stroke patients.

Because of the large variability of human stroke type and severity, studies attempting to show improvements in functional outcomes such as motor skill and cognition, require large sample sizes. Greater activity levels prior to stroke (11) and more intense and frequent therapy during the recovery phase of stroke (1,2,12) are all advantageous for functional recovery. Hence, activity level of stroke patients is the most practical and appropriate surrogate outcome to assess in initial studies, before embarking on large multicentre studies assessing functional outcomes. Importantly, given the major components of environmental enrichment as it is defined in animal models includes physical, cognitive, and social stimulation, we will measure the level of activity of stroke patients in all three domains. We hypothesize that enriching the environment of stroke patients is feasible and will significantly increase their activity levels.

There are currently no well-validated tools to determine multidomain activity levels in this patient population. Therefore an observational tool was developed prior to this pilot study to measure where and with whom stroke survivors spend a typical day on the rehabilitation ward, and the time spent engaged in physical, social, and cognitive activities. This tool will be used to measure any change in activity that occurs over time in both the standard and EE.

Methods

Design

It is a prospective nonrandomized block design intervention study (see Fig. 1). In the first phase (control phase) we will determine the change in activity levels of patients treated in a usual rehabilitation setting. In the second phase the change in activity levels of patients exposed to environmental enrichment (intervention group) will be determined. Structured observational techniques (behavioural mapping) will be used to quantify the change in activity levels before and during exposure to the intervention.

Patient population

Stroke patients receiving rehabilitation for stroke in a rehabilitation ward.

Inclusion criteria

Patients will be included in the study if they meet the following criteria: a premorbid modified Rankin Scale score of ≤ 2, an ability to follow at least one-step commands, and able to stand with the assistance of two people or less.

Exclusion criteria

Patients will be excluded if there are behavioural, medical, or other factors, which will prevent safe participation in standard rehabilitation activities and procedures usually undertaken in this rehabilitation ward. Patients will be automatically excluded if the estimated length of stay is less than the 16-day observational period required to collect the observational data.

All research will be conducted according to national guidelines and approval has been obtained from the Hunter New England Health Human Research Ethics Committee (HNEH HREC 09/09/16/5.08). Any adverse events will be reported to this committee.

Intervention

During the two-week intervention phase, patients will have access to both individual and communal forms of environmental enrichment. In addition to standard rehabilitation therapies delivered on the ward, participants will be given access to a communal enrichment area, which will include computer with internet connection, reading material (fiction and nonfiction books, coffee table books, newspapers), jigsaw puzzles, board games, and a dining area for eating meals. Nintendo Wii gaming will be made available twice a week in this communal enrichment area and recreational activity groups (including Nintendo Wii gaming) will be held in this same setting every Saturday morning. Individual enrichment will involve the provision of activities of the participant's choice including music, audio books, books, word and number puzzles, and board games. Family members of participants will be encouraged to bring in hobbies and activities that participants enjoyed prior to their stroke.

Rehabilitation team members will be advised to encourage participants to attend the communal enrichment area. Additionally, team members will be advised to encourage the participants to utilize the enrichment activities provided to them if the participant is witnessed to be inactive. At no stage will the participants be coerced into utilizing the enrichment equipment and activities. They will be used at the discretion of the participants.

In both the control and intervention phase, patients will be advised they are in a study investigating the effect that the

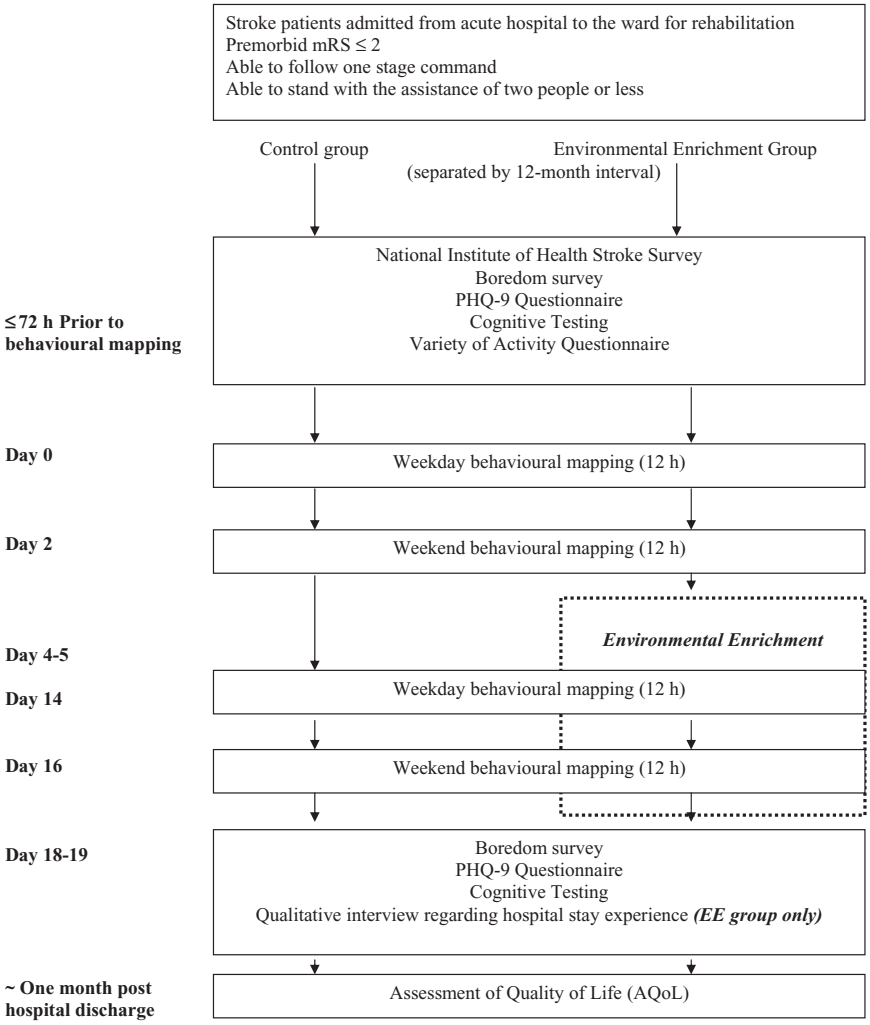

Fig. 1 Flow chart of patients through study. EE, enriched environment; mRS, modified Rankin Scale; PHQ-9, Patient Health Questionnaire 9.

environment has on a stroke survivor's activity levels during rehabilitation. There will be no mention of 'environmental enrichment', nor will there be any instructions or suggestions to the patient encouraging anything other than normal behaviour in this setting.

Setting

Both phases of the study will be conducted in the same ward of a stand-alone rehabilitation hospital. This ward accepts rehabilitation referrals from two large tertiary hospitals, both of which have acute stroke units and teams involved in a large number of clinical stroke trials. The typical rehabilitation ward has four four-bed, one two-bed and two single-bed rooms. There are two main communal areas: the dining room, located in the centre of the ward opposite the nurses' station, and the 'solarium', a multipurpose area located at the end of the ward hallway. The occupational therapy Activities of Daily Living rooms (kitchen and bathroom) and the Independent Living Unit are located on the same level as the rehabilitation ward. All other allied health therapy rooms, including the physiotherapy and occupational therapy gyms, are on the floor above the rehabilitation ward.

Primary outcome

The primary outcome will be change in activity level as measured using behavioural mapping. The behavioural mapping tool that will be used to observe participants recruited in this study is a modification of that which has been used extensively in observational research involving stroke patients in similar settings (3,4,13); it enables the observation of more than one patient at a time through the use of checklists containing predetermined categories that encapsulate the patient's activity, their location, and whether other people are present.

Participants will be followed for approximately 16 days and behaviour will be observed on two weekdays (Thursdays, day 0, and day 14) and two weekend days (Saturday, day two, and day 16) during this time (Fig. 1). A total of 48 h of mapping

will be conducted on each participant. Every 10 min, patient location, with whom they are with (people present) and what they are doing (physical, cognitive, or social activity) will be recorded. When participants are not able to be observed directly (i.e. because of curtains being drawn or while in showers and toilets), activity will be estimated after conferring with nursing staff or nearby patients. If a participant is unable to be clearly seen and activity unable to be estimated, this will be classified as an unobserved episode and will not contribute to the total number of observations made for the participant.

Behavioural mapping categories

The observation of physical, cognitive, and social activity will be a yes or no response. A physical activity is defined as any everyday, personal, athletic, recreational, or occupational activities that require physical skills and utilize strength, power, endurance, speed, flexibility, range of motion, or agility. This encompasses virtually any purposeful physical movement and as such included activities such as eating or drinking using utensils, etc., all personal activities of daily living and active participation in transfers, ambulation and physical, occupational, and speech therapies.

A cognitive activity is defined as any nonphysical leisure activity that involves the participant actively engaging in a mental task. Examples include reading a book or newspaper, listening to music or the radio, crosswords, puzzles, games, speech therapist-prescribed language exercises, occupational therapy prescribed cognitive exercises, video games, writing, computer use, and playing a musical instrument.

Social activity is defined as any interaction, which involves verbal communication with people present or through telecommunication devices, and other nonverbal interactions such as touching, kissing, or holding. Examples include: talking, laughing, touching, telephone/mobile phone/email/internet forum use and being present within a group of people engaged in 'group therapies/activities'.

For anticipated situations in which participants may be engaged in more than one type of activity at once, guidelines were prespecified for whether the behaviour or activity should be classified as one, two, or three activity categories. The decision process involved careful consideration of the predominant action (physical, cognitive, or social), the participant was executing. For example, reading while holding a book or writing to complete written puzzle was classified as cognitive alone, not physical and cognitive. Most allied health therapies involved a combination of activities and as such were coded to reflect this. For example, physiotherapy treatments that involved manual assistance (touching) during movement training were recorded as physical and social activity. A participant observed to be playing the Nintendo Wii with someone else was categorized as performing physical, cognitive, and social activities.

The location categories will encompass the following areas: bedside (any area within a two-metre radius of their bed), therapy area/room, communal (dining room, hallway, reception area, solarium, nurses station), amenities (toilet and shower rooms), offsite (attending tests at other hospitals, home visit, gate leave), and other (outside, nonallied health room, and veranda).

The category of people present will include: medical, nursing, or hospitality staff; other patients; therapists; visitors; others and alone.

Behaviour observations will be made inconspicuously for less than two-seconds, with a rater selecting subcategories based on the initial people present and activity observed. Participants will be first sought by their bedside and then when not present, elsewhere within the ward, hospital, and then outside. Five randomly selected 15-min breaks will be taken during each 12 h day, making for a possibility of 65 observations for each participant, each day (total of 260 observations for each participant over the period of the study).

Inter-rater reliability

All research assistants involved in the behavioural mapping phase of the study will receive a minimum of three-hours of training, which will involve explanation of the category definitions, working through examples and practice observations. The first author will provide supervision during the trial and study behavioural mapping phases until ≥90% consensus is reached across all categories.

Other variables collected

Physical and psychosocial function

Additional data collected on entry to and exit from both control and intervention phase includes: function using the Functional Independence Measure, mood using the Patient Health Questionnaire 9 (14), and boredom using the Stroke Rehabilitation Boredom Survey (a purposely designed short Likert questionnaire) (Online Supplement 1·0). Quality of life will be assessed using the Assessment of Quality of Life instrument approximately 1 month postdischarge from the rehabilitation setting.

Cognitive function

A battery of cognitive tests will be administered on entry to and exit from both Phase One and Phase Two of the study. Premorbid IQ will be measured using the Wechsler Test of Adult Reading (15) and screening for dementia or mild cognitive impairment will be performed using the Montreal Cognitive Assessment (16). A set of neuropsychological tasks will be used to assess auditory and visual working memory (Digit Span Forward and Backward from Wechsler Adult Intelligence Scale and Symbol Span from the Wechsler Memory Scale-IV); immediate and delayed memory in auditory and visual modalities (Logical Memory and Visual Reproduction from the Wechsler Memory Scale-IV and Pattern Recognition from Cambridge Neuropsychological Test Automated Battery) (17).

Attention will be assessed using the simple and choice reaction time tasks and aspects of executive functioning will be assessed using the intradimensional/extradimensional Shift task from the Cambridge Neuropsychological Test Automated Battery.

Baseline characteristics

Severity of stroke will be determined using the National Institutes of Health Stroke Scale. File audits will be conducted at entry to the study to collect: demographics (age and gender) and premorbid histories including comorbidities, mobility status and living arrangements; stroke profiles including length of acute admission and day of admission to the rehabilitation ward; type, location, and Oxfordshire Classification of stroke and current level of function including mobility, transfer, continence, and communication status. Premorbid involvement in physical, cognitive, and social activities and exercise will be estimated using the Variety of Activity Questionnaire (18) (Online Supplement 2·0). Highest level of education achieved and main occupation will be obtained during interview.

Mobility status throughout the study period and any events, which prevented participation in typical rehabilitation activities, will be noted. Additionally, participant involvement in clinical trials, staffing levels, and ward activities, which deviate from the norm for this rehabilitation setting, will be recorded.

Experience of participant and staff

In order to determine acceptability of the intervention to participants and to nursing and allied health staff, both will undertake qualitative interviews. Patient interviews will be conducted following completion of the intervention period, whereas staff interviews will take place following completion of the entire study. Interview with patients will aim to explore the experience of both their rehabilitation admission and exposure to the environmental enrichment. Qualitative interviews with staff will explore their experience of and attitudes towards the environmental enrichment.

Measures for feasibility

The main measure of feasibility in this study will be a statistically significant increase in activity of the intervention group compared against the control group. Other determinants of feasibility will include: recruitment (ease of and suitability of inclusion and exclusion criteria), tolerability of the environmental enrichment (communal and individual), and completion of the other variables collected.

Facilitators and barriers to environmental enrichment will be observed and recorded throughout the period of the study.

Sample size

Assuming that the correlation between repeated measurements on subjects is 0·6 and using an alpha level of 0·05, 11 subjects per intervention arm will give the study 80% power to detect a one standard deviation difference between study groups in the mean level of any activity in the postintervention period.

Statistical analysis

Observed location, people present and behaviour will be collected using behavioural mapping spreadsheets.

Only observed or 'estimated' behaviour will be included in the analysis. For each observation, the patient will be presumed to have participated in that activity for the preceding 10-min block of time. This will permit estimation of the proportion of time undertaking each type of activity, and calculation of the change over time and postintervention. To determine if the mean change is different between the control and treatment groups Poisson regression within a Generalized Estimating Equation framework to adjust for the repeat measurements on individuals will be used. The unit of time for observations in the model will be day, with outcome being the number of times the individual is doing the activity on that day. The predictor variables in the model will include day (weekday or weekend), an indicator variable for time (before and after), a group variable (control or treatment) and an interaction term for group by time. The *P*-value associated with the coefficient of the interaction term will be used to determine whether there is a statistically significant difference in change in the treatment group compared with the control group.

Difference scores (post- minus prerehabilitation) will be computed for each of the memory, attention, and executive function measures to examine changes in performance over the rehabilitation period. Differences between control and enriched groups will be compared statistically using analysis of variance. We will also look at individual profiles across all the cognitive tasks and examine these in relation to location of stroke and activity measures.

Nonparametric testing will be used to compare baseline measures of the control and intervention group.

An inductive thematic approach will be used to analyze qualitative data.

Study organization and funding

Control phase

Participants in the control phase will be followed for approximately 16 days and behaviour will be observed on two weekdays (Thursdays, day 0, and day 14) and two weekend days (Saturday, day two, and day 16) during this time. The Functional Independence Measure, Patient Health Questionnaire 9, Stroke Rehabilitation Boredom Survey, and the battery of cognitive tests will be collected just prior to and following the first and last weekday and weekend observation days (Fig. 1).

Intervention phase

Observational procedures and data collection performed in the control phase will be repeated on participants in the inter-

vention phase. Patients will be orientated to the communal enrichment area and will be provided with individual enrichment activities on days four and five, following the completion of the first weekday (day 0) and weekend (day two) behavioural mapping days (Fig. 1).

This trial is registered with the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), ACTRN12611000629932.

Summary

Increasing activity levels is central to better functional outcome in poststroke rehabilitation, yet current approaches are not achieving this. High-intensity treatments and more frequent therapy have been shown to effect better functional outcomes in patients recovering from stroke. However, therapist-driven therapy is costly and observational studies in this patient population reveal low levels of therapeutic activity (5,19,20). Stroke remains one of the leading causes of adult disability in developed countries (21). Over 50% of stroke survivors who are functionally dependent after stroke, remain so up to 18 months later (22). Stroke incidence is also predicted to increase significantly in coming decades with the ageing of the population (23). Hence, it is crucial that those involved in stroke research focus on discovering cost-efficient treatment interventions.

Environmental enrichment is an appealing method to increase activity levels within budgetary constraints. Evidence accumulated over many years of experimental stroke research using environmental enrichment indicates there is great potential to improve physical and cognitive functioning of stroke patients (10). Environmental enrichment is relatively inexpensive, requiring a one-off purchase of equipment and relying on little staff involvement. To date there has been little study of the effectiveness of this intervention in stroke patients. We seek to redress this deficit with an initial study to determine the feasibility of environmental enrichment of a rehabilitation ward, and whether this is able to increase the activity levels of patients. As in animal models of stroke, interaction with the environmental enrichment used in this pilot will be voluntary, not coerced. It remains to be seen whether this is sufficient to facilitate activity in human stroke survivors. As the experimental work has highlighted the importance of enrichment in multiple domains we have modified a behavioural mapping tool to enable assessment of social, cognitive, and physical activity.

Making changes to the recovery environment is a potentially very cost-effective way to improve activity, and if demonstrated to enhance recovery, would be a broadly applicable technique with enormous potential public health impact.

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CHAPTER 5

QUANTIFYING PHYSICAL COGNITIVE AND SOCIAL ACTIVITY LEVELS POST-STROKE

PUBLICATION 3

Janssen H, Ada L, McElduff P, Pollack M, Nilsson M, Berhardt J, Spratt NJ. Physical, cognitive and social activity levels of stroke patients undergoing rehabilitation in a mixed rehabilitation unit. *Clin Rehabil*. 28 Nov 2012; Epub ahead of print.

Prior to the completion of the first phase of our pilot trial, the majority of observational research conducted on stroke patients undergoing rehabilitation focused on physically based activities such as walking, and or participation in physical and occupational therapies. Very little, if any, data on the cognitive and social activity levels of stroke patients undergoing rehabilitation had been published.

The first publication arising from the clinical trial of this thesis quantified physical, cognitive and social activity levels of stroke patients in a non-enriched mixed rehabilitation unit. This cohort of patients formed the control group of the pilot study **[Chapter 6: Publication 4]** and involved estimating how activity levels change over a

two week period. These data represents the change in patient activity which occurs in response to a combination of: (i) natural rate of stroke recovery, and (ii) access to standard inpatient stroke therapies and management.

This was the first study to define and quantify cognitive and social activity, and is the first to monitor activity levels over time (two week period). Additionally, the following chapter and included publication outlines the relationship between the change in activity levels of patient's undergoing rehabilitation in a mixed rehabilitation unit, and the change in their level of independence and mood.

"As co-authors of the paper Janssen H, Ada L, McElduff P, Pollack M, Nilsson M, Berhardt J, Spratt NJ. Physical, cognitive and social activity levels of stroke patients undergoing rehabilitation in a mixed rehabilitation unit. *Clin Rehabil*. 28 Nov 2012; Epub ahead of print.

we confirm that Heidi Janssen has made the following contributions:

• 75% conception and design of the research

• 75% analysis and interpretation of the findings

• 75% writing the paper and critical appraisal of content."

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Physical, cognitive and social activity levels of stroke patients undergoing rehabilitation within a mixed rehabilitation unit

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Abstract

Objective: To determine physical, cognitive and social activity levels of stroke patients undergoing rehabilitation, and whether these changed over time.

Design: Observational study using behavioural mapping techniques to record patient activity over 12 hours on one weekday and one weekend day at baseline (week 1) and again two weeks later (week 2).

Setting: A 20-bed mixed rehabilitation unit.

Subjects: Fourteen stroke patients.

Interventions: None.

Main measures: Percentage of day spent in any activity or physical, cognitive and social activities. Level of independence using the Functional Independence Measure (FIM) and mood using the Patient Health Questionniare-9 (PHQ-9).

Results: The stroke patients performed any activity for 49%, social activity for 32%, physical activity for 23% and cognitive activity for 4% of the day. Two weeks later, physical activity levels had increased by 4% (95% confidence interval (CI) 1 to 8), but levels of any activity or social and cognitive activities had not changed significantly. There was a significant: (i) positive correlation between change in physical activity and change in FIM score (r = 0.80), and (ii) negative correlation between change in social activity and change in PHQ-9 score (r = –0.72). The majority of activity was performed by the bedside (37%), and most physical (47%) and cognitive (54%) activities performed when alone. Patients undertook 5% (95% CI 2 to 9) less physical activity on the weekends compared with the weekdays.

Conclusions: Levels of physical, cognitive and social activity of stroke patients were low and remained so even though level of independence and mood improved. These findings suggest the need to explore strategies to stimulate activity within rehabilitation environments.

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Stroke, rehabilitation, behavioural mapping, social and leisure activities

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Introduction

Patients undergoing inpatient rehabilitation after stroke spend very little of their day active. Synthesis of observational research conducted in mixed rehabilitation units suggests that stroke patients spend as little as 20% of their day engaged in physical activity related to rehabilitation (therapeutic activity), spend the majority of their day by their bedside (~70%), and half of their day alone.[1] At weekends, relative to weekdays, activity levels are significantly lower, and a greater percentage of the day is spent by the bedside and alone.[2,3] The uniformly low levels of activity in these studies is concerning given the evidence from both animal[4] and human[5] stroke research of a strong association between higher levels of activity and better functional recovery.

Not surprisingly, most activity research conducted on stroke patients undergoing rehabilitation has focused on measurement of physical activities. Little emphasis has been placed on non-physical behaviours such as cognitive (i.e. reading or listening to music) and social activities (i.e. talking or touching), and hence the extent of engagement in such during rehabilitation has yet to be determined. In addition, we are yet to understand how physical, cognitive and social activity levels of stroke patients change during their time in hospital. It is conceivable that as patients recover in response to rehabilitation, become more independent and their mood improves, activity levels would increase. Although logical, there is very little objective data to support this hypothesis. For example, findings from one observational study suggest functional ability on admission to rehabilitation does not influence activity levels.[3] Another reveals mood is a significant predictor of activity levels, but this is from observation of stroke patients once they have returned home.[6]

Although stroke patient engagement in therapeutic activity is lower on weekends relative to weekdays,[2,3] how cognitive and social activity levels change between these days remains unknown. Furthermore, who is present during each particular activity (physical, cognitive and social) has yet to be explored.

Hence the aim of this study was to observe stroke patients in a mixed rehabilitation unit to determine the level of cognitive and social activity, as well as physical activity, and how these levels change over time. The specific research questions were:

1) How frequently do stroke patients on a rehabilitation unit engage in activity – specifically, physical, cognitive and social activity?
2) Do activity levels change over time?
3) What is the relationship between change in activity and change in level of independence and mood?
4) Is there a difference between activity levels on weekdays and weekends?
5) Are activity levels of stroke patients dependent on their location and which people are present?

Method

An observational longitudinal study of activity levels of stroke patients was conducted in a mixed rehabilitation unit. The design and flow of the study is outlined in Figure 1. Patients admitted to the unit for stroke rehabilitation over a four-month period were screened for inclusion. Physical, cognitive and social activity levels of patients were collected using behavioural mapping with checklists containing predetermined categories to map the distribution of behaviour.[7] Time spent in activity was collected at the beginning of the observation period (baseline, week 0) on one weekday (Thursday, day 0) and one weekend day (Saturday, day 2), and then

collected again on the same days, two weeks later (week 2) (Thursday, day 14 and Saturday, day 16). Activity was measured by two trained researchers (HJ and SR) every 10 minutes from 8 am until 8 pm. A total of 48 hours of direct observation was conducted on each participant. Level of independence and mood were collected at the beginning and end of the observational period. The study was approved by the Hunter New England Health Human Research Ethics Committee (HNEH HREC 09/09/16/5.08).

The study was conducted in the 20-bed mixed rehabilitation unit of a stand-alone rehabilitation hospital. This unit receives referrals to rehabilitate patients with both medical and neurological conditions from two large tertiary hospitals, both of which have acute stroke units and teams involved in stroke research. The unit has 4 × four-bed, 1 × two-bed and 2 × single-bed rooms. Two main communal areas include: the dining room, located in the centre of the unit opposite the nurses' station, and the 'solarium', a multipurpose area located at one end of the unit. The occupational therapy activities of daily living rooms (kitchen and bathroom) and the independent living unit are located on the same level as the bedrooms. All other therapy rooms, including the physiotherapy and occupational therapy gyms, are on the floor above. Access to these therapy areas is via stairs or a lift. Staff to patient ratios on the weekday were: nurses 1 : 3 (morning) and 1 : 5

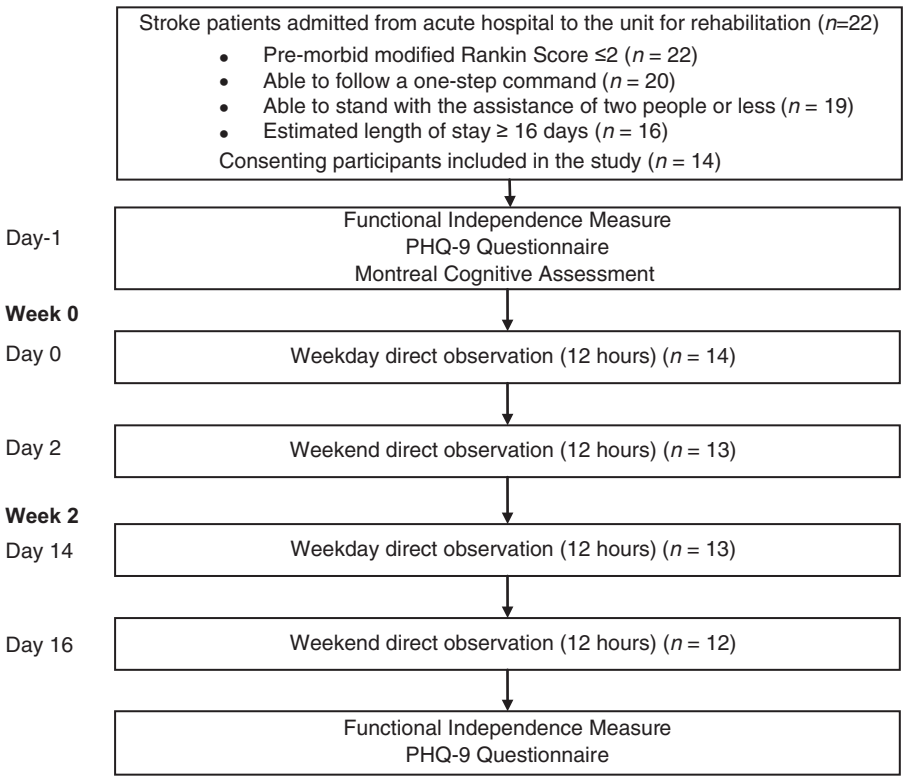

Figure 1. Design and flow of patients through the study.

(afternoon), physiotherapists 1 : 10, occupational therapists 1 : 8, speech therapists 1 : 10, social workers 1 : 12, physiotherapy aides 1 : 18, and occupational therapy aides 1 : 20.

Patients admitted to the mixed rehabilitation unit from an acute stroke unit or equivalent were screened for eligibility by an investigator (HJ) and were eligible for the study if they had an estimated length of stay ≥16 days, had a pre-morbid modified Rankin Score[8] of ≤2 (indicating no or little pre-morbid disability), were able to follow at least one-step commands, and were able to stand with the assistance of two people or less. Patients were excluded if there were behavioural, medical, or other factors which prevented their safe participation in standard rehabilitation.

In order to describe patient characteristics, stroke severity, pre-morbid engagement in activity and post-stroke cognition were collected. Characteristics of patients including: age, gender, language spoken at home, years of education, main occupation, type, date and side of stroke were obtained from medical records by an investigator (HJ). Severity of stroke was determined by an investigator (HJ) using the National Institute of Health Stroke Scale (NIHSS), which is a neurological examination scale grading motor, sensory and cognitive impairments, speech, language, visual deficits and ataxia.[9] Stroke severity is categorized as mild (NIHSS <8), moderate (NIHSS 8–16), or severe (NIHSS >16).[10] Frequency of engagement in physical, cognitive and social activities prior to stroke was determined using the self-report Variety of Activity Questionnaire.[11] This comprises four categories – cognitive, social and physical activity, and exercise – where a higher score reflects greater participation in activity (range 0–152). Cognition was determined by a research student (NB) using the Montreal Cognitive Assessment (MoCA) (0–30). A score ≥26 indicates normal cognition.[12]

The main measures were time spent in any activity and the three main types of activity (physical, cognitive and social), level of independence and mood. Time spent in activity was measured via direct observation using purpose-designed behavioural mapping checklists similar to those used previously.[2,13,14] Observations were made inconspicuously for a few seconds every 10 minutes during a 12-hour day. Five randomly selected 15-minute breaks were taken each day, making a possibility of 65 observations for each participant each day (total of 260 observations for each participant over the four days of observation).

Activity was categorized at the time of observation as physical, cognitive, social or sleeping. Physical activity encompassed virtually any purposeful physical movement, including activities such as eating, drinking, all personal activities of daily living and active participation in transfers, ambulation and activity during physical, occupational and speech therapies. Cognitive activity encompassed any non-physical mental activity in which the participant could be observed to be actively engaging in a mental task, including reading a book or newspaper, listening to music or the radio, crosswords, puzzles, games, speech therapist-prescribed language exercises, occupational therapy-prescribed cognitive exercises, video games, writing, computer use and playing a musical instrument. Watching television was not classified as a cognitive activity. Social activity encompassed any interaction which involved verbal communication with people present or through telecommunication devices, and other non-verbal interactions such as touching, kissing or holding. This included: talking, laughing, touching, use of the telephone/mobile phone/email/internet forums and being present within a group of people engaged in 'group therapies or activities'. Participants could be recorded as engaged in more than one type of activity. Sleeping was defined as sitting or lying with eyes closed.

'Any activity' was defined as behaviours or tasks which involved any one, or a combination of the activities which were classified as being physical, cognitive or social. As there was potential to have more than one type of person present and to be performing multiple activities at the one time, the percentage of people present and activity are not discrete (i.e. nursing staff could have been present while a participant was walking (physical activity) while talking (social activity) to a visitor).

People present and location were also recorded. People present were categorized as medical, nursing

or hospitality staff, other patients, therapists, visitors, others and alone. Alone describes circumstances where there was no one within a 2-m radius of the patient conducive to interaction. 'Inactive and alone' was defined as not being within a 2-m radius of a person conducive to interaction and not performing physical, cognitive and or social activity.

Location was categorized as bedside (any area within a 2-m radius of their bed), therapy area/room, communal (dining room, hallway, reception area, solarium, nursing station), amenities (toilet and shower rooms) and other (attending tests at other hospitals, home, outside, non-therapy room and verandah).

Participants were first sought by their bedside and then elsewhere within the unit, hospital and then outside. When participants were not able to be directly observed (e.g. because curtains were drawn or while in showers and toilets), activity was recorded after conferring with nursing staff or others nearby. In circumstances where activity was not able to be estimated, participants were classified as unobserved and these episodes did not contribute to the total number of observations made for that participant. The investigator (HJ) and research assistant (SR) who conducted the behaviour mapping received a minimum of 3 hours of training which involved explanation of the category definitions, working through examples and practice observations. Training was provided by investigators (HJ and LA) until ≥90% consensus was reached across the categories.

Level of independence was measured by nurses on the unit accredited in the use of the Functional Independence Measure (FIM).[15] Mood was measured using the Patient Health Questionnaire (PHQ)-9, a 9-item self-report questionnaire used to screen for depression,[16] where scores range from 0 (no symptoms) to 27 (severe depression, symptoms occurring daily).[17] Both measurement tools have been found to be both valid and reliable for use in the stroke population.[18,19]

Activity, location and people present for each participant, for each day (day 0, 2, 14 and 16), was expressed as a percentage of the total number of observations made. Mean change in activity from week 0 (day 0 and 2) to week 2 (day 14 and 16) was calculated within a generalized estimating equation framework to adjust for the repeat measurements on individuals. The unit of time for observations in the model was day, with outcome being the number of times the individual was doing the activity on that day. The predictor variables in the model included day (week or weekend) and period (week 0 and week 2). The mean difference between level of independence and mood at week 0 and week 2 was calculated using a paired *t*-test.

A Pearson product–moment correlation coefficient (*r*) was calculated to assess the relationship between change in activity and (i) change in level of independence (FIM) and (ii) change in mood (PHQ-9). The 95% confidence intervals (CI) for Pearson's *r* was calculated using Fisher's transformation.

The mean difference between activity on the weekend (averaged across day 2 and day 16) and weekday (averaged across day 0 and day 14) was calculated within a generalized estimating equation framework. The mean percentage of observations of activity for people present and location is presented as an average the two weeks (day 0, 2, 14 and 16). Statistical significance for all analyses was set at 0.05. All statistical analyses were performed using STATA 11.0.[20]

Results

The flow of participants through the study is summarized in Figure 1. Twenty-two patients were admitted to the stroke rehabilitation unit during the study period. Sixteen of these met the inclusion criteria, of whom 14 consented to participate in all study procedures. Two of the 14 participants recruited for the study were discharged unexpectedly prior to the completion of observations, but all available data was included in the analyses.

The characteristics of participants at baseline are summarized in Table 1. The median age of participants included in the study was 78 years, the majority had a right hemiparesis, and had suffered a mild stroke (i.e. median NIHSS score of 3). All participants had cognitive impairment (which is <26/30 on the MoCA). Educational level was low, with only four receiving formal education beyond the age of

16. Pre-morbid level of activity of the group was low, with a median score of 49 out of 150 on the Variety of Activity Questionnaire.

The median time from onset of stroke to the beginning of the observational period (week 0) was 17 days. Observational data of the main measures are presented in Table 2. There were 114 (3%) instances of unplanned non-observations out of a total of 3353 observations. A total of 1758 observations were made at week 0 (869 on a Thursday and 889 on a Saturday), and 1481 were made at week 2 (714 on a Thursday and 767 on a Saturday). After accounting for occasions when participants were unobserved, were discharged prior to completion of collection of activity data and for breaks taken by researchers conducting the behaviour mapping, the mean number of observations of activity made each day was 63 (SD 5). This equates to 10.5 hours of observation spread over a 12-hour day. Results are expressed as a function of time, where 100% is 10.5 hours, which for the purposes of this study is considered representative of a stroke patient's typical day (i.e. waking hours) within this mixed rehabilitation unit.

Group mean (SD) of all activity at each week and the mean (95% CI) difference between activity over two weeks as calculated using a generalized estimating equation are presented in Table 3. At baseline, approximately three weeks following stroke, patients were engaged in any type of activity for 49% of the day, social activity for 32% of the day, physical activity for 23% of the day, and cognitive activity for 4% of the day. Two weeks later, physical activity levels had increased by 4% (95% CI 1 to 8) but any, social and cognitive levels had not changed significantly.

At baseline, participants had a mean FIM score of 69/126, indicating a moderate level of independence, and a mean PHQ-9 score of 10/27, indicating low mood given (10 is the lower limit of moderately severe depression).[21] Level of independence and mood both improved over two weeks, with a mean 19-point (95% CI 12 to 26) increase in FIM score and a 4-point (95% CI 1 to 8) reduction in PHQ-9 score.

Table 1. Baseline characteristics of participants

Characteristic	(*n* = 14)
Age (years), median (IQR)	78 (68–81)
Gender, *n* males (%)	9 (64)
English second language, *n* (%)	3 (21)
Number of patients receiving formal education beyond the age of 16, *n* (%)	4 (29)
Variety of Activity Questionnaire (0–152), median (IQR)	49 (41–57)
Physical activity (0–36)	18 (16–19)
Cognitive activity (0–36)	17 (12–20)
Social activity (0–36)	11 (7–15)
Exercise (0–44)	4 (1.5–7)
First ever stroke, *n* (%)	9 (64)
Infarct, *n* (%)	12 (86)
Severity of stroke, NIHSS (0–21), median (IQR)	3 (2–8)
Mild (<8), *n* (%)	10 (71)
Moderate (8–16), *n* (%)	3 (21)
Severe (>16), *n* (%)	1 (7)
Side of hemiparesis, right (%)	10 (71)
Time from stroke to first observation (days), median (IQR)	17 (10–28)
Time from admission to rehabilitation unit to first observation (days), median (IQR)	5 (2–8)
Cognition, MoCA (0–30), median (IQR)	16 (12–19)

NIHSS, National Institute of Health Stroke Scale; MoCA, Montreal Cognitive Assessment.

Table 2. Number of observations (% of total observations)[a] of main measures for each day

Main measure	Week 0		Week 2	
	Weekday *n* = 869	Weekend *n* = 889	Weekday *n* = 714	Weekend *n* = 767
Any activity	434 (50)	413 (46)	382 (54)	368 (48)
Physical activity	227 (26)	180 (20)	214 (30)	197 (26)
Cognitive activity	39 (4)	36 (4)	41 (6)	30 (4)
Social activity	281 (32)	274 (31)	205 (29)	184 (24)
Inactive and alone	328 (38)	382 (43)	254 (36)	288 (38)
Sleeping	115 (13)	153 (17)	111 (16)	116 (15)
Alone	448 (52)	506 (57)	384 (54)	423 (55)

[a]Activity was not mutually exclusive therefore percentages do not add up to 100.

Table 3. Mean percentage of day spent in activity (SD), level of independence and mood at each week and mean (95% CI) difference between weeks[a]

Main measures	Weeks		Difference between weeks
	Week 0	Week 2	Week 2 minus Week 0
Any activity	49 (18)	51 (15)	4 (–2 to 10)
Physical activity	23 (9)	28 (10)	4 (1 to 8)
Cognitive activity	4 (4)	5 (7)	1 (–2 to 3)
Social activity	32 (18)	27 (15)	–3 (–9 to 3)
Inactive and alone	40 (17)	36 (17)	–5 (–11 to 2)
Sleeping	16 (13)	15 (14)	–2 (–7 to 3)
Alone	54 (20)	54 (22)	0 (–8 to 7)
Level of independence, FIM (18 to 126)	69 (20)	86 (27)	19 (12 to 26)
Mood, PHQ-9 (0 to 27)	10 (7)	6 (7)	–4 (–8 to –1)

[a]Data averaged across the weekday and weekend day observed.
FIM, Functional Independence Measure; PHQ-9, Patient Health Questionnaire 9.

The correlation between change in activity and change in level of independence and mood over the two weeks is presented in Table 4. There was a significant positive correlation between change in physical activity and change in FIM score, and a significant negative correlation between change in social activity and change in PHQ-9 score. That is, social activity levels increased as mood score decreased (improved).

Group mean (SD) of weekday versus weekend day activity and the difference between them are presented in Table 5. On average, patients undertook 5% (95% CI 2 to 9) less physical activity on the weekend compared with the weekday. There was no significant difference between weekdays and weekends for all other activity types.

Mean percentage of observations of activity (SD) according to people present and location are presented in Table 6. Most physical and cognitive activity was carried out when patients were alone, whereas, as anticipated, the majority of social activity was carried out in the presence of medical, nursing or care staff and visitors. The majority of activity was performed by the bedside.

Discussion

Activity levels of stroke patients during the first week of inpatient rehabilitation were very low. Patients spent more than half of the day inactive, and this did not change significantly following

Table 4. Correlation between change in activity and (i) change in level of independence (FIM) and (ii) change in mood (PHQ-9) presented as a Pearson's *r* (95% CI)

Change in activity	Correlation with change in level of independence	Correlation with change in mood
Any activity	–0.51 (–0.84 to 0.09)	–0.43 (–0.81 to 0.19)
Physical activity	0.80 (0.42 to 0.94)	0.08 (–0.52 to 0.63)
Cognitive activity	0.21 (–0.41 to 0.70)	0.07 (–0.53 to 0.62)
Social activity	–0.20 (–0.69 to 0.42)	–0.72 (–0.92 to –0.25)
Inactive and alone	–0.26 (–0.73 to 0.37)	0.44 (–0.18 to 0.81)
Sleeping	0.10 (–0.50 to 0.64)	0.23 (–0.40 to 0.71)

Table 5. Mean percentage of day spent in activity (SD) activity on week and weekend days and mean (95% CI) difference between days[a]

Activity type	Days		Difference between day
	Weekend	Week	Weekend minus week
Any activity	47 (17)	52 (16)	–4 (–10 to 1)
Physical activity	23 (9)	28 (9)	–5 (–9 to –2)
Cognitive activity	4 (5)	5 (6)	–1 (–3 to 1)
Social activity	28 (19)	31 (16)	–3 (–9 to 2)
Inactive and alone	40 (17)	36 (17)	4 (–3 to 10)
Sleeping	17 (12)	14 (15)	3 (–2 to 8)
Alone	56 (22)	52 (20)	4 (–4 to 11)

[a]Data averaged across week 0 and week 2.

Table 6. Mean percentage of observations of activity (SD) according to people present and location[a]

Activity	People present					Location				
	Medical, nursing and care staff	Therapists	Other patients	Visitors	Alone	Bedside	Common areas	Therapy rooms	Amenities	Other
Any activity	11 (5)	5 (3)	10 (11)	17 (12)	16 (9)	37 (15)	7 (7)	2 (1)	4 (2)	0 (1)
Physical activity	21 (17)	10 (15)	13 (16)	17 (21)	47 (27)	15 (5)	4 (5)	2 (1)	4 (2)	0 (0)
Cognitive activity	8 (12)	10 (27)	15 (27)	21 (35)	54 (43)	4 (4)	1 (1)	0 (1)	0 (0)	0 (0)
Social activity	32 (19)	12 (19)	21 (23)	44 (32)	9 (19)	22 (12)	4 (5)	2 (1)	1 (2)	0 (1)

[a]Data averaged across week 0 and week 2.

two weeks of rehabilitation. Furthermore, they were 'inactive and alone' for approximately 40% of the day. The majority of time spent active involved social activity, followed closely by physical activity. Less than 5% was spent in cognitive activity. Activity levels during the week were similar to those on the weekend, except for physical activity which decreased on the weekend. An increase in physical activity was associated with an increase in level of independence, while an

increase in social activity was associated with improvement in mood.

The study population was broadly representative of patients in rehabilitation units in terms of age, admission and level of independence,[22] although slightly biased towards men and stroke patients with a right hemiparesis. Furthermore, the design and staff-to-patient ratios of this unit reflect that typical of units in Australia.[22] These factors support the generalizability of our results. In addition, the large number of observations made on each patient, longitudinally, gives us confidence that the majority of behaviour and activity typically undertaken by a rehabilitating stroke patient was captured. This compensates somewhat for the fact that our sample size was relatively small ($n = 14$).

Those performing the behaviour mapping were instructed to be as unobtrusive as possible, and consequently, given that participants rarely acknowledged their presence, it is unlikely that they influenced participant behaviour. Finally, it is possible that patient characteristics other than those included in the correlation analyses (level of independence and mood) influenced post-stroke activity levels in this unit. For example, as in the study by Kulzer et al.,[23] the pre-morbid level of activity of the cohort was low, which could reflect personality traits that predispose an individual to be inactive following stroke.

Our finding that 49% of the day was spent in 'any' activity, physical, cognitive and or social, is a novel finding; as is the evidence that the overwhelming majority of this activity was performed by their bedside. In addition, the definition of physical activity used in our study was very broad, encompassing activities such as eating, drinking and self-care tasks, which in previous observational research have often been excluded from the definition of 'activity'.[1] Hence, it is not surprising that our result is slightly higher than that from studies conducted previously, where between 15 and 20% of the day was spent engaged in therapeutic activities.[2,3] These results add further to the already substantial level of evidence indicating that although medically stable and 'appropriate' for intensive therapy, stroke patients undergoing rehabilitation do very little.[2,3,24,25]

Over the two-week period there was a small but statistically significant increase in the cohort's level of physical activity (4%), while cognitive and social activity remained unchanged. At an individual level, an increase in physical activity was associated with an improvement in level of independence. Although the direction of this relationship remains unclear, this echoes findings from a recent observational study where improvements in mobility function were associated with a small but significant increase in time spent walking, both in and out of therapy sessions.[26] However, this is the first study to highlight the link between an increase in social activity and an improvement in mood in stroke patients within a hospital environment. Similarly, the study design does not permit attribution of a causal relationship between these two factors, but there is evidence from community-based research to suggest that post-stroke depression results in poor social integration[27] and social isolation.[28]

The low and relatively unchanging levels of activity, even in light of improvements in level of independence and mood, suggest that current rehabilitation units may lack sufficient stimulation and challenge for stroke patients. This has to change – not only is there a need to increase the frequency and intensity of inpatient stroke therapy,[29] but as this study highlights, there is great potential to increase patient activity in general during the entire day. There is strong potential here to improve outcomes, considering the evidence from both animal[4,30,31] and human studies,[5] associating higher levels of post-stroke activity with better functional recovery.

Throughout the observation period it became apparent that certain policies and procedures within the unit may have in fact discouraged activity. For example, placing the patient by their bedside after and between therapy sessions. Although this practice may assist unit organization by making it easier to find patients for therapy and meals, it may have unintended consequences, limiting the patients' opportunities to engage in physical, cognitive and social activity. Reorganization of routines to facilitate activity would be a potential strategy to improve rehabilitation.[29]

In what other ways might we alter the environment of rehabilitation units to increase activity levels, enrich the rehabilitation experience, and hopefully improve recovery from stroke? One paradigm developed in animal models that by design promotes activity is an enriched environment. An enriched environment is one where conditions facilitate physical, cognitive and social activity through the presence of equipment and organization of the surroundings.[32] Animals recovering from stroke within an enriched environment demonstrate better sensorimotor and cognitive function than animals recovering in non- enriched environments.[4] Enriched conditions have been shown to trigger neuronal changes instrumental in the process of neuroplasticity.[33] Enriching the environment has yet to be systematically investigated in humans, however this paradigm shows great potential as a means to increase activity of stroke patients. The current study suggests that there is ample room for an increase in activity. A feasibility study is warranted to explore the ability of an enriched rehabilitation environment to increase activity.[34]

Clinical messages

- Stroke patients spend less than 50% of the day in activity and approximately 40% inactive and alone, and this does not change after two weeks of rehabilitation.
- These findings suggest the need to explore strategies to stimulate activity within rehabilitation environments.

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Conflict of interest

There are no conflicts of interest to report.

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CHAPTER 6

PILOT STUDY RESULTS

PUBLICATION 4

Janssen H, Ada L, Bernhardt J, McElduff P, Pollack M, Nilsson M, Spratt NJ. An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: A pilot non-randomised controlled trial. *Disabil Rehabil*. 30 Apr 2013; Epub ahead of print.

This pilot study was the first known attempt to translate a multi-modal model of environmental enrichment (as defined in the laboratory setting).

"As co-authors of the paper Janssen H, Ada L, Bernhardt J, McElduff P, Pollack M, Nilsson M, Spratt NJ. An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: A pilot non-randomised controlled trial. *Disabil Rehabil*. 30 Apr 2013; Epub ahead of print.

we confirm that Heidi Janssen has made the following contributions:

• 75% conception and design of the research

• 75% analysis and interpretation of the findings

• 75% writing the paper and critical appraisal of content."

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REHABILITATION AND PRACTICE

An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: a pilot non-randomized controlled trial

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Abstract

Purpose: An enriched environment (EE) facilitates physical, cognitive and social activity in animal models of stroke. The aim of this pilot study was to determine whether enriching the environment of a mixed rehabilitation unit increased stroke patient activity. *Methods*: A non-randomized controlled trial was conducted. Direct observation was used to determine the difference in change in physical, cognitive, social or any activity over 2 weeks in patients exposed to an enriched versus non-enriched environment. *Results*: Stroke patients in the EE ($n = 15$) were 1.2 (95% CI 1.0–1.4) times more likely to be engaged in any activity compared with those in a non-enriched environment ($n = 14$). They were 1.7 (95% CI 1.1–2.5) times more likely to be engaged in cognitive activities, 1.2 (95% CI 1.0–1.5) times more likely to be engaged in social activities, 0.7 (95% CI 0.6–0.9) times as likely to be inactive and alone and 0.5 (95% CI 0.4–0.7) times as likely to be asleep than patients without enrichment. *Conclusions*: This preliminary trial suggests that the comprehensive model of enrichment developed for use in a rehabilitation unit was effective in increasing activity in stroke patients and reducing time spent inactive and alone.

➤ Implications for Rehabilitation

- Stroke patients within a mixed rehabilitation unit who are exposed to an enriched environment (EE) are more likely to be engaged in activity than those not exposed to the enriched environment.
- Patients in enriched conditions are less likely to be ''inactive and alone'' or asleep during waking hours.
- These results suggest a comprehensive model of enrichment is effective in increasing activity levels.

Keywords

Environmental enrichment, physical activity leisure activities, social activity, stroke

History

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In animal models of stroke, exposure to an enriched environment improves neurobehavioural function and learning [1] and is an appealing and potentially applicable intervention for the clinical setting. An enriched environment refers to conditions in which the provision of equipment and organization of the environment facilitates physical, cognitive and social activity [2]. It enables voluntary exploration and ''challenge-free'' interaction of the animals with each other and with a stimulating environment [3] ie. animals are not ''forced to do any particular task'' [4]. Such stimulating conditions are thought to enhance post-stroke brain recovery by triggering structural changes within the brain which are instrumental in the process of neuroplasticity [5]. These cellular alterations include: an increased number of dendritic spines [6], normalized astrocyte-neuron ratios [7] and advantageous levels of one of the most important neurotrophic factors associated with plasticity, brain derived neurotrophic factor (BDNF) [8].

Stroke patients undergoing inpatient rehabilitation do so in conditions which do not appear to facilitate activity. Observational research conducted over the last thirty years has consistently shown that stroke patients in multiple different rehabilitation units and countries spend the majority of their waking hours physically inactive [9–12]. Post stroke motor impairments cause significant disability, rendering the majority of survivors dependent on others to engage in activity [13]. Engaging in higher levels of therapeutically based physical activity after stroke is associated with achieving better physical function [14] and greater independence [15]. Hence, improving

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sensorimotor function through greater physical activity is an important focus of stroke rehabilitation. There is evidence emerging that the other two components of environmental enrichment – cognitive and social activity – may also be important in maximizing stroke recovery.

Being more cognitively or socially active may reduce the burden associated with stroke related mood disorders and cognitive dysfunction. Cognitive stimulation (listening to music or audio books) for as little as one hour a day for eight weeks early following stroke, has been shown to enhance cognitive recovery and improve mood [16]. Playing challenging board games (ie. Mahjong) has been found to impede cognitive decline and reduce depressive symptoms in elderly people with dementia [17]. Clinical data regarding the efficacy of social activity is scarce but research in experimental stroke indicates that certain aspects of socialisation such as physical contact [18] and being surrounding by others [19], may augment recovery. Simply talking to people or engaging in structured leisure activities, both early (<2 months) [20] and much later (>2–7+years) [21] following stroke, is associated with better health related quality of life (HRQoL).

It is important to investigate the role cognitive and social activity plays in stroke recovery because a significant number of survivors experience cognitive and emotional problems. For example, approximately 20% of stroke survivors experience depression [22] and one in four suffer anxiety [23]. One in five have persisting cognitive impairments [24] and 30–40% develop dementia after their stroke [25]. These, in conjunction with motor impairments, can restrict activity and participation. It is not surprising then that the majority of stroke survivors report a poor quality of life [26].

There is potential to improve the cognitive and social activity levels of stroke survivors undergoing inpatient rehabilitation. Despite the high value they place on personal interactions, both with their fellow patients and their therapists [27], stroke patients spend the majority of the day socially isolated [9,12,28,29]. Work recently completed by our team confirms trends found in previous observational studies [12,30] that less than 5% of a stroke patient's day is spent engaging in cognitively stimulating leisure activities [28]. The aim of this trial, therefore, was to determine whether a human equivalent model of environmental enrichment is effective for stroke survivors undergoing rehabilitation. While the conduct of a multi-unit trial powered to determine the effect of an enriched environment on functional outcomes in patients is our ultimate goal, we first sought to establish whether enriching the environment increases activity levels in humans affected by stroke. To date, there is no data to indicate whether patients exposed to an enriched environment do increase their activity. Without an increase in activity, there is little hope for a functional improvement as a result of this intervention. Given that the mechanism of benefit of EE in animal studies is thought to be through increasing physical, cognitive and social activity, this study examined all three domains. The specific research questions were:

(1) Does exposure to an enriched environment increase the activity levels of stroke patients undergoing rehabilitation?
(2) How do physical, cognitive and social activity levels change with exposure? and
(3) Does an enriched environment reduce the amount of time stroke patients spend sleeping or ''inactive and alone'' during waking hours?

Method

Design

A prospective, non-randomized controlled trial was conducted (Figure 1) [31]. Using intention-to-treat analysis, the activity levels of stroke patients treated in the absence of enrichment (control) were compared with those treated in the same unit immersed in an enriched environment (experimental). All patients admitted to the unit for rehabilitation following stroke during April to August 2010 were screened and recruited to the control group, and those admitted during April to July 2011 were screened and recruited to the experimental group. The intervention period for individual participants was 13 days. Activity levels were collected at baseline (Week 0) on one week day (Thursday, Day 0) and one weekend day (Saturday, Day 2), and then collected again on the same days two weeks later (Days 14 and 16, Week 2). Activity was measured by trained researchers every ten minutes from 8 am until 8 pm on each observation day, making a total of 48 hours of direct observations for each participant. The trial was approved by the Hunter New England Human Research Ethics Committee (HNE HREC 09/09/16/5.08) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000629932).

Setting

The trial was conducted in the 20-bed mixed rehabilitation unit of a stand-alone rehabilitation hospital. This unit receives referrals to rehabilitate patients with both medical and neurological conditions from two large tertiary hospitals, both of which have acute stroke units and teams involved in stroke research. Within this rehabilitation unit there were 4 x four-bed, 1 x two-bed and 2 x single-bed rooms. There were two main communal areas: the dining room, located in the centre of the unit opposite the nurses' station, and the ''solarium'', a multipurpose area located at the end of a hallway. Activities of daily living rooms (kitchen and bathroom) and the Independent Living Unit were located on the same floor. All other allied health areas including the physiotherapy and occupational therapy gyms were located on the floor above. Access to these therapy areas were via stairs or a lift. Staff:patient ratios on the weekday were: nurses 1:4, physiotherapists 1:10, occupational therapists 1:8, speech therapists 1:10, social workers 1:12, physiotherapy aides 1:18 and occupational therapy aides 1:20. These were unchanged over the two time periods.

Participants

Stroke patients were eligible for the trial if they had an estimated length of stay ≥16 days, had a pre-morbid modified Rankin Score [32] of ≤2 (indicating no or little pre-morbid disability), were able to follow at least one-step commands, and were able to stand with the assistance of two people or less. Patients were excluded if there were behavioural, medical, or other factors which prevented their safe participation in standard rehabilitation.

In order to describe patient characteristics, stroke severity, pre-morbid engagement in activity and post stroke cognition were collected. Characteristics of patients including: age, gender, language spoken at home, years of education, main occupation, type, date and side of stroke were obtained from medical records by an investigator (HJ). Severity of stroke was determined by the same investigator using the National Institute of Health Stroke Scale (NIHSS) , which is a neurological examination scale grading motor, sensory and cognitive impairments, speech, language, visual deficits and ataxia [33]. Stroke severity was categorized as mild (NIHSS <8), moderate (NIHSS, 8 to 16), or severe (NIHSS >16) [34]. Frequency of engagement in physical, cognitive and social activities prior to stroke was determined using the self-report Variety of Activity Questionnaire [35]. This comprises four categories, cognitive, social and physical activity, and exercise, where a higher score reflects greater participation in activity (range 0–152). Cognition was determined by research students (NB and RH) using the Montreal Cognitive Assessment

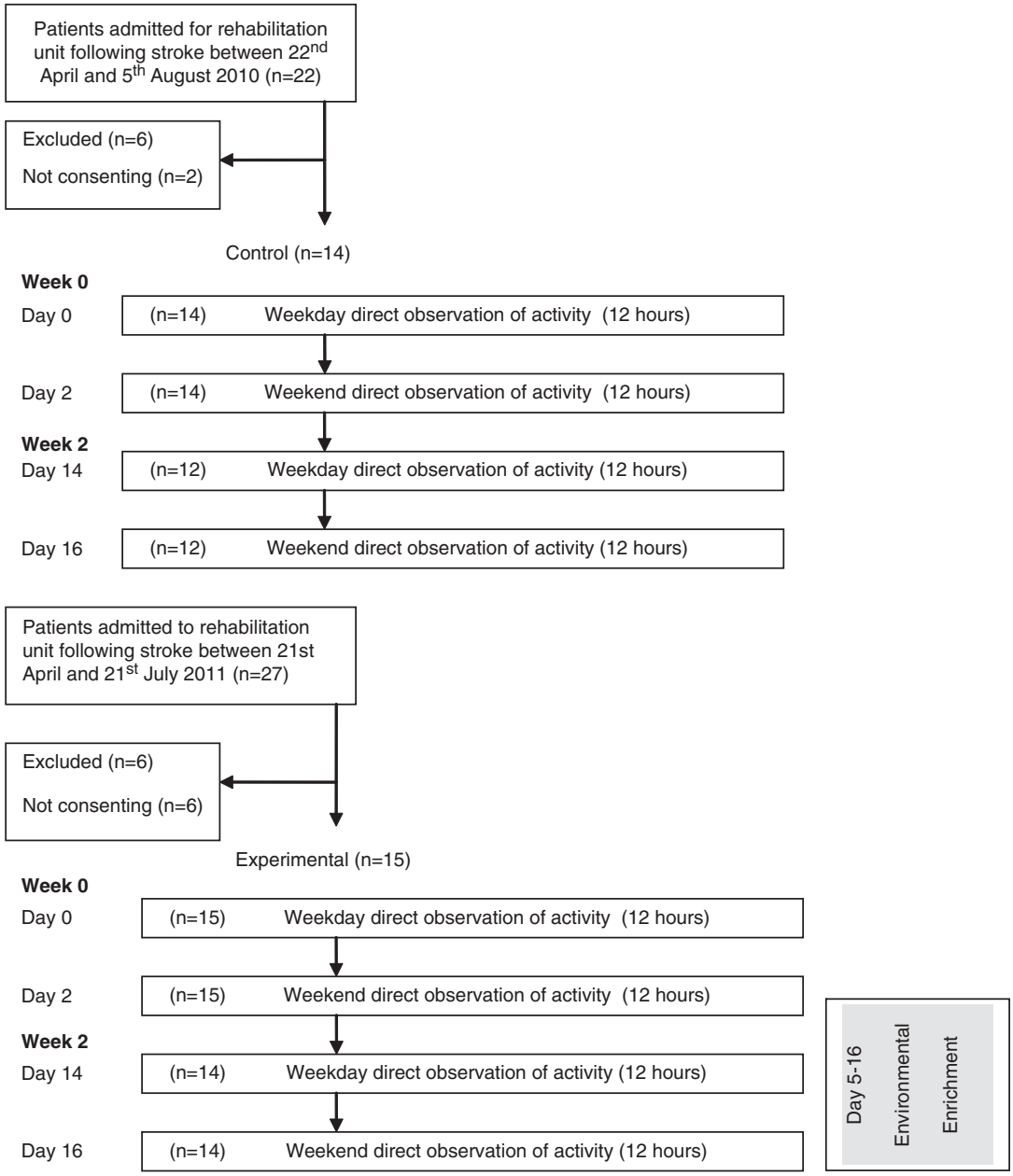

Figure 1. Study design and flow of participants through the study.

(MoCA) (0 to 30). A score $\geq$26 indicates normal cognition [36]. Level of independence was measured by nurses on the unit accredited in the use of the Functional Independence Measure (FIM) [37]. Mood was determined using the Patient Health Questionnaire (PHQ)-9, a 9-item self-report questionnaire used to screen for depression [38] where scores range from 0 (no symptoms) to 27 (severe depression, symptoms occurring daily) [39]. Both measurement tools have been found to be valid and reliable for use in the stroke population [40,41].

Intervention

The experimental group was exposed to an enriched environment from Day 5 until Day 16 of the observation period (Figure 1). During this 12-day period, participants were given access to both communal and individual environmental enrichment equipment and activities. Communal enrichment involved provision of an area (the dining room) in which participants had easy access to a computer with internet connection, reading material (ie, books, newspapers), games, and an area for eating meals. Nintendo Wii gaming and recreational activities (ie, bingo) were made available (with assistance from a member of the rehabilitation team) throughout the intervention period. Individual enrichment involved the provision of activities of the participant's choice including music, audio books, books, word and number puzzles, and board games. Family members were encouraged to bring in hobbies and activities that participants enjoyed prior to their stroke. Individual enrichment activities and equipment were stored in a satchel by the participant's bedside. This meant that the individual enrichment was mobile which enabled access and use at places other than the participant's bedside. To promote patient-driven activity, rehabilitation team members were advised to encourage, but not coerce, the participants to utilize either communal or individual forms of enrichment (ie, use of environmental enrichment was at the discretion of the participants). For example, nursing staff were advised to remind the participants of the activities available in their satchel and to help them with equipment they may have had difficulty setting up themselves.

The control group received standard care, with no additional therapies, equipment or activities other than that which was usual within the rehabilitation unit. Both groups received standard rehabilitation therapies. Participants were informed that the purpose of the trial was to gather information to improve understanding of how the rehabilitation surroundings of a stroke survivor influence their stay in hospital, their activity levels and their recovery. The experimental group was unaware that access to the enrichment activities was not ''standard care''.

Outcome measures

The primary outcome was the level of ''any activity'' reported as the percentage of observations. Secondary outcomes included the percentage of observations spent sleeping, or ''inactive and alone''. ''Any activity'' was defined as behaviours or tasks which involved any one, or a combination, of physical, cognitive or social activity. Physical activity included virtually all purposeful physical movement, including activities such as eating, drinking or using utensils, all personal activities of daily living and active physical participation in transfers, ambulation and physical, occupational and speech therapies. Cognitive activity was defined as any non-physical leisure activity that involved active engagement in a mental task including activities such as reading a book or newspaper, listening to the radio, crosswords, puzzles, games, speech therapist-prescribed language exercises, occupational therapist-prescribed cognitive exercises, video games, writing, computer use and playing a musical instrument. Social activity was defined as any interaction that involved verbal or non-verbal communication such as talking, laughing, touching, kissing, telephone/mobile phone/email/internet forum use and being present engaged in ''group therapy''. ''Inactive and alone'' was defined as not being within a two-meter radius of a person conducive to interaction and not performing physical, cognitive and or social activity. Sleeping was defined as sitting or lying with eyes closed.

Behavioural mapping was used to collect outcomes, according to an established approach [42] which was a modification of the approach used in previous observational research involving stroke patients in similar settings [11,43]. In brief, every ten minutes researchers observed the participants, recording a yes or no response on spreadsheets regarding activity (physical, cognitive, social, ''inactive and alone'' and/or sleeping). Performance of physical, cognitive and social activity was not mutually exclusive. Observations were made inconspicuously for less than two seconds, with participants first sought by their bedside and then elsewhere within the unit, hospital and then outside. When participants were not able to be directly observed (ie, due to curtains being drawn or whilst in showers and toilets), activity was recorded after conferring with nursing staff or others nearby. In circumstances where activity was not able to be estimated, participants were classified as unobserved and these episodes did not contribute to the total number of observations made for that participant.

Behavioural mapping was conducted on each participant on four separate 12-hour days. Five randomly selected 15 minute breaks were taken each day, making for a total of 260 observations per participant. The research assistants who conducted the behaviour mapping had no knowledge of the specific purpose of the study. They received a minimum of three hours of training which involved explanation of the category definitions, working through examples and practice observations. Training was provided by two investigators (HJ and LA) until $\geq$90% consensus was reached across the categories.

Statistical analysis

Using data of ''any activity'' from the first eight participants, sample size calculation determined that with an alpha level of 0.05, 11 participants per group were required to give the trial 80% power to detect a one standard deviation between groups in the mean level of ''any activity'' as a result of the intervention. Activity levels were averaged across the week and weekend day. Poisson regression within a Generalized Estimating Equation framework to adjust for the repeat measurements on individuals was used to determine the between-group difference. The unit of time for observations in the model was day, with outcome being the number of times the individual was observed carrying out the activity on that day. The *p*-value associated with the coefficient of the interaction term was used to determine whether there was a statistically significant difference in change in the experimental group compared with the control group. Between-group differences for each type of activity are presented as incidence rate ratios (IRR). An IRR provides a way to compare the rate at which an activity is more likely to be observed in the experimental group than the control group. All statistical analyses were performed using STATA 11.0 [44].

Results

Flow of participants through the trial

Patients admitted to the unit for rehabilitation following stroke between April and August 2010 were recruited to the control group, and those admitted between April and July 2011 recruited to the experimental group. The flow of participants through the trial is summarized in Figure 1. Two participants from the control group and one from the experimental group were discharged early. However, data available for these participants was used in the analysis. The characteristics of participants are summarized in Table 1. There were 31% fewer participants with right hemiplegia and 31% fewer males in the experimental group than in the control group. Participants in the experimental group had more severe stroke and were more dependent than those in the control group. Overall, the majority of participants in this trial had impaired cognitive function (median Montreal Cognitive Assessment (MoCA) was 16 in both groups). They also had low levels of educational attainment – seventy nine percent did not receive education beyond the age of 16.

The median time from admission to the rehabilitation unit to initial observation (Week 0) in both groups was similar. Because of occasions when participants were unobserved or were discharged prior to completion of collection of activity data and for breaks taken by observers, the mean number of valid observations of behaviour made each day were 59 (SD 9) for the experimental and 63 (SD 5) for the control group out of a possible 65 observations, equating to 94% complete data.

Effect of intervention

Group data are presented in Table 2 with IRR graphed in Figure 2. The experimental group were 1.2 (95% CI 1.0 to 1.4, $p = 0.02$) times more likely to be engaged in any activity than the control group. Specifically, they were 1.7 (95% CI 1.1 to 2.5, $p = 0.02$) times more likely to be engaged in cognitive activity, 1.2 (95% CI 1.0 to 1.5, $p = 0.04$) times more likely to be engaged in social activity, 0.7 (95% CI 0.6 to 0.9, $p < 0.001$) times as likely to be inactive and alone and 0.5 (95% CI 0.4 to 0.7, $p = < 0.001$) times as likely to be asleep. The between-group difference in physical activity was not significant (IRR = 1.1, 95% CI 0.9 to 1.4, $p = 0.21$).

Table 1. Baseline characteristics of participants.

Characteristic	Experimental group ($n = 15$)	Control group ($n = 14$)
Age (yr), median (IQR)	76 (66–83)	78 (68–81)
Gender, *n* males (%)	5 (33)	9 (64)
English second language, *n* (%)	2 (13)	3 (21)
Education after 16 yr, *n* (%)	2 (13)	4 (29)
Infarct, *n* (%)	12 (80)	12 (86)
Side of hemiparesis, n right (%)	6 (40)	10 (71)
Severity of stroke (NIHSS) *(0–21)*, median (IQR)	8 (6–11)	3 (2–8)
Mild <8, *n* (%)	6 (40)	10 (71)
Moderate 8 to 16, *n* (%)	7 (47)	3 (21)
Severe >16, *n* (%)	2 (13)	1 (7)
First ever stroke, *n* (%)	11 (73)	9 (64)
Time from admission to stroke rehabilitation unit to first observation (days), median (IQR)	3 (1–6)	5 (2–8)
Time from stroke to first observation (days), median (IQR)	14 (11–16)	17 (10–28)
Variety of Activity Questionnaire *(0–152)*, median (IQR), $n = 14/12$	44 (39–55)	49 (41–57)
Physical activity *(0–36)*	17 (14–21)	18 (16–19)
Cognitive activity *(0–36)*	14 (10–15)	17 (12–20)
Social activity *(0–36)*	12 (9–12)	11 (7–15)
Exercise *(0–44)*	7 (2–8)	4 (1.5–7)
Function (FIM) *(18–126)*, median (IQR)	56 (45–72)	77 (57–81)
Mood (PHQ–9) *(0–27)*, median (IQR)	8 (7–14)	11 (5–15)
Cognition (MoCA) *(0–30)*, median (IQR)	16 (10–22)	16 (12–19)

IQR, inter quartile range; NIHSS, National Institute of Health Stroke scale; FIM, functional independence measure; PHQ-9, patient health questionnaire 9; MoCA, Montreal cognitive assessment.

Table 2. Mean (SD) activity* expressed as % of observations and between-group difference expressed as incidence rate ratio (IRR) (95% CI).

	Groups				
	Week 0		Week 2		Incidence rate ratio
Activity	Exp ($n = 15$)	Con ($n = 14$)	Exp ($n = 14$)	Con ($n = 12$)	Exp relative to control
Any activity	45 (13)	49 (18)	58 (15)	51 (15)	1.2 (1.0–1.4)
Physical activity	23 (8)	23 (10)	31 (13)	28 (9)	1.1 (0.9–1.4)
Cognitive activity	6 (7)	4 (4)	13 (10)	5 (7)	1.7 (1.1–2.5)
Social activity	24 (12)	32 (18)	27 (14)	27 (16)	1.2 (1.0–1.5)
Inactive and alone	25 (13)	40 (17)	17 (12)	36 (17)	0.7 (0.6–0.9)
Sleeping	12 (12)	16 (13)	5 (8)	15 (14)	0.5 (0.4–0.7)

*Activity averaged over weekday and weekend.

Discussion

This is the first trial to investigate the introduction of comprehensive model of environmental enrichment into the clinical setting. In this pilot trial, we showed that stroke patients exposed to an enriched environment were significantly more likely to be engaged in activity than those in non-enriched conditions. Specifically, patients undertaking rehabilitation in the enriched environment were more likely to be engaged in cognitive and social activity, and less likely to spend their waking hours inactive and alone. Importantly, with a median age of 76 and 78 years and admission FIM scores of 56 and 77 (out of 126), the stroke patients in the cohorts of this trial are representative of patients recovering from stroke in mixed rehabilitation units across Australia [45]. Furthermore, the group exposed to the enriched environment had more severe strokes and were more dependent at baseline than the control group, which would have been expected to favor controls in the analysis. These encouraging results were achieved through a relatively simple intervention applied over a short period of time.

Previous attempts to increase activity levels of patients undergoing rehabilitation have done so through predominantly staff-driven strategies such as group physiotherapy [46], scheduled recreational sessions [47,48], staff-supervised individualized therapy programs [47] and or a change in hospital processes aimed at increasing social interaction [48] (ie. moving patients to communal areas for morning and afternoon tea). These strategies are labor intensive, with success reliant on the availability, attitude and enthusiasm of staff [47,49]. In animal models of stroke, enrichment models rely on the environment driving behaviour. We aimed to replicate this approach with enrichment primarily achieved through alteration of the surrounds and/or the addition of equipment with which patients voluntarily engage. As the aim was to replicate the model successfully used in animal studies, cognitive and social stimulation were key components. To date there is very little data available on whether these factors are important in recovery of stroke patients, unlike the case for physical activity. Perhaps future trials will help address this issue.

The incidence rate ratios (IRR, 95% CI) were similar for any-, physical- and social activity. In contrast, the wide CI for cognitive activity indicates that the effect of an enriched environment varied between individuals. This large variability in response may be due to the low level of cognitive activity at baseline (4% of the day). Furthermore, the large mean effect on levels of cognitive activity may reflect the nature of the environmental enrichment, since a key feature of the intervention involved better access to cognitive activities.

Throughout the trial, numerous barriers to activity were observed. Most of these barriers related to the ease with which patients were able to engage in physical activity. For example, a large number of patients relied on help to mobilize beyond their bedside. At certain times of the day, hospital processes and routines discouraged physical activity in order to compensate for low staff numbers. Furthermore, the occupational and physiotherapy gyms were off limit during non-therapy hours and inaccessible on weekends.

Nevertheless, we have shown that our model of environmental enrichment is feasible and led to an increase in the activity levels of stroke patients during two weeks of rehabilitation in a mixed rehabilitation unit. Whether this increase in activity translates into better outcomes is yet to be determined. Previous research demonstrates that when used in isolation, components of the enrichment used in this pilot trial (ie. music [50,51] and Nintendo Wii [52–54] are associated with better mood [50,51], physical activity [52–54], cognition [50,51], and greater participation in activities of daily living [54]. We believe the multi-component approach used here is more likely to result in measurable gains in patient outcomes.

Several aspects of the design of this trial support the validity of the findings. As with the model of enrichment employed in animal models of stroke, patients were not forced or coerced to engage in activity and had easy access (individually and communally) to equipment which was designed to be stimulating and novel. Activity levels were measured across usual waking hours for patients in this unit. The large number of observations per patient (~260) overcomes some of the limitation imposed by the small number of participants in both groups. Additionally, participants

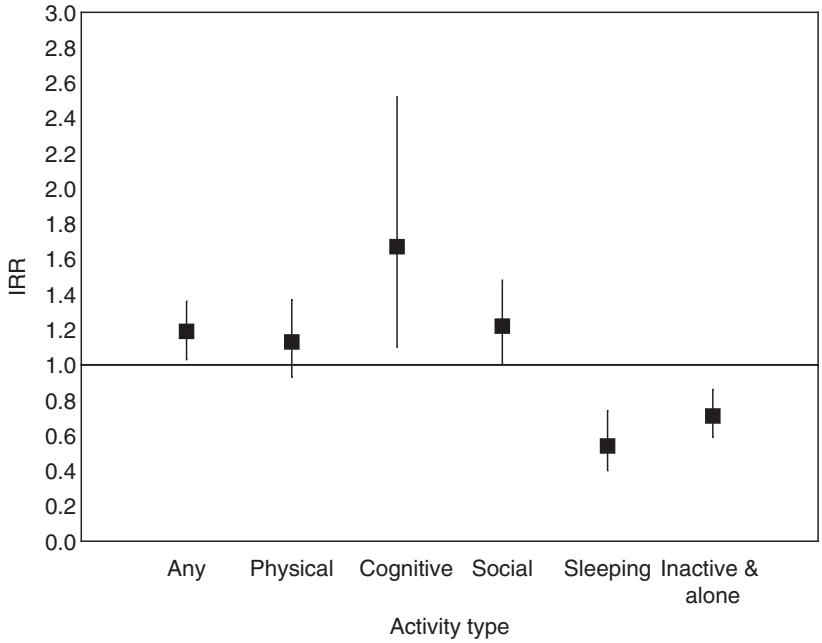

Figure 2. IRR (95% CI) between experimental and control group (where control group served as reference group) for activity type. Horizontal line at 1.0 represents line of no difference.

in both groups were observed during the same months of the year preventing any seasonal variation in activity (such as spending more time inactive and or sleeping during colder months) [48]. The definitions of activity – physical, cognitive and social – were broad in order to ensure that all forms of purposeful activity were captured. Observations were as unobtrusive as possible, supported by the fact that the majority of participants reported that they were unaware of being observed.

Limitations

There are some limitations to this trial. First, this preliminary trial, conducted at one site and involving change at the ward level, prevented the use of a parallel study design. To avoid contamination, groups were collected at different times. Second, our trial sample size was small, and is likely to have contributed to an imbalance in groups in favor of the control group in terms of stroke severity and level of independence. With such an imbalance, one would expect the experimental group (ie. which had more severe strokes and were more dependent) to be less active. It is unclear whether the higher proportion of women and those with left hemiplegia in the experimental group would have influenced outcomes. Third, to minimize potential further contamination of the trial, very little time or labor was allocated to embedding the model of environmental enrichment into ''normal practice''. The rehabilitation team was aware of the trial, but their role was simply to remind patients of the enrichment activities and equipment available and assist with set up if required. An even greater increase in activity may have been achieved had more time and resources been allocated to implementing the intervention. Lastly, this trial was not adequately powered to explore the influence that an individual's personality traits, interests and or stroke-related impairments (physical and or cognitive) may have had on their desire or ability to interact with either the non-enriched or enriched rehabilitation environment.

Conclusions

Exposure to an enriched environment is associated with a significant increase in the activity levels of stroke patients undergoing rehabilitation in a mixed rehabilitation unit. This increase in activity included increases in cognitive and social activity, and a decrease in time spent ''inactive and alone'' and sleeping. These results are encouraging and suggest that a randomized trial is warranted to determine whether the higher activity levels in the enriched environment improves function, mood and quality of life of stroke survivors in a cost-effective manner.

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Declaration of interest

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CHAPTER 7

DISCUSSION

Environmental enrichment is example of an intervention which has been investigated extensively in animal models of stroke, found to be effective, but has had little formal evaluation in human stroke survivors. This thesis sought to commence this process of translation. We found:

(i) through systematic review and meta-analytic methods that the use of an enriched environment in animal models of stroke is effective in improving sensorimotor function, potentially learning and results in a small increase in lesion size [265],

(ii) that patients undergoing stroke rehabilitation spend very little of their day engaged in physical, cognitive and social activity and despite gains in function and improvements in mood, these levels remained relatively unchanged [266], and

(iii) the use of a human equivalent model of environmental enrichment increases the likelihood that stroke patients undergoing rehabilitation will be engaged in activity during normal waking hours [267].

Although it is clear that animals recovering from stroke in an enriched environment perform better on tests of sensorimotor function (than animals recovering in deprived or standard laboratory housing conditions), there are many issues still to be resolved. For example in these animal models the ideal dose and time to commencement post-stroke,

the underlying mechanisms of and the risk of harm of environmental enrichment, are all still yet to be determined.

Translation of this paradigm into the clinical setting need not wait until all these questions have been answered. Evidence of efficacy at a functional level and the low probability of harm supports the argument to commence testing of a comparable model with human stroke survivors. Experimental testing of the unknowns outlined above (and more) can be conducted whilst concurrently undertaking scientifically rigorous clinical studies. Discussions between investigators at either ends of the translation pipeline is essential to ensure that any benefits to stroke patients, if present, are detected and better post-stroke outcomes are achieved [268].

7.1 QUESTIONS STILL YET TO ANSWER IN ANIMAL MODELS OF STROKE

7.1.1 Gaps in knowledge

Methodologically, it is possible that the bigger improvements found in enriched animals when compared against animals in deprived conditions is due to the negative consequences associated with a lack of physical, social and cognitive stimulation. Alternatively, the effectiveness of an enriched environment may not be as large or even seen when animals exposed to this intervention are compared against animals housed in standard conditions. Animals housed in such conditions are somewhat 'stimulated', albeit only socially. Hence there is a possibility that the inclusion of extra animals initiates similar physiological and behavioural changes as those in more comprehensive models of enrichment [193]. Additionally, the importance of each component of enrichment (ie. physical vs cognitive vs social) is still unknown. The influence of the inclusion (or exclusion) and manipulation of specific cage contents such as running wheels, toys and other movement and cognitive promoting objects, warrants further investigation as well.

7.1.2 Better designed studies in the future

The quality of enrichment studies conducted in animal models of stroke can be improved. Study quality was on average moderate, but similar to that obtained from other meta-analyses conducted in animal models [269,270]. The majority of animal models of focal ischemia included in our meta-analysis failed to report randomisation, blinded assessment of study outcomes, *a priori* sample size calculation or mortality rates.

Randomisation and blinded assessment have been reported more frequently in studies published since, but sample size calculations and mortality rates remain absent [271-280]. The mean quality scores of these recently published studies of enrichment in animal models of stroke are similar to those of the studies which were included in our meta-analysis.

The absence of any one of these design features threatens study validity, and in particular raises concerns about whether the results obtained were biased in any way. These are basic requirements for any animal study and our results in conjunction with the recent publication of 'good laboratory guidelines'[281] reinforces the need for greater efforts to include them and report their use in associated publications. Even though there were limitations in the design and methodology of some of the studies included in the analysis (**Publication 1**), the rigorous and accepted meta-analytic methods used on the pooled data in this review overcame many of these shortcomings.

7.1.3 The ideal time to commencement and dosage

The ideal time to commencement and dosage of exposure to an enriched environment has still yet to be determined. The majority of studies included in the meta-analysis commenced approximately one day post-stroke but favourable effects have been seen up to two weeks post-stroke [204]. Additionally, research in animal models of stroke to date has most commonly used a dosage of exposure to the enriched environment 24 hours a day.

These two variables are examples of study design features where discussions between basic scientists and clinicians would be beneficial and could potentially enhance future translational research in the clinical setting. For example, is it feasible to test these

models so early post-stroke? Unlike the four legged animal used in these models of stroke, an acute stroke patient is commonly much more medically unstable. The majority of stroke survivors who require inpatient rehabilitation often do not commence such until approximately two weeks after their initial stroke-at a time when they have been assessed as being medically well and capable of engaging in activity. Therefore, it may be more relevant to explore the benefits of enrichment in animals at a slightly later time point.

In regards to dosage, the likelihood that stroke patients in the clinical setting will be able to actively engage in enrichment activities or enriched environments 24 hours a day is uncertain. Although participants of the pilot trial theoretically had access to the enriched environment (individual and communal enrichment) '24 hours a day', in reality it is likely that the ability of patients to interact with the surrounding environment was (and will continue to be) influenced by many ward rules, routines and staffing related factors (ie. rest times, availability of staff during nursing handover). To ensure translational success, it may be more appropriate to focus on conducting animal studies which use a dosage (ie. limited access to an enriched environment) which reflects what is feasible to reproduce in the clinical setting.

There is a small amount of data in animals to suggest that lower doses of environmental enrichment can be beneficial[186,190]. Similar functional effects may be obtained by exposing patients to these enriched conditions two to three hours each day. If so, the act of placing stroke patients in an enriched area or environment for discrete periods of the day may prove useful. Improving patient access to stimulating and novel activities for short periods of the day could potentially be structured in a similar fashion to that of other non-pharmacological movement based stroke therapies (ie. physiotherapy or

occupational therapy treatment sessions). The attractive benefit of this form of 'environmental enrichment therapy' is that no, or a minimal number of, rehabilitation staff would be required. That is, simply enough staff to supervise a group of stroke patients engaging in enriched activities, assisting them if or when needed. A greater number of high quality animal studies with data supporting the benefits of smaller doses of this paradigm would help the future development of 'environmental enrichment therapy'.

7.1.4 Adverse effects of environmental enrichment: lesion size.

Pooling data from individual studies enabled the statistical power to draw conclusions on the effect of enrichment on infarct volume. Small studies conducted previously have been unable to do so, with the majority failing to detect a significant difference between groups.

Interestingly, our meta-analysis revealed that animals recovering from stroke in an enriched environment had a small but statistically significant increase in infarct size. The impact that an increase in lesion size of this magnitude (8%) remains unknown. The relevance of improvements in post-stroke function despite an increase in lesion size is very unclear as well.

It is highly probable that the infarct changes observed in animals in these models of environmental enrichment are a result of behavioural and species specific factors. For example, the major stress of co-housing with a large group of unknown animals could contribute to the increase in infarct volume observed. It is important as well to consider

the time of assessment and the standard histological techniques used to measure lesion size.

These two aspects of design complicate interpretation of our finding as they fail to account for the influence environmental enrichment itself could potentially have on the rate of brain repair. Lesion size has been shown to evolve over time [282]. Additionally, the methods used to measure lesion size varied amongst the included studies. This is important because some researchers measured absolute lesion volume whilst others measured relative lesion volume. The latter method compares the volume of each hemisphere to determine the volume of loss. Residual oedema or inflammatory infiltrate which remains in the lesioned hemisphere at the time of assessment can make the lesion (tissue loss) appear smaller. Hence, where brain recovery is fast (ie. oedema and inflammation resolve quickly) lesions can appear relatively larger using this method. Two thirds of the studies included in the analysis for infract volume in our meta-analysis used this method.

7.1.5 Stress and mood in post-stroke environmental enrichment

The definition of stress and the methods to induce stress in animal models, and in particular in animal models of stroke are varied, as are the outcome measures and measurement tools used to quantify this mood state. Stress in any form, has yet to be thoroughly explored in environmental enrichment following stroke.

Those studies included in the meta-analysis which referred to this mood state used it to describe the possible reason behind an increase in lesion size. Whether or not an expansion in infarct size is caused by higher levels of stress in the animals remains

unknown. Very few researchers in the field of post-stroke enrichment have investigated this outcome specifically (ie. stress). The evidence we have regarding the effects of an enriched environment on stress in healthy animals [201] and that which we are beginning to gather about the major influence emotions play in human stroke recovery [283-285], indicates much could be gained from exploring the role of stress and or anxiety/mood in animals exposed to this paradigm.

7.1.6 Are animals recovering in an enriched environment more active: The need for objective evidence.

The definition of an enriched environment in animal models of stroke stipulates that relative to standard housing conditions, enriched conditions should facilitate physical, cognitive and social activity. Surprisingly, no studies conducted in healthy or disease models have quantified how much more active animals in enriched cages are relative to those in standard or deprived conditions.

Quantifying activity levels of animals in deprived, standard and enriched conditions may prove very useful in gaining a better understanding of how this paradigm exerts its effect on the brain. Comparison of activity levels between non-enriched and enriched conditions, and correlation of these activity levels with observed changes in the brain and improvements in function (both sensorimotor and cognitive) may prove useful in determining the underlying mechanism of environmental enrichment.

Observing and interpreting an animal's behaviour is difficult, but not impossible. The frequency of engagement in behaviours of a physical, cognitive and social nature could be estimated. Physical activity could be measured using electronic devices attached to the animals to record the distance traversed and counters attached to cage contents and

running wheels could record the frequency of animal use [286]. The animal's level of cognitive activity could be measured with specially coded video footage to quantify the animals interest in cage contents, time spent in the tunnels and how expansively the enriched cage is explored. Lastly, video analysis of animal behaviour may be an avenue to quantify their level of social activity.

7.1.7 Underlying mechanism of environmental enrichment: Motor activity or neuronal activity, or both?

A key question is whether the increased neuronal activity resulting from the extra stimulation and cognitive activity available within an enriched environment drives functional recovery, or if physical and cognitive gains are simply a result of the animals using their affected limbs and challenging their memory more. That is, is it a simple positive dose-response relationship between functional recovery and amount of activity undertaken (dosage). Interacting with an environment which is much more stimulating and varied may be the mechanism that triggers the cellular changes seen in animal brains. Stimulating conditions may even prime the brain to be more receptive to the recovery process. These research questions illustrate the need for further high quality studies of environmental enrichment in animal models of stroke.

7.1.8 Voluntary activity in environmental enrichment: is this an important factor?

A popular theory used to explain the mechanism of environmental enrichment is the arousal theory [207]. The arousal theory is complex but emphasises the important relationship between how novel the stimuli is, the electrical activity of the enriched

animal's brain and the subsequent neuronal changes observed. In particular, the stimuli (within the enriched cage) should be novel or "…hold special significance to the animal…" (Walsh and Cummings 1975, p 989). This novelty does not last long, as the animal habituates to the stimuli, highlighting the importance of rearranging and exchanging the cage objects [207].

As believed to be in animal models of enrichment, exposure to novelty may be important in driving functional recovery in human stroke survivors. Additionally, better access to a greater number of 'pleasurable' activities could arouse a stroke patient, increase neuronal activity and favourably influence brain plasticity. Determining what role 'pleasurable' or 'enjoyable' activities, physical, cognitive and or social, play in stroke recovery is important. For example, children are motivated to engage in physical activity when they perceive the activity is enjoyable or that it alleviates boredom [287]. A similar effect may occur with adults and importantly with adults recovering from a brain injury within a relatively non-enriched rehabilitation environment. Enjoyable activities, exercise or therapy regimes may encourage greater compliance during both therapy and non-therapy times [288]. Activity may be facilitated and subsequently functional gains achieved because an enriched environment contains novel objects and enjoyable tasks which entice the subject (animal or human) to 'actively' engage with their surrounds. Furthermore, the favourable effects observed may result from the release of hormones which most commonly occurs when an animal or human participate in an activity which they enjoy [289].

The enrichment activities investigated in the clinical stroke setting to date (as outlined in Section 1.4) have been reported to bring pleasure to stroke survivors [237-240]. Extending the definition of an enriched environment to encompass any sort of

‘stimulating and novel’ activities, suggests recreational activities such as reading, dancing, visual arts and or music, may prove to be beneficial to incorporate into post-acute rehabilitation.

Review of the literature outlined in Chapter 1 highlights that very little research to investigate the functional benefit of these stimulating activities has been conducted to date, and much of what has, is of low quality. Although there is some qualitative evidence to indicate stroke patients enjoy participating in these activities whilst undergoing inpatient rehabilitation, quantitative data, especially in regards to the effects on important patient outcomes, is lacking. Our growing appreciation of how experience and the environment affects both a healthy and injured brain supports the need to allocate more research time and money to determining the effect multimodal or ‘enriching’ activities such as these have on the recovering brain. Knowledge gained through this process may contribute to our understanding of how tasks or environments which facilitate physical, cognitive and social activity achieve the effects shown in animals.

7.2 IMPLEMENTING AN ENRICHED ENVIRONMENT IN THE CLINICAL SETTING: LESSONS LEARNT

The model of enrichment investigated in the clinical trial was designed to mimic as best as possible that used in animal models of stroke. The individual and communal enrichment activities on offer were integrated within a busy rehabilitation unit with instruction for the staff to encourage and assist patients as required [290]. Although this aspect of the study design could be argued to be a weakness, the rationale behind minimal implementation (ie. education and involvement of the rehabilitation staff) was to test whether simply improving access to stimulating or 'enriching' activities would see an increase in patient activity levels. It did.

Stroke survivors may have a greater number of and more restrictive barriers to activity than a rodent recovering from stroke. For example, similar limb impairments may result in greater activity restrictions in a biped than in a quadruped. There is another important difference between an animal and a human after stroke; animals in the enriched environment in the laboratory cages are relatively free to explore and select which activities they engage in. Human stroke survivors in a clinical setting are at times restricted by rules and routines [263] .

Barriers to either patient activity or implementation of the model of enriched environment under investigation in the pilot study were investigated in collaborative projects. These qualitative studies [**Appendix B**] revealed that both staff and patients perceived that access to the enriched environment was beneficial.

For example a patient exposed to the enriched environment reported,

"When I start to feel bored I just ask one of the nurses to take me to the common room and I find something to do there, generally other people are there already." (Participant 4)[263].

One staff member summarised some of the benefits, both to themselves and the patients, like so:

"[Environmental Enrichment] has lightened the load on us, 'cause [the patients] are not down and feeling sad... it gives them a better outlook." (Participant 3) [264].

Both groups identified potential barriers to patient activity and specifically, utilisation of this unit based paradigm. For example physical impairments were nominated by both staff and patients as being a significant obstacle to interacting within the enriched conditions [263,264]

Many of the problems raised by staff and patient during interview are difficult to change (eg. physical dependency of stroke patients). Additionally, some barriers to activity are quite ingrained and are likely to require a change in rehabilitation culture and staff philosophy. (eg. a reluctance to encourage socialisation after dinner time). Researchers designing enrichment studies in the future would be wise to consider these issues [**Appendix B**]. Dedicating more time and resources to including staff ideas and opinions of how best to implement an enriched environment within their specific unit, is likely to result in even greater increases in activity levels than that achieved in our pilot trial.

7.3 CONCLUSION

The use of an enriched environment after stroke is efficacious in animal models of stroke but many questions remain unanswered. Furthermore, the quality of environmental enrichment research in animal models of stroke is moderate. Hence researchers designing future studies of enrichment in animal models of stroke must seek to improve certain aspects of experimental design (ie. ensure animals are randomised to groups, blinded assessment of outcome measures are performed, mortality rates reported and a priori sample size calculations are performed and published).

Activity levels of stroke patients undergoing rehabilitation in mixed rehabilitation units suggest that these environments are currently more deprived than they are enriching. The stagnant nature of activity levels, even despite improvements in the patient's level of independence and mood, highlights the importance of devising sustainable ways to encourage activity and interaction more generally with their surrounding rehabilitation environment.

The pilot study presented in this thesis demonstrates that a human equivalent model of environmental enrichment can increase activity levels and reduce the likelihood that a stroke patient's waking hours would be spent inactive and alone or sleeping. A larger adequately powered clinical trial is now required to determine if this increase in activity results in similar improvements in sensorimotor and cognitive function as is observed in animal models of stroke. Complete translation of this intervention relies on the ability of basic and clinical researchers to work together. Successful translation of this intervention from 'bench to bedside' has the potential to revolutionise the delivery of inpatient stroke rehabilitation. More importantly, done well, integration of

environmental enrichment into the clinical stroke setting is potentially a very cost effective intervention through which we can enhance functional recovery and more importantly maximise quality of life.

7.4 WHERE TO NOW?

The results from the pilot study associated with this PhD are promising and support the need for a Phase II Trial to explore the generalisability and safety of this model of environmental enrichment in a clinical stroke setting. This next phase will also provide an opportunity to explore research questions which were not addressed in the pilot study or which have since arisen. For example, the opportunity to record stroke patient activity in greater detail; specifically determine the type of physical, cognitive or social activities patients are likely to engage in. Additionally, the chance to consider why this model of enrichment was unable to facilitate physical activity, adjust the model and then re-examine physical activity levels using similar measurement tools.

Unlike the pilot study, much more work will be dedicated to developing an implementation plan to accompany this model of environmental enrichment. Importantly, conducting a Phase II Trial will enable exploration of how well this model, and an accompanying implementation plan, is accepted at a clinical level. The acquisition of funds as well as commitment from three of the four rehabilitation units required in our proposed trial design has enabled this process to begin. This Phase II Trial is planned to commence August 2013. Referred to as Altering the Rehabilitation Environment to Improve Stroke Survivor Activity (AREISSA), this trial is a crucial step prior to the conduct of a cluster randomised controlled trial involving many more rehabilitation units (ie. 20 units) to determine both the functional efficacy and cost effectiveness of a human equivalent model of environmental enrichment after stroke.

CHAPTER 8

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APPENDIX A

(i) Example of behavioural streaming data

DATE 14/12.	SETTING, PEOPLE PRESENT OTHER INFORMATION OF INTEREST: 1:30-2:30. Very noisy environment EARLY (THERAPY) AFTERNOON / EVENING	Gym. PT student AFO x1 SPS, helmet
TIME	**ACTIVITIES AND BEHAVIOURS**	**COMMENTS**
1.27pm	PT enters and pt walks to chair to perform stretches Talking to PT throughout Pt sits on chair. (A) as needed from PT Pt removes shoes, (A) as needed from PT stud	facing out to window walk x1 stick
1.29pm	Pt stands on wedge against wall (gastroc stretch) bilateral Talks ± PT throughout stretches.	supported stand ± duration, distractⁿ re home visit Problem solving re. mobility issues
1:34pm	PT aide walks past pt looks at same briefly, but continues talking ± PT stud	
1:35pm	Another pt walks into pt's view, looks at same, continues to talk ± PT stud. Looks at pt intermittently throughout stretch	this talking was mainly regarding mobility movements around home
1:38pm	Pause in conversation, pt looks at pts passing by. Commences to talk with PT stud again.	
1:41pm	Pause in conversation, pt looks at pt near parallel bars as pt makes noise. Conversation (talk) recommences b/w PT stud + pt.	
1.42	Pause in conversation, pt looks around. PT student assists Pt to move from wall (standing) to sitting in chair. Pt removes/rest	No talking once sitting
1:44	PT stud reviews (touch) calf length whilst pt in sitting. PT stud helps roll TEDs down. PT watches Pt moves foot.	
1:45	Pt and PT stud commence talk	
1:46	Pt stands ± (A) from PT stud. Standing balance ± PT stud close standby +/- touch as needed Talk throughout	changing BOS instruction + feedback
1.48	Pt assisted by PT stud to sit (rest) in chair Pt watches another pt + another PT stud.	

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DATE	SETTING, PEOPLE PRESENT OTHER INFORMATION OF INTEREST: EARLY / THERAPY / AFTERNOON / EVENING	
TIME	**ACTIVITIES AND BEHAVIOURS**	**COMMENTS**
1:49	PT stud sets pt up to do ankle exercises whilst in sitting. [Starts] exercises Pt looks behind her at other gym activities	
1:50	[Stops] ankle exercises [Starts] ankle exercises. Looking at ankles whilst doing exercises	
1:51	Pt looks towards another [illegible] Continues ankle exercises	
1:52	PT stud returns. Pt stands [illegible] Commences: Standing balance [illegible] ahead & PT stud close standby + touch as needed Talking/feedback throughout	changing BOS
1:56	Pt walks c SPS + close standby + touch c PT stud Talking/feedback throughout	
1:57	Pt sits in chair (rest) PT stud assists pt to apply AFO + adjust TEDs using both hands Talking starts	
1:59	Pt stands and walks c SPS and close standby leaves gym, looking at other pts throughout journey Talking/feedback c PT stud Another pt crosses pt path on journey to lift Lift travel	
2:01	Walks from lift → outside c PT stud	Outside Stairs Grass
2:02	Pt walks down stairs c close standby c PT stud Outdoor mobility training: (A) from PT stud Talking throughout Looking mostly at ground	[illegible] determined by priorities

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DATE	SETTING, PEOPLE PRESENT OTHER INFORMATION OF INTEREST: 1:30–7:15 EARLY / THERAPY / AFTERNOON / EVENING	4 bedded room. Only one other pt. MRSA+ve
TIME	ACTIVITIES AND BEHAVIOURS	COMMENTS
2:09	Pt walks up stairs close standby. End of outdoor mobility training Walks back to room	
2:11	Pt sits in chair near bed, talking c PT stud PT stud puts table in front of pt. PT stud leaves R.M.O approaches pt, talks c some	feedback instruction THERAPY ENDS
2:12	R.M.O leaves Pt turns on television, not working Rearranges table, applies lip balm, UNAFFECTED hand only Stares out window	
2:14	Pt pours self a drink UNAFFECTED hand Drinks. Moves table away, walks c SPS towards door, doctors approach, pt returns to sit in chair Pt and doctors talk	
2:19	Doctors cease "consult", pt walks c SPS to nurses station, Pt talks c nurse, both walk back to room, nurse leaves, pt sits in chair and has a drink.	Doctors still in room
2:21pm	Pt reads SP.Tx folder, does SP.Tx exercises	SELF DIRECTED LEARNING.
2:22pm	Nurse enters checks television, pt looks at some and talks c nurse. Television on	
2:23pm	Pt watches television and intermittently looks at SP.Tx exercises. Television on, but pt doing SP.Tx exercises.	crosswords SELF DIRECTED LEARNING
2:27pm	Other pt in the room [illegible] conversation starts and continues until	STOPS SP.Tx EXERCISES.
2:29pm	Talking stops, commences SP.Tx exercises again	SELF DIRECTED LEARNING
2:33pm	Nurse enters room for other pt, pt looks briefly then returns to SP.Tx exercises	

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(ii) Example of ‘enrichment’ behavioural mapping data

23072011
WEEKEND IP15 IP16

not being fed through

DATE	location						people present						physical		cognitive		social		unobserv	comments
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N		
T 800																				
IP15																			X1	curtains drawn
IP16	X											X		X		X		X		R I B EO.
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 810																				
IP15				X			X						X			Y	X		(2)	Shower ± NS
IP16	X											X		X		X		X		RIB EO.
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 820																				
IP15				X			X						X			X	X	'	(2)	shower ± NS
IP16	X											X		X		X		X		RIB EO.
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 830																				
IP15	X						X						X			X		X		SOOB eat.
IP16	X						X						X			X	X			assistance ± eat
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 840																				
IP15	X											X		X		X		X		SOOB.
IP16	X						X						'	X		Y	X			touched by NS.
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 850.																				
IP15	X											X		X		Y		X		SOOB EO
IP16	X							X					X			X		X		holding newspaper but not reading

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23072011
WEEKEND IP15 IP16

DATE	location						people present						physical		cognitive		social		unobserv	comments
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N		
T 900																				
IP15	X						X							X		X		X		~~BAB~~ SOOB EO
IP16	X							X						X		X		X		RIB EC
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 910																				
IP15	X											X		X		x		Y		SOOB EC
IP16	X							X					X			Y		Y		RIB holding newspaper
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 920																				
IP15	X						~~X~~					X		Y		~~X~~	~~X~~	Y		~~RIB~~ SOOB EO
IP16	X						X							X		X	X			RIB talk + touched
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 930																				
IP15	X											X		X		X		X		SOOB EO.
IP16	X						X							X		X		X		RIB EO.
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 940																				
IP15	X											X		X		X		X		SOOB EC
IP16	X						X							X		X		X		RIB EO.
	bedside	therapy	comm ar	amenitites	offsite	other	medical &	patients	therapists	visitors	other	alone	Y	N	Y	N	Y	N	unobserv	comments
T 950																				
IP15	X									X				X		X		X		SOOB EO
IP16																			(1)	curtains closed

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APPENDIX B

COLLABORATIVE WORK AWAITING REVIEW IN PEER REVIEWED JOURNALS

COLLABORATION 1

Bartley E, White J, **Janssen H**, Spratt NJ. Exploring stroke survivors experience of participation in an enriched environment: A qualitative study. *Under review.*

COLLABORATION 2

Alborough K, White J, **Janssen H**, Spratt NJ, Jordan L, Pollack M. Exploring staff experience of an 'enriched environment' within stroke rehabilitation: A qualitative sub-study. *Under review.*

International Journal of Stroke

Exploring stroke survivors' experience of environmental enrichment in a rehabilitation setting: a qualitative study.

Journal:	*International Journal of Stroke*
Manuscript ID:	Draft
Manuscript Type:	Research
Date Submitted by the Author:	n/a
Complete List of Authors:	Bartley, Emma; Kids OT White, Jennifer; Hunter New England Area Health Service, Hunter Stroke Service Janssen, Heidi; Hunter New England Area Health Service, Hunter Stroke Service Spratt, Neil; Hunter New England Area Health Service, Hunter Stroke Service; The University of Newcastle, School of Biomedical Sciences & Pharmacy, and Hunter Medical Research Institute
Keywords:	Enrichment, Environment, Stroke, Rehabilitation, Qualitative, Activity

TITLE PAGE

Title:

Exploring stroke survivors' experience of environmental enrichment in a rehabilitation setting: a qualitative study.

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Indexing Terms:

Enrichment, environment, stroke, rehabilitation, qualitative, activity.

Word count:

3677

Conflicts of Interest:

There are no conflicts of interest to declare.

ABSTRACT

Background: Environmental enrichment has been shown to improve post-stroke motor and cognitive function in animal models of stroke. The first known attempt to translate this intervention into the clinical setting suggests it may be an effective strategy to increase stroke patient activity during inpatient rehabilitation. However, stroke patients experience of undertaking rehabilitation within an enriched environment has yet to be investigated. Stroke patient experience of undertaking rehabilitation within an enriched environment has yet to be investigated.

Aim: To qualitatively explore stroke survivors' experience of participation in environmental enrichment within a rehabilitation setting, to identify benefits and limitations to implementation.

Method: A qualitative study consisting of analysis of semi-structured interviews with ten stroke survivors following two weeks exposure to environmental enrichment. An inductive thematic approach was used to collect and analyse data using a process of constant comparison.

Results: Three primary qualitative themes emerged from the data concerning the implementation of the environmental enrichment paradigm within the rehabilitation ward.

1) Perceived benefits of implementation of environmental enrichment including stimulation and socialisation.

2) Factors promoting use of environmental enrichment including: reflexivity, insight, motivation, social support and resilience.

3) Limitations to utilisation of environmental enrichment particularly pertaining to the presence of residual impairments.

Conclusions: This study provides preliminary support for the implementation of environmental enrichment within a stroke rehabilitation setting. While patients identified a number of barriers restricting participation in the enriched environment, overall their experience was positive. These

results will inform the design of future implementation studies of environmental enrichment after stroke.

RESEARCH ARTICLE

Introduction

The incidence of stroke is expected to increase rapidly over the coming years as a result of changing demography and an ageing population, placing increasing strain on health services, many of which are already operating at maximum capacity[1,2]. For individuals who experience a stroke, access to and engagement with stroke specific rehabilitation is a critical component of post stroke care to achieve optimal recovery[1,3,4].

Within stroke rehabilitation, research highlights the importance of intense and frequent activities to maximise recovery[4-6]. However increasing evidence indicates stroke patients in rehabilitation wards have limited opportunities to engage in physical, cognitive and social activities, other than during specialised therapy [7-10]. Research has demonstrated that stroke patients recovering in Australian rehabilitation units spend less than 20% of the day engaged in therapeutic activities and between 40-50% of the day alone[11]. Recently published evidence by Janssen et al., extends our understanding of patient inactivity further with findings reporting approximately 30% of the day is spent engaged in social activities and less than 5% is spent engaging in cognitively stimulating activities[12]. Lack of engagement in rehabilitation is a significant concern and consequently there is a critical need for innovative interventions to increase activity levels of stroke patients.

Increased access to stimulating activities and complex environments has been shown to promote neuroplasticity and neurological recovery[13-17]. Environmental enrichment is one paradigm which aims to facilitate this increased stimulation through use of activity and alteration of the environment[12]. Originating from experimental research, environmental enrichment refers to conditions, which relative to standard animal housing conditions, facilitates sensorimotor, cognitive and social stimulation[18]. Compared to those in standard housing conditions, animals recovering from stroke in these enriched environments were found to make significant improvements in the areas of sensorimotor functioning and learning[13].

The implementation of environmental enrichment to increase opportunities for activity, is an appealing treatment paradigm for use in human recovery[10,13,16,18,19]. However, the efficacy of this intervention with stroke survivors is yet to be determined. This study aimed to qualitatively explore stroke survivors' experience of exposure to environmental enrichment within a rehabilitation unit and to identify benefits and limitations of implementation.

Method

Study Design

This qualitative study consisted of semi-structured interviews with stroke survivors exposed to an environmental enrichment paradigm. Participants were identified from a prospective non randomised controlled intervention study, examining the feasibility of environmental enrichment in a rehabilitation unit[19]. The intervention study consisted of providing individual and communal forms of environmental enrichment, for a two week period, to stroke patients within a rehabilitation unit. Participants were exposed to and encouraged to access a communal enrichment area consisting of a computer with internet access, Nintendo Wii gaming, reading materials, puzzles and board games and a common dining area for eating meals. Individual environmental enrichment included the provision of activities of the participants' choice including music, audio books, word puzzles, books and board games. Family members or significant others were encouraged to provide additional activities of interest to the stroke patient from the home environment, such as art and craft supplies, music and books.

Recruitment

All patients admitted for stroke rehabilitation in the participating rehabilitation unit between April and August 2011 were screened for eligibility for the main intervention study[19]. The main

inclusion criteria for this qualitative study was participation in the intervention study. However, consent to participate in this qualitative study was not a pre-requisite for the intervention study. Participants were excluded if they had partial exposure to the enriched environment (defined as less than two weeks), or had severe cognitive or communication impairments resulting in the inability to partake in an interview. One participant declined an interview and four participants were excluded, resulting in a sample of ten participants for this qualitative study. Approval for this research project was obtained from the Hunter New England Human Ethics Research Committee (H-2010-1020).

Data Collection

Qualitative interviews were conducted following the intervention period, and prior to discharge. The interviews were conducted by a researcher not involved in the intervention program or outcome measurement. An interview schedule of open-ended questions was utilised to guide the semi-structured interviews[20,21]. Questions explored participant experiences of routine rehabilitation, recovery and exposure to the environmental enrichment. The iterative nature of this study meant that discussion was informant led and emergent themes inspired continuing data collection. The term 'environmental enrichment' was not used during the interviews contributing to the blind nature of the study. As a result, participant interpretations of exposure to environmental enrichment were made within the context of participants' general rehabilitation experiences. No new categories emerged at the end of the tenth interview, implying thematic saturation had occurred (two co-coders, E.B. and J.W., in agreement of no new emergent themes).

Data analysis

Interview duration ranged between 20 to 60 minutes. Each interview was recorded with participant consent and transcribed verbatim, with identifying data removed. An inductive thematic

approach using the process of constant comparison was utilised, incorporating simultaneous data collection, coding and analysis[22].

Firstly, coding involved use of open coding to identify common themes, ideas and concepts directly from the data to further develop provisional codes. These codes then underwent axial coding to further categorise and group codes on the basis of similarity. Finally, selective coding resulted in the recognition of relationships between categories and integration to develop core themes[19]. The first two authors (E.B. and J.W.) coded the data independently and consistency of findings was upheld through discussion of interpretations between researchers to confirm codes and categories. Differences in researcher perspectives were resolved by negotiation and consensus and fed back into the analysis to cross-check codes and themes and develop an overall interpretation of the data. To enhance the accuracy and rigour of the data, researchers employed techniques of constant comparison, consensus coding, peer reviews, peer meetings and memo writing[20,21].

Results

Participant demographics are outlined in Table 1. The sample of 10 participants consisted of seven females and three males, with a mean age of 70.5 years. All participants had experienced a stroke resulting in admission to the designated rehabilitation unit, and nine participants had experienced a moderate stroke, defined by a score of between 5-15 as measured by the National Institute of Health Stroke Scale[23]. The majority of participants were discharged home with support from a family member as a primary carer.

Insert Table 1 here

Three primary themes emerged from the data:

1) Perceived benefits of environmental enrichment
2) Factors promoting use of environmental enrichment

3) Limitations to participation in environmental enrichment

Perceived benefits of environmental enrichment

The enrichment phase was characterised by individual and communal forms of environmental enrichment. Both forms of environmental enrichment were reported to provide additional motor, cognitive and sensory stimulation within the rehabilitation ward.

> *"It was something to do and it was something to keep your mind active and everything, something to do with other people." (Participant 1)*

> *"I liked the Wii. It got me moving and it was a bit of a competition between me and one of the other patients." (Participant 9)*

Without the opportunity to engage in additional activities participants reported feeling *"bored" (Participant 5)* and spent much of their time alone, predominantly at their bedside, as a result of limited access to therapy. Participants' noted that exposure to environmental enrichment activities interrupted a perceived cycle of inactivity and discussed experiencing increased stimulation and decreased sense of boredom due to access to communal or bedside activities.

> *"When I start to feel bored I just ask one of the nurses to take me to the common room and I find something to do there, generally other people are there already." (Participant 4)*

Visits from family and friends were reported to be a significant source of additional stimulation asides from environmental enrichment. In isolated examples family and friends were found to promote access to and engagement in the communal environmental enrichment.

> *"Sometimes when my family would visit we would go there [communal area]]." (Participant 7)*

Families were encouraged to provide familiar items from home which reportedly reduced the unfamiliarity of the hospital environment. Increased familiarity enhanced feelings of confidence, improved motivation and rates of participation.

> *"I read the magazines that the kids bring in and they bought in my iPod and my journal...all the things I used to do during the day at home." (Participant 5)*

Overall, the majority of participants found it beneficial to have access to increased activities and social opportunities that were part of the communal environmental enrichment and being able to *"go down there [communal area] whenever you wanted to" (Participant 3).* Access to the communal area also promoted socialisation between patients which was highly valued. In particular, participants reported a benefit of being able to share their experiences with other stroke survivors *"who are in the same circumstances" (Participant 4).*

> *"So you got to talk to other people as well…everybody that sort of had the same problems as what you had so that was quite good." (Participant 1)*

Factors promoting use of environmental enrichment

Participation in environmental enrichment varied considerably amongst participants. A number of individual factors were identified as having an impact on participation including: insight, reflexivity, motivation, social support and resilience. Participation appeared to be influenced by elevated levels of insight. For example, some participants recognised that participation in activities resulted in enhanced recovery, and this promoted increased use of activities in the environmental enrichment setting.

> *"The more I do, the better I get." (Participant 8)*

Participants with good insight were noted to be self-directed with their therapy and actively sourced their own activities. These participants appeared to demonstrate a strong internal locus of control (the belief that outcomes resulted primarily from their own behaviour or actions) and were less reliant on external sources for motivation, such as staff and family members.

> *"There is probably only a few minutes of the day that I am bored and then I think well it is up to you to do something. You can be bored or you can be busy, you make the choice." (Participant 3)*

Some participants demonstrated increased reflexivity, which appeared to be closely linked to insight gained from comparing their own situation with that of other stroke survivors. Furthermore, this was enhanced by use of the communal area. Participants reflected that seeing others with more severe disabilities helped them to appreciate their progress as *"there is a lot worse than me in here…I really am lucky" (Participant 2).*

> *"It is hard but some days I get a bit teary and that but then when I look around [I think] I am lucky." (Participant 3)*

However, participant motivation levels towards recovery fluctuated throughout their rehabilitation stay, influencing uptake of activities and equipment offered through environmental enrichment. Some participants were motivated by the concern of being a burden on their family.

> *"I have to be [motivated] for my own good, for my wife's good, for my children's benefit. By getting better myself I am helping other people by taking the burden off them." (Participant 8)*

Other participants experienced reduced motivation which was linked to feelings of low morale and having *"had enough of the hospital" (Participant 1).*

"At first I was so positive and I said I am doing this because I am getting out of here...but now I have lost that positivity. I still want to get out but I just sort of slackened off." (Participant 7)

Overall, environmental enrichment provided an avenue for increased involvement of family and friends. The support of loved ones was a beneficial source of extrinsic motivation for participants and enhanced participation in the enriched environment to *"keep me going." (Participant 5)*

Limitations to participation in environmental enrichment

Functional abilities reportedly influenced patient use of the enriched environment. Mobility limitations were identified as a significant barrier to accessing the communal enrichment area. Participants who were able to mobilise independently, reported they could *"go there myself" (Participant 2)* at any time and were better able to access environmental enrichment. This was in contrast to participants who were dependent on staff to mobilise, reporting it was *"they are the only way I can get there" (Participant 3).*

Moreover, existing health conditions acted as additional barriers to accessing environmental enrichment for some participants. In particular, those with visual impairments found it difficult to participate in many activities which relied on adequate vision, such as reading, use of the computer and playing the Nintendo Wii.

"I did not use the computer a lot because of my eyes, because of the double vision." (Participant 8)

Participants with significant physical impairments were more likely to report feelings of boredom as they found it difficult to access communal area. Those whom were dependent on staff to mobilise reportedly spent more time by their bedside. Participants appeared to rationalise their decreased mobility and boredom as the *"need to rest [since] there is nothing else to do." (Participant 6)*

The experiences of participants with restricted mobility, who were more dependent on staff, were mixed. Some participants found staff responsive and nurturing.

> *"They basically took you whenever you wanted to go providing there were staff free and available." (Participant 8)*

Others reported that they did not want to intrude on staff or be a *"nuisance" (Participant 4)* to them by constantly asking to go to the communal enriched environment.

> *"I don't like to make them [staff] busier than what they are, they [staff] have got plenty to do..." (Participant 10)*

Overall participants' indicated that assistance to access the communal area was dependent on staff availability. Some participants' expressed access to more assistance from staff would have reduced feelings of frustration and difficulty related to accessing environmental enrichment activities.

> *"Maybe it would be useful if there was more [staff to help you], but the staff are stretched out pretty, pretty thin." (Participant 8)*

Furthermore, participants recounted that access to the environmental enrichment was compromised by ward restrictions. Set daily routines were reported to be *"the same thing every time" (Participant 4),* and *"a bit regimented, like being in the Army" (Participant 10).* Participants noted that their preferences for accessing the communal area, was compromised by set ward routines, amplifying feelings of frustration.

> *"I didn't think I was allowed to go there by myself" (Participant 6)*

> *"You had to wait for a staff member to set it (Nintendo Wii) up...you weren't allowed to do it yourself." (Participant 1)*

When attempting to access the enriched environment, some participants reported disobeying staff recommendations, particularly regarding mobility. For example one participant mobilised without

supervision, which resulted in being *"roused at" (Participant 2).* In these scenarios participants often felt reprimanded by staff if they did not follow the *"set rules" (Participant 7).* Most participants felt they could do nothing about this or voice a complaint, stating they *"had to put up with it" (Participants 2, 7, 10).*

While the majority of participants found it beneficial to have increased access to activities through environmental enrichment, participation varied greatly depending on individual preference towards the range of activities provided, such as "*using the computer everyday to reading the daily newspapers." (Participant 7)*

> *"They had a few things to do, they had the Wii and I used to play ten pin bowling on that. Got to be quite good at it and I had never played it before so that was okay and interaction with other people." (Participant 1)*

Discussion

This study qualitatively explored stroke survivors' experiences of participation in environmental enrichment within a rehabilitation setting. A number of results emerged exploring patient's perceptions of benefits and limitations of individual and communal environmental enrichment within a stroke rehabilitation ward.

Within this study, a number of specific and generalised benefits of environmental enrichment were perceived by participants, suggesting high patient acceptability. We identified participation in both individual and communal forms of environmental enrichment resulted in increased access to activities and reportedly provided increased opportunities for stimulation. Furthermore, this increased access to and participation in activities was found to interrupt the ongoing cycle of boredom and inactivity experienced by many participants. These preliminary results suggest that environmental enrichment may be effective in reducing the significant amount

of time that stroke patients spend not engaged in activities promoting external stimulation and addressing the associated causes of boredom.

Communal environmental enrichment was found to provide a means for increased social interaction. Participants reported discussion with other patients facilitated increased insight, encouragement and support. Environmental enrichment also encouraged the utilisation of activities from participants' home settings, which reportedly facilitated adaptation to the unfamiliar hospital environment for participants.

We identified variations in the frequency of use of the individual and communal environmental enrichment which was closely linked with participants' activity preferences, motivation levels, ward restrictions, set routines and the availability of family and staff support. Factors such as the experience of residual symptoms, in particular mobility restrictions, and time spent in therapy, were barriers to access and participation in environmental enrichment. Set-up of the environment and assistance from staff was not part of the environmental enrichment protocol used in this study[19]. Therefore, it is not known if increased participation would have resulted from increased staff support to assist participants' access to activities, especially for participants requiring support to mobilise.

We propose that a large variety of resources are required to accommodate the varied functional abilities and personal preferences of patients, in future implementation of environmental enrichment. For example, visual impairments commonly affected the use of activities. Therefore, future implementation should consider the use of a wide range of activities that have tactile, vestibular, proprioceptive or auditory components as well as visual components[19].

This is the first qualitative study to explore exposure to implementation of environmental enrichment within a rehabilitation setting. The strength of this study is the use of a in-depth interviews to explore the experience of participants who were blinded with regards to knowledge of their exposure to an environmental enrichment. Our study results suggest that environmental

enrichment facilitated increased participation and socialisation within a rehabilitation setting. However, these results need to be objectively confirmed with a larger study population and across varying stroke rehabilitation settings. The use of observational behavioural mapping and other quantitative measures will also assist in objectively confirming these preliminary results.

There were limitations to this study. By necessity, stroke survivors with cognitive and language impairments were excluded and these individuals may have noted different experiences. This was a cross-sectional study and therefore did not capture changes over time. Furthermore it is not known if increased participation would have resulted from increased staff input, including allied health, support staff, service management and carers.

Overall our study results provide preliminary support for the implementation of environmental enrichment with stroke survivors in a rehabilitation setting, providing baseline findings for comparison in future studies. Increased research is needed to further explore the utilisation of environmental enrichment in stroke setting with increased collaboration from all stroke clinicians within the ward. In conclusion, this study revealed that the perception of environmental enrichment was positive for stroke survivors' and facilitated increased activity and socialisation; supporting the concept of a human environmental enrichment paradigm.

Table 1 – Participant Demographics

Participant	Sex	Age (Years)	Living Situation (Prior hospital admission)	First Ever Stroke	NIHSS †	MoCA ‡	Study Entry FIM |	Study Exit FIM |	Length of Rehab Stay (Days)	Discharge Destination
1	F	60	Lives with Spouse	No	7	16	45	47	46	Home with Carer
2	M	83	Lives alone	Yes	6	18	86	107	35	Home Alone
3	F	73	Lives alone in Retirement Village	Yes	8	26	51	82	62	Home Alone
4	F	78	Lives with Spouse	Yes	5	16	47	81	36	Home with Carer
5	F	75	Lives alone	Yes	11	18	46	58	34	Home with Carer
6	F	41	Lives with Partner	No	13	9	37	47	30	Home Alone
7	M	72	Lives with Partner	Yes	8	25	58	113	27	Home with Carer
8	M	76	Lives with Spouse	Yes	6	N/A	72	116	28	Home with Carer
9	F	66	Lives alone	Yes	21	4	38	67	65	Home with Carer
10	F	81	Lives alone	No	8	9	58	60	28	Nursing Home
Mean	-	70.5	-	-	9.3	15.7	53.8	77.8	39.1	-

† National Institute of Health Stroke Survey. Scores range between 0 and 42, representing stroke severity. No stroke = 0; Minor stroke = 1-4; Moderate stroke = 5-15; Moderate to severe stroke = 15-20 and Severe stroke = 21-42[23].

‡ The Montreal Cognitive Assessment. Total possible score is 30 points, with a score of 26 or above considered normal[24].

| Functional Independence Measure. Total scores range from 18 to 126, with a lower score indicating functional dependence and higher scores equating with normal functioning[25].

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COLLABORATION 2

Alborough K, White J, Janssen H, Spratt NJ, Jordan L, Pollack M. Exploring staff experience of an 'enriched environment' within stroke rehabilitation: A qualitative sub-study. *Under review.*

TITLE PAGE

Title:

Exploring staff experience of an 'Enriched Environment' within stroke rehabilitation: A qualitative sub-study

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Abstract

Background: Environmental Enrichment (EE) is shown to facilitate recovery of motor and cognitive function in animal models of stroke. The efficacy of EE in the clinical setting with stroke survivors remains unknown. Successful implementation of EE in a busy rehabilitation unit requires identification of barriers and enablers which are best informed by staff feedback.

Aim: To qualitatively explore the experiences of nursing staff involved in a pilot study investigating the feasibility of an EE in a rehabilitation ward.

Methods: Baseline qualitative data was collected through a focus group (n=9) with nursing staff before the EE study was implemented. Three months after implementation, nine in-depth individual interviews were conducted with staff, who were asked to reflect on 'routine care' and their own 'experience of the EE study'. An inductive thematic approach was utilised to collect and analyse data using a process of constant comparison.

Results: Male and female staff with varying years of experience working in stroke rehabilitation participated in focus group and individual interviews. Five key themes were identified concerning the implementation of EE including: (i) routine care, (ii) staff experience of implementing an EE, (iii) benefits of the EE, (iv) barriers to the EE, and (v) recommendations for EE implementation

Discussion: Staff perceived the use of an EE in their rehabilitation unit promoted activity/participation. The barriers and enablers experienced by staff in this study may be

used to inform the design and conduct of future studies investigating the efficacy of environmental enrichment during inpatient stroke rehabilitation/after stroke.

Key words: Stroke, Rehabilitation, Attitude of Health Personnel, Qualitative Research, Environment

Introduction

Stroke causes neurological damage that results in symptoms related to the affected area of the brain, these symptoms cause disabilities that affect the functional abilities of stroke survivors. Goal orientated rehabilitation in a stroke unit is shown to improve promoting functional recovery after stroke by reducing symptoms and teaching adaptation techniques that compensate for changes in ability (1).

In animal models of stroke environmental enrichment (EE) involves organisation of environment and the provision of equipment to facilitate sensorimotor, cognitive and social activity (2). A recently published meta-analysis revealed exposure to an enriched environment after stroke is associated with significant improvements in function and a trend towards better learning (3).

Effective implementation of new models of care delivery, such as EE, is strongly associated with adequately trained multidisciplinary teams (4). However, sustained implementation of innovative models in stroke services is challenging (5,6) since staff are required to adopt new practices and 'unlearn' previous approaches (7,8). Research indicates that feedback concerning staff attitudes is an important component of uptake of new evidence based practice (9,10). A relevant example is the slow uptake of evidence concerning how staff promote the active involvement of patients in their care (9,11). Active patient involvement in

rehabilitation processes is shown to improve outcomes, feelings of autonomy and patient satisfaction (12). However, evidence suggests that staff fail to include patients in care decisions or respond to patient priorities (13,14). Such findings are contrary to the delivery of patient centred care, which is an essential element of stroke rehabilitation (15).

Equitable provision of active patient care has been shown to be compromised by staff attitudes towards patient demeanour, age and stroke severity (16,17). Understanding staff perceptions and identifying barriers to and enablers of a new intervention is best achieved by structured qualitative research methods(10).

Aim

To explore qualitatively the experiences of staff involved in a pilot study to translate the use of an enriched environment into the clinical setting (i.e. a mixed rehabilitation unit).

Methods

This qualitative study (involving two stages) was conducted in a rehabilitation hospital servicing an Australian mixed rural/urban region, as part of a larger pilot study investigating the feasibility of translating the use of an EE into the clinical setting for use with stroke patients. The first stage was conducted prior to the commencement of the EE study on the rehabilitation unit and involved a focus group formed from nursing staff on the ward (n =10).

The focus group was conducted before researchers provided staff with education about their role in the EE study. The second stage involved individual in-depth interviews with nursing staff, following completion of the EE study (n=9). Approval for this project was obtained from the Hunter New England Human Ethics Research Committee (H-2010-1020).

Recruitment

All nurses who worked on the stroke ward were provided with detailed information about the study and invited to participate in this qualitative study (focus group and individual interviews). All participants gave informed consent.

Implementation of EE

Regular education sessions were provided to staff prior to implementation of the EE study. The responsibly of nurses was to offer EE activities to stroke patients participating in the study during non-therapy times and to assist them to access or set up the EE equipment and or activities. Patients were not alerted to the changes to the ward. The EE was comprised of two main components, communal and individual enrichment (18). Communal enrichment involved converting the patient dining area into an environment which encouraged social, cognitive and motor stimulation. This involved refurnishing and decorating the room to facilitate social interaction , access to a computer with internet connection, newspaper and other reading materials, board games and interactive gaming. Individual enrichment included the provision of music, books, puzzles and any other equipment of interest to the patient. Individual enrichment was designed to enable patients to have access to enrichment at their bedside.

Data Collection Methods

Focus Group

The aim of the focus group was to explore factors that might affect the implementation of EE. Nine nurses attended a 60-minute focus group in a meeting room on the ward. Focus group participants sat around a large table to facilitate discussion and eye contact during the focus

group. Two moderators, experienced researchers (JW, LJ) conducted the focus group and an observer (KA) took detailed notes. These researchers were not associated with the implementation of EE on the ward; this assisted to reduce bias and facilitated open discussion that allowed participants to express their opinions about EE (19). The moderators outlined the purpose of the discussion and explained guidelines that apply to conducting focus groups, including confidentiality(20). A schedule of questions guided the discussion and participants were asked about the factors that that might affect the implementation of EE on the ward. These results assisted in the development of the interview guide for the individual interviews.

Qualitative Interviews

The first and second author (KA, JW) conducted in-depth interviews with consenting staff following the implementation of EE. Interviews were conducted in a private meeting room in the hospital, using an interview schedule to guide the semi-structured interviews. Some example of questions included: “What was your experiences of EE?” and “What affected the implementation of EE?” The iterative nature of this study meant that discussion was not limited to predetermined areas of inquiry, allowing researchers to explore new topics as identified by participants (21). The average duration of each interview was 30 minutes.

Data Analysis

The focus group and individual interviews were digitally recorded with permission and transcribed verbatim removing any identifying data. Focus group and interview data were analysed together using an in-depth thematic analysis approach incorporating constant comparison (22). At each stage of analysis, two authors (KA, JW) coded the data independently and discussed emerging themes. Any disagreement in interpretation of the data was resolved by negotiations and consensus, ensuring rigor (22,23).

Initial coding included labelling each line with emerging themes and searching for difference and similarities in themes by forming categories (23,23). To facilitate retrieval between transcripts, researchers gave each category a conceptual label (for example, patient socialisation was labelled SOCL). Following this, axial coding confirmed, interpreted, elaborated and outlined the emerging thematic categories (23). The final level of analysis involved the identification of major themes as related to the staff experience of the EE.

Results

These five key themes summarise the results:

i) Routine Care
ii) Staff Experience of implementing an EE
iii) Benefits of the EE
iv) Barriers to the EE
v) Recommendations for the implementation of EE

Routine Care

Participants reflected that routine care was seemingly boring for patients, while the EE occupied patients. Participants expressed concern that outside therapy, self-care activities and visiting times, patients spent "hour after hour sometimes doing nothing" (Participant [P] 1) or "sitting and waiting for things to happen" (Focus Group [FG]). Participants also commented on the lack of therapy input on weekends which perpetuated a cycle of inactivity and boredom since there was no other 'stimulation' and the amount of time spent alone was greater than on weekdays.

"On the weekends ... people do tend to get bored." (P 6)

However, participants readily identified that "visitors coming" (P 1) outside of the formal aspects of rehabilitation was beneficial for the patients since these provided an opportunity for greater socialisation.

Staff Experience of EE

Workload

Most participants felt that the EE added an extra demand to their typical workload and was "too much work" (P 5). Participants expressed that incorporating the additional duties associated with EE into their routine was difficult, because they already had "a lot of different things to do" (P 2).

> *"Nurses [are] so busy ... [trying to get] patients ... ready by certain times for therapies." (P 7)*

In many cases, participants expressed that they were too busy to prioritise facilitating patient access to EE over their other demands. This was despite concerns that patients were often sedentary. However, other participants embraced EE as a part of their daily routine beyond showering or taking patients to therapies and meals. In fact taking patients to the communal enrichment area became just a matter of "taking someone somewhere else" (P 5). These participants identified that as they grew familiar with the enrichment protocols, EE was slowly becoming part "just a part of normal daily routine." (P 6)

Change of Practice

Overall, participants expressed that they felt "well informed" (P 1) regarding their role in the EE study. Reminders to promote EE with enrolled patients were communicated in handover and through notes in patient files. However, some participants stated that they were unsure of

the extent of assistance they needed to provide to patients. While this was not an expectation of the study, many staff indicated that they felt a sense of obligation to assist patients. The reported extent of support depended on the severity of patient symptoms and often involved encouragement, set-up of tasks or assistance with mobilisation

> *"You're taking time out of your work to do [EE] … it's the setting up, it's getting the person motivated." (P 6)*

In contrast, other participants found that EE was "not that hard to implement" (P 5) and readily embraced the importance of EE, commenting that it should be common practice.

Benefits of EE

Environmental Impact

Many participants identified feelings of commitment to the EE protocol over time, which replaced initial concerns regarding increased workload and commented that EE was "better for [patients] than lying in bed" (P 8). Participants also reported that patient morale improved when patients were engaged and enjoying the EE activities. Patients appeared less bored and "had their mind occupied" (P 3), this was perceived as a "calming thing on their mind" (Participant 6).

Overall, participants commented that EE provided patients with more opportunities for engagement in different activities. This was especially the case on weekends or during times when patients previously appeared 'bored'.

> *"It's a good thing for weekends when there's no other activity." (P 6)*

Some participants identified that EE made taking care of patients easier and relieved her workload. This was reportedly due to the fact that patients participating in the EE study were

less demanding since they were occupied and "less likely to ring the bell" (P 3). This change in patient behaviour was attributed to the fact that patients were more stimulated, which improved their mood.

> *"[EE] has lightened the load on us, 'cause [the patients] are not down and feeling sad... it gives them a better outlook." (P 3)*

Motivation

Levels of motivation towards the implementation of EE fluctuated among participants and partly depended on individual levels of patient motivation. Participants observed that patients who were inherently motivated were more likely to initiate involvement in EE activities.

> *"The patients ... actually asked to go to [EE] or can I have my music ...they don't want to just stop... they want to do more." (P 5)*

Such patients would seek out activity and request assistance to access EE activities. As a result, participants indicated that that they were more likely to facilitate motivated patients to access EE activities.

> *"If the patient was willing we were quite happy to get them there." (P 4)*

In contrast, participants perceived that some patients were unmotivated to participate in EE activities and "just wanted to sit back" (P 4) or "couldn't be bothered" (P 6). As a result, participants were either cautious not to 'force' these patients to engage in EE or identified that they required "a lot of encouragement" (P 5) to be involved in EE.

Socialisation

Participants readily identified that access to EE provided opportunities for increased social interaction among staff, families and other patients. Patients were observed to sit together playing games, watching television and building relationships.

> *"[The patients] get benefit out of that sort of interaction… there would be laughing and just general chit chat." (P 3)*

This was especially the case for patients who did not have people visiting them and were more isolated.

> *"A couple of [patients] don't have a lot of visitors or family, so I think they like someone taking an interest in them." (P 1)*

Barriers to EE

Residual Stroke Symptoms

Participants identified several barriers regarding the implementation of EE. For instance, mobility was identified as a key barrier to patient participation in EE. Patients who mobilised unaided were more likely to access communal enrichment independently and participate in these activities. Whereas patients who were more dependent on nursing staff to mobilise were more likely to experience "more difficultly" (P 5) accessinf EE and remain at their bedside.

> *"[Ambulant patients] could get there … whereas the others are reliant on someone taking them down there in a wheelchair." (P 1)*

Participants also identified that patient fatigue was a significant barrier to willingness to participate in EE. This was especially the case in the afternoons and after therapy. In these

cases, participants perceived patients as "probably just too tired" (P 3) and were more likely to leave these patients in bed.

> *"In the afternoon during the week, a lot of people are tired anyway and all they want to do is have a rest on the bed" (P 6)*

Furthermore, patients considered 'challenging', such as those with depressive symptoms or who were agitated or confused were less likely to be offered access to EE activities.

> *"Depression is a big part ... they're just not going to participate, they just don't want to ... [they have] sort of given up in a way." (P 5)*
>
> *"Patient very confused, agitated, and can't do much." (P 2)*

Individual Factors

Many activities of the EE where perceived to be dependent on technology. Some participants indicated they were surprised by the extent that older patients could engage in activities associated with technology, such as Wii and computer.

> *"Some of the older ones, even though you would think 'oh this is technology way beyond what they would normally know,' but they get in there and they have a good time." (P 5)*

Socialisation reportedly varied due to the age and gender mix on the ward. Similarly, some patients were more "interested…others like to be on their own more" (P 8).

> *"Some patients ... love to get up there and be in the lime-light, be the centre of attention ... others didn't like it because it was too noisy, too many men, not enough women or vice versa." (P 4)*

Participant Recommendations for EE Implementation

There was a common experience of confusion among participants as to whether it was the role of staff to set up the EE area for patients. As a result one participant suggested the need to employ a staff member.

> *"A lot of people just don't think that it's their position to be doing [EE]. It is an extra duty ... an activity officer's job." (P 6)*

Participants also noted that patient family involvement was an opportunity to promote participation in EE. It was readily identified that it was "*helpful if you can encourage family and let family know*" (P 2) about EE in order to promote active patient participation.

Discussion

We have conducted previous research in the Hunter region on the provision of EE to stroke survivors (18) and their experiences (24). This is the first study that exploring staff attitudes and experience of the use of an EE with stroke patients in a rehabilitation ward. Staff reports noted the significant degree of patient boredom and inactivity in routine care. Following implementation of EE, staff responses varied concerning the extent that EE affected work practice. Despite these discrepancies, staff reportedly felt that the EE improved the ward environment, chance for socialisation and provided additional opportunities for motivated patients. Barriers to the EE were also noted including conflicts with existing ward routines, the complexity of patient symptoms and differing patient demographics on the ward.

Implementation of the EE paradigm had an impact on staff workload, it involved asking patients to participate in EE and providing assistance to mobilise patients to communal enrichment areas. However, a key result of interest pertains to staff reports that patient access

to EE positively affected ward morale and improved patient mood. In some cases, staff reported that patients were less likely to call on staff for extra assistance, which alleviated workload. Staff attributed these results to patients experiencing increased stimulation, socialisation and less boredom. These findings reflect both existing data indicating that stroke patients in rehabilitation wards spend less than a fifth of their time in therapy and spend the majority of their day inactive and alone (25,26) and results from the EE implementation showing dramatic increases in activity following EE implementation (18).

Many staff indicated that they were less likely to promote access to EE in patients with more severe stroke symptoms, altered mood and poor motivation. These patients required more assistance, which was considered additional work for staff. Interestingly, results from the larger pilot study revealed that despite having greater neurological deficits and lower levels of independence, patients exposed to the EE were significantly more active than those undergoing rehabilitation in a standard (non-enriched) rehabilitation unit (27). It is not known if increased patient participation would have resulted from increased input from allied health staff.

The barriers identified in this study align with practice change literature (5,9), which indicates that staff workload, routine and attitudes can inhibit the implementation of a new practice. This study identified variations among staff in their commitment to assisting patient access the EE, with some promoting patient access to EE more readily than others. This is consistent with the Transformation Theory (7), which is a form of subjective interpretation of workplace experiences, where staff are encouraged to understand and critique new practices. Transformation Theory considers that positive insight gained from exposure to new

experiences can result in sustained changes in practice, when staff are willing to incorporate new research into practice (7).

Overall, further research is required to improve the understanding of staff behaviour towards and barriers to EE. Evidence suggests that in order to successfully implement new interventions it is important to challenge existing work cultures and facilitate learning, change and innovation among staff (7).

Strengths and Limitations

Results from this study, in conjunction with those from the other studies associated with the EE study (18, 25) assist in determining the feasibility of the use of EE in the clinical setting. The qualitative nature of these results provide the first in-depth analysis of the staff perspective of EE in stroke rehabilitation in this series of studies.

There were some unavoidable limitations to this study. This pilot study involved only one rehabilitation unit meant only a relatively homogeneous sample of nurses could be analysed. This may have implications for generalisability and may not have allowed for the achievement of thematic saturation, a key component of qualitative research (13). Qualitative analysis would have also been strengthened with quantitative data, for example, the amount of time staff spent implementing EE. Since this is an emerging area of research, there is no data from similar studies to compare the findings.

Conclusion

Although, barriers to staff promotion of the EE emerged from the data, staff also acknowledged the positive impact of the EE paradigm on rehabilitation. Further investigation

is required to understand the effects of EE during stroke rehabilitation and the role of staff in this process.

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Declaration of interest

There are no conflicts of interest to report.

APPENDIX C
OTHER RESEARCH PUBLISHED

Janssen H, Speare S, Spratt NJ, Sena ES, Ada L, Hannan AJ, McElduff P, Bernhardt J. Exploring the efficacy of constraint in animal models of stroke: Meta-analysis and systematic review of the current evidence. *Neurorehabil Neural Repair.* 2012;27:3-12 [291].

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OR

PREPARED FOR PUBLICATION DURING THE TIME OF THIS PHD

Egan KJ*, **Janssen H***, Sena E.S, Bernhardt J, Longley L, Speare S, Howells DW, Spratt NJ, Macleod M, Mead GE. Exercise reduces infarct volume and facilitates neurobehavioural recovery: Results from a systematic review and meta-analysis of exercise in experimental models of focal ischemia. *Under review*[292].

*Joint first authorship

Neurorehabilitation and Neural Repair

Exercise reduces infarct volume and facilitates neurobehavioural recovery: a systematic review and meta-analysis of exercise in models of ischaemic stroke

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Keyword:	Stroke, Exercise, Systematic review, Meta-analaysis, Focal ischemia

Title: Exercise reduces infarct volume and facilitates neurobehavioural recovery: results from a systematic review and meta-analysis of exercise in experimental models of focal ischaemia

Running title: Exercise in experimental stroke

(31 characters with spaces)

Abstract

Background: Regular exercise reduces the risk of a first ever stroke and is associated with smaller infarcts. While evidence has suggested therapeutic exercise following stroke is beneficial, we do not yet know whether exercise reduces stroke severity of improves functional recovery. The mechanisms underlying any benefit remain unclear.

Objective: To conduct a systematic review and meta-analysis of studies investigating exercise in animal models of ischaemic stroke where outcomes were measured as infarct volume, neurobehavioural score, neurogenesis, or a combination of these. We also sought evidence of publication bias.

Methods: We searched three online databases for publications reporting the use of exercise in focal cerebral ischemia. We used DerSimonian and Laird normalised random effects meta-analysis and meta-regression to determine the impact of study quality and design on the efficacy of exercise.

Results: Overall, exercise reduced infarct volume by 25.2% (95% confidence interval (CI) 19.0 to 31.3%, 65 experiments, 986 animals) and improved neurobehavioural score by 38.2% (29.1 to 47.3%, 42 experiments, n=771). For both infarct volume and neurobehavioural score, larger effects were seen when exercise preceded ischaemia rather than came after it. For neurobehavioural score we found evidence of publication bias. Reported study quality was moderate (median score 5/10). Both model specific (e.g. type of ischemia) and exercise-specific characteristics influenced reported outcome.

Conclusion: Exercise, either before or after ischaemia, had favourable effects on both infarct volume and neurobehavioural score, and we

characterise the limits to this efficacy. However, these results are confounded by moderate internal validity and by publication bias.

Introduction

Physical activity contributes to good health throughout life[1]. Regular participation in mild or moderately intense physical activity prior to stroke has been associated with a reduction in the risk and initial severity of stroke and with improved functional recovery[2,3], most evidence comes from unreliable self-reported data. Early and more frequent physically based therapeutic activity during the first six months post stroke is associated with reduced disability[4], better mobility and greater independence[4-6], but the most effective timing and intensity of therapeutic activity is not known. Physical activity undertaken during the chronic phase of stroke recovery may improve cardio-respiratory fitness and aspects of mobility[7], but its effects on death and disability, and the most effective timing and intensity, are not known.

Animal models of stroke might provide insights into the optimal dose and timing of physical activity or exercise, and this knowledge could be used to inform the design of definitive clinical trials in stroke.

Current evidence from animal studies about the effect of exercise in focal ischaemia are contradictory, with reports that exercise either improves[8,9] or worsens[10] outcome. Recent systematic reviews have highlighted concerns regarding the internal and external validity of such studies[11-13], and it may be such problems explain the contradictions described above. The range and quality of research describing the impact of exercise in focal ischaemia has not been described.

Systematic review and meta-analysis are well-established methods of characterising the body of evidence describing interventions in animal models of stroke[14-16]. Systematic review provides a comprehensive and unbiased

overview of the literature, and meta-analysis can quantify the impact of experimental design and study quality characteristics. This empirical evidence can be used to inform future experimental work and assist the clinical development of therapies for stroke[12-14, 17]. Across a number of reviews of focal ischemia models the failure to report measures to reduce bias (e.g. randomisation) is associated with overestimation of efficacy[14]. This prompted the development of guidelines for good laboratory practice[18] and informed the development of the Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines[19], similar to the CONSORT reporting guidelines for human clinical trials[20].

Here we use systematic review and meta-analysis to study the impact of exercise, both before and after the induction of ischemia, in animal models of ischemic stroke. Our objectives were firstly to identify all studies describing the use of exercise in animal models of ischemic stroke; secondly, to investigate the effects of exercise on infarct volume,neurobehavioural score and (if there were sufficient data) neurogenesis. Finally we aimed to quantify any influence of study quality and design characteristics on reported efficacy.

Methods

Identification of relevant studies

We searched MEDLINE, EMBASE and Web of Science Proceedings in July 2011 for [‘exercise’ OR ‘fitness’ OR ‘locomotion’ OR ‘ambulation’ OR ‘walk*’ OR ‘run*’ OR ‘treadmill*’ OR ‘wheel*’ OR ‘swim*’ OR ‘physical therap*’ OR ‘physical exercise’ OR ‘physical conditioning’ OR ‘physical activit*’ OR

'physical exertion'] AND [('stroke*' OR 'cva' OR 'aca' OR 'mca' OR 'pca' OR 'cerebrovascular' OR (('cerebral' OR 'cerebellar' OR 'brain*' OR 'vertebrobasilar') AND ('infarct*' OR 'ischemia*' OR 'ischaemia*' OR 'thrombo*' OR 'emboli*' OR 'apoplexy' OR 'artery' OR 'vascular')) OR 'hemipleg*' OR 'hemipar*' OR 'poststroke' OR 'post-stroke'] AND ['animal*' OR 'mice' OR 'mouse' OR 'rat*' OR 'rodent*' OR 'murine' OR 'cat*' OR 'feline' OR 'pig*' OR 'porcine' OR 'primate*' OR 'mammal*'] NOT ['Coronary' OR 'myocardial'] limiting the results to animals.

Quality of studies

Study quality was assessed using the CAMARADES 10-item study quality checklist[14] which comprises (1) publication in a peer-reviewed journal; (2) allocation concealment; (3) randomisation to treatment or control group; (4) control of temperature; (5) blinded assessment of outcome; (6) avoidance of anaesthetics with marked intrinsic neuroprotective properties; (7) use of co-morbid animals (hypertensive, aged or diabetic); (8) sample size calculation; (9) statement of compliance with regulatory requirements; and (10) statement regarding possible conflicts of interest.

Inclusion criteria

We included controlled animal studies of focal cerebral ischemia reporting the use of exercise as an intervention and reporting outcomes as infarct volume, neurobehavioural score or neurogenesis (measured with bromodeoxyuridine (BrdU), Ki67, or ^{3}H-thymidine or neuron number or density). For the purposes of this review we defined exercise as physical

activity or movement of the body through the action of skeletal muscles that would be expected substantially to increase energy expenditure over resting levels[21]. Where animals received additional treatments (for example environmental enrichment or reach training) data were included if the co-treatment was administered to both the control and treatment groups. Environmental enrichment paradigms often include free access to a running wheel, but unless there was a control group with the same exposure except for the absence of a running wheel these data were excluded from further analysis.

Where studies met our inclusion criteria but did not provide sufficient data (sample size, mean and a measure of variance) for meta-analysis these were included in the assessment of study quality. Three independent reviewers (KE, SS and HJ) screened titles and abstracts and where appropriate full text articles; where a consensus could not be reached on inclusion of data or of an individual article, a fourth reviewer was consulted.

Data extracted

We identified individual comparisons where the outcome in a group of animals receiving exercise was compared with that of a control group. For each comparison we extracted data for the number of animals per group, mean outcome and variance. Where an outcome was measured serially only data from the last time-point were analysed. Where data were only presented graphically and numerical data were unavailable after emailing authors, we measured values from the published graphs.

We extracted details of study design including details of animal (species, strain, sex), surgical details (anaesthetic, method of ventilation, type of stroke model and duration of ischemia), details of the intervention (type of exercise, time of day for exercise, dose [total minutes performed over study duration], regime details, duration of exercise [total days of study period] and the time of the start of treatment [days pre or post ischemia]) and of outcome assessment (the time period between the end of exercise and sacrifice or other assessment). Exercise was categorised as either 'voluntary' or 'forced'; Voluntary exercise referred to modes of exercise where the animal was presented with the opportunity to engage in exercise but without any "motivating" stimulus (i.e. free access to a running wheel). Forced exercise referred to modes of exercise in which the animal was subjected to a noxious stimulus (e.g. electric shock) if it did not perform the exercise or was restrained such that participation was inevitable. Where animals had unrestricted access to the exercise apparatus we considered this 'continuous exercise', whereas where access was regulated we considered this 'single-session' or 'multiple- session" exercise. Where there were multiple co-treatment combinations, we calculated effect size as the difference between control sedentary animals given the co-treatment and exercise treated animals given the same co-treatment.

Data analysis

For each comparison we calculated a normalised effect size (the percentage improvement in outcome relative to control) and a corresponding standard error. For neurobehavioural score, where multiple outcomes were

measured in the same cohort of animals we used fixed effects meta-analysis to combine these data to give an overall estimate of outcome. We then aggregated effect sizes using DerSimonian and Laird random effects meta-analysis[22]. To assess the impact of study quality and the likelihood of publication bias we analysed the entire datasets for each outcome. Because study characteristics might have different effects depending on whether the exercise intervention was given before or after stroke we considered these studies in separate groups.

We assessed the presence and impact of publication bias using funnel plotting[23], Egger regression[23] and Trim and Fill[24]. Where more than one outcome was measured in a single cohort of animals the process of combining these to give an overall outcome might confound the assessment of publication bias and so we used individual rather than pooled outcomes from these cohorts for this analysis.

Factors modifying the effects of exercise

We assessed the impact of study characteristics and quality on outcomes using both stratified meta-analysis and meta-regression. The significance of differences between n groups was assessed by partitioning heterogeneity and using the chi-square (χ^2) distribution with n-1 degrees of freedom (df). We considered p values of less than 0.05 to be statistically significant. Correction for the number of comparisons made gave critical p values of 0.05 for the analysis of pre ischaemic versus post ischaemic exercise; 0.004 for the analysis of study characteristics; and 0.017 for the

analysis of study quality. We used meta-regression to assess the impact of continuous variables on observed outcomes (i.e. time of commencement, dose and time of assessment and time to sacrifice) with a critical value for p of 0.008.

Results

Forty publications met our inclusion criteria and were included in this review. Of these, 35 reported data suitable for inclusion in the meta-analysis (see Figure 1). These studies described 107 experiments. Data for infarct volume were reported for 65 experimental cohorts (n=986 animals) and for neurobehavioural score 73 outcomes were reported for 42 experimental cohorts (n=771 animals). There was significant heterogeneity for both infarct volume and neurobehavioural score (infarct volume, χ^2=557 df=64, p=9x10^{-80}; neurobehavioural score χ^2=189.3, df=41, p=6x10^{-21}). The number of experiments reporting neurogenesis outcomes (7 experiments, n=114 animals, χ^2=31.1) was small, and as different outcome measures were reported these were not analysed further

Study Quality

Important measures to minimise potential sources of bias were frequently reported; randomisation was reported in 28 of 40 publications (70%), and the blinding of the assessment of outcome by 17 of 40 (43%), (Figure 1). However, the details of randomisation (coin toss, random number table, computer generated random number) were not reported.. The median number of study quality checklist items scored was 5 out of a possible 10 (inter-quartile range (IQR) 4 to 6). The aggregate study quality score

explained a significant proportion of the heterogeneity both for infarct volume (χ^2=126, p<0.02; Figure 2A) and for neurobehavioural score (χ^2=74.0, p<0.02; Figure 2B) For neurobehavioural score efficacy was lower in the highest quality studies. For infarct volume, efficacy was significantly higher in studies that reported random allocation to treatment group compared to those which did not (28.2% (21.3 to 35.0), 51 experiments, 737 animals (randomised) versus 15.8% (4.5 to 27.0), 14 experiments, 249 animals (not randomised) (χ^2=60.9, p<0.02; Figure 2C,). For neurobehavioural score there was little difference (39.6% (27.2 to 51.9), 27 experiments, 428 animals (randomised) versus 35.2% (23.2 to 47.3), 15 experiments, 343 animals (not randomised)) (χ^2=0.75, p>0.02;not shown). Blinded assessment of outcome accounted for significant proportion of heterogeneity for both infarct volume and neurobehavioural score. For infarct volume, efficacy was higher in studies that reported the blinded assessment of outcome (43.9% (20.0 to 67.8; 11 experiments, 128 animals) versus 22.8% (16.4 to 29.2; 54 experiments, 858 animals), χ^2=12.8, p<0.02; figure not shown) but for neurobehavioural score the reverse was seen (blinded 28.4% (16.5 to 40.3; 17 experiments, 276 animals) versus unblinded 43.7% (31.9 to 55.5; 25 experiments, 496 animals); χ^2=48.2, p<0.02; Figure 2D).

No study reported a sample size calculation. The studies were generally small; for infarct volume the median numbers of animals for control and treatment groups were 7 (IQR 5 to 9) and 8 (IQR 6 to 10) respectively, and for neurobehavioural score the median numbers of animals for control and treatment groups were. 7 (IQR 3.3 to 8) and 10 (IQR 8 to 12) respectively.

Publication bias

For infarct volume there was evidence of publication bias from Egger regression but not from funnel plotting, or trim and fill. For neurobehavioural score, both funnel plot and Egger regression analyses were consistent with publication bias, and this finding was confirmed using Trim and Fill analyses which imputed an additional 14 unpublished individual outcomes and an adjusted efficacy of 31.0% (23.0 to 39.1) compared with the unadjusted summary estimate of efficacy from 73 individual outcomes measured of 40.0% (32.4 to 47.8)

Effect of exercise on Infarct Volume

Exercise reduced infarct volume by 25.2% (19.0 to 31.3, χ^2=557, p<0.001). Pre-ischemic exercise reduced infarct volume by 42.2% (25.0 to 59.3, 18 experiments, 277 animals) and post- ischemic exercise reduced infarct volume by 18.9% (12.4 to 25.5, 47 experiments, 709 animals, Figure 2E). Whether exercise was initiated pre or post-ischemia accounted for a significant proportion of the observed heterogeneity (p<0.05).

Effect of exercise on Neurobehavioural Score

Exercise improved neurobehavioural outcome by 38.2% (29.1 to 47.3, 42 experiments, 771 animals, χ^2=189, p<0.001). Pre-ischemic exercise was

more effective (54.2% (31.7 to 76.7), 6 experiments, 86 animals) than post-ischemic exercise (32.7% (24.9 to 40.5), 36 experiments, 685 animals) ($p<0.03$, Figure 2F).

Effects of pre-ischemic exercise

For these 18 experiments (277 animals), stratifying outcome by the anaesthetic used ($\chi^2=35.4$, $p<0.003$, Figure 3A; chloral hydrate was associated with larger effect sizes) or species ($\chi^2=79.7$, $p<0.003$, Figure 3B) explained a significant proportion of the observed heterogeneity.

Characteristics of the exercise itself seemed to be important: Forced exercise was associated with a substantially greater reduction in infarct volume than voluntary exercise (58.5 (41.8 to 75.1; 12 experiments, 170 animals versus 10.4% (-4.0 to 24.8; 6 experiments, 107 animals; $X^2= 119$, $p<0.003$ Figure 3C). Continuous exercise was less effective in reducing infarct volume than multiple-session exercise (10.5% (-4.7 to 25.7, 5 experiments, 88 animals) versus 56.6% (40.2 to 72.9, 13 experiments, 189 animals); $X^2= 117$, $p<0.003$, Figure 3D). Swimming and treadmill exercise reduced infarct volume more than the use of a running wheel ($\chi^2=119$, $p<0.003$, Figure 3E). However, the same group of experiments involved the running wheel; voluntary exercise; and (with one exception) continuous exercise, so which of these characteristics might be responsible for the lower observed efficacy is not clear.

Only 5 of 18 experiments reported the time of day at which exercise was performed, but within these exercise in darkness only was significantly

more effective (28.9% (17.3 to 40.5), 2 experiments, 26 animals) than where animals had 24 hour access to exercise (8.7% (-12.4 to 29.8), 3 experiments, 54 animals) (X^2=13.8, p<0.003, Figure 3F). Interestingly, efficacy was substantially higher in those experiments where the timing of exercise was not stated (53.4% (33.3 to 73.6), 13 experiments, 197 animals).

Using metaregression there was no association between reported efficacy and the time of treatment starting, amount of exercise, or time of outcome assessment (see Table 1.3).

For neurobehavioural score only 6 experiments using 87 animals reported the effects of treatment started before ischaemia, and these data were not analysed further.

Effects of post-ischemic exercise

Infarct Volume: Where exercise began after ischaemia, the type of ischaemia explained a significant proportion of the observed heterogeneity, with larger effect sizes in models of temporary ischemia (X^2=24.9, p<0.003 Figure 4A). The means of induction of ischaemia (χ^2=123, p<0.003; ligation was associated with larger estimates of effect sizes; Figure 4C) and anaesthetic used (χ^2=161, p<0.003, effect size was greatest with chloral hydrate; Figure 4B) both explained a significant proportion of observed heterogeneity. Animal sex was also a significant source of heterogeneity, where the significant improvement in outcome seen in males (21.8% (15.3 to 28.3), 43 experiments, 655 animals) was not seen in females (1.1% (-4.4 to 6.6), 3 experiments, 39 animals) (X^2=85.5, p<0.003, Figure 4D). Efficacy in

aged animals (20.2% (7.2 to 33.3), 3 experiments, 40 animals) was comparable to that in animals without comorbidities (20.3% (13.1 to 27.6), 42 experiments, 635 animals), but in hypertensive animals these was no significant benefit of exercise (-4.6% (-13.3 to 4.1), 2 experiments, 34 animals)(χ^2=47.7, p<0.003, Figure 4E).

Forced exercise was again more effective than voluntary exercise (23.8% (17.4 to 30.2), 39 experiments, 606 animals versus 1.0% (-3.4 to 5.4), 8 experiments, 103 animals; $\chi^{2=}$136, p<0.003, Figure 4F). Of the different exercise types treadmill exercise was the only one to significantly improve outcome ($\chi^{2=}$126, p< 0.003, Figure 4G). The time of day at which exercise was performed was described in 31 experiments, and for these training in daylight only was associated with greater efficacy ($\chi^{2=}$104, p<0.003, Figure 4h); and the number of exercise sessions performed also appeared important, with multiple exercise sessions having greatest efficacy ($\chi^{2=}$60.6, Figure 4I). There was no impact of whether the intensity of exposure to exercise was constant or increased through the period of treatment.

Using meta-regression we found that over a fifth of the observed variation in outcome could be explained by the interval between the start of ischaemia and the start of treatment, with improvement in infarct volume being larger the earlier treatment was initiated (adjusted R^2=21.6, df=55, p<0.004).There was no significant impact of either the total duration of exercise or the time to outcome assessment.

Neurobehavioural score: For post ischaemic exercise the effect on neurobehavioural score was significantly higher in models of transient rather

than permanent ischaemia (40.7% (27.3 to 54.08), 23 experiments, 361 animals versus 24.1% (15.1 to 33.1), 11 experiments, 260 animals; $\chi^{2=}$14.66, p<0.003, Figure 5A). The anaesthetic agent explained a significant proportion of the observed heterogeneity ($\chi^{2=}$26.0, p<0.003, Figure 5B) but there was no significant effect of species (Figure 5C). In contrast to the effects on infarct volume, efficacy was highest with voluntary (48.7% (35.5 to 61.9), 6 experiments, 82 animals) rather than forced (30.7% (22.8 to38.6), 30 experiments, 603 animals) exercise paradigms ($\chi^{2=}$13.2, p<0.003, Figure 5D). While the type of exercise explained a significant proportion of the observed heterogeneity the confidence limits around most of the point estimates were large due to the small number of studies. However, there was again an apparent superiority of the treadmill (38.1% (27.8 to 51.4), 16 experiments, 313 animals) over the running wheel (26.0% (13.7 to 38.2), 12 experiments, 188 animals). Continuous exercise appeared more effective (50.1% (36.3 to 63.9), 2 experiments, 32 animals) than multiple-session regimes (32.5% (24.7 to 40.2), 33 experiments, 632 animals), and only one experiment tested the efficacy of a single exercise session (5.4% (-5.5 to 16.3), 20 animals) ($\chi^{2=}$25.2, p<0.003, Figure 5F).

Finally, we examined the effect of intensity of exercise; most studies used constant intensity (30.2% improvement (19.5 to 40.9), 22 experiments, 388 animals), and efficacy was lower where training intensity increased throughout the experiment (24.1% (18.3 to 29.8), 8 experiments, 182 animals) and higher where training intensity increased to begin with but then plateaued (62.0% (25.9 to 98.0), 6 experiments, 115 animals) ($\chi^{2=}$11.45, p<0.003, Figure 5G).

Using metaregression there was no impact of variables describing the time of start of treatment, dose, and time of outcome assessment (Tables 1.1 to 1.3).

Discussion

In this systematic review and meta-analysis of the use of exercise in animal models of focal cerebral ischemia we show that exercise, either before or after ischaemia, is associated with significant improvements in infarct volume and neurobehavioural function.

In contrast to systematic reviews of other interventions in animal models of stroke we found the reporting of study quality items was relatively high[12,25], specifically, the proportions of publications reporting randomisation (65%) and blinding (42%). However, the methods of randomisation were not described, and so we cannot be certain that the methods used were adequate. While the relationship between study quality and effect size in this dataset was less clear than in some other analyses, the smallest effect on neurobehavioural outcome was seen in the highest quality studies. For neurobehavioural score there was evidence of a substantial publication bias. Small study effects may be observed for reasons other than publication bias, but as we have argued before[26] few of these are relevant in animal models of stroke.

Our stratified analyses suggest that both model- and exercise-specific methodology can influence observed outcomes. For both infarct volume and neurobehavioural function, exercise was more effective when administered

before ischemia, and improvements in infarct volume were greatest with shortest delays to treatment.

Exercise was more effective where cerebral ischaemia was transient (rather than permanent), and this is reflected in the observation that the largest reductions in infarct volume where seen when a luminal filament was used to induce ischaemia; these findings are typical of neuroprotective interventions[27].

The optimal exercise regime is not clear; for infarct volume, forced exercise regimens were more effective than voluntary exercise whereas the reverse was true for neurobehavioural outcome. For both outcomes treadmill exercise appeared more effective than other forms. However, in these other experiments there was a high proportion where exercise was continuous rather than intermittent, and in this univariate analysis it is not clear which of these factors is responsible for the observed differences in efficacy. There were insufficient data to analyse any effect of the amount of exercise undertaken, or to allow multivariate analysis of the influence of study design factors.

These findings contrast with those of a previous systematic review and meta-analysis of environmental enrichment, which found that environmental enrichment led to a small but significant increase in infarct volume, in contrast to the reduction seen here following exercise. However, in both reviews the effect on neurobehavioural outcome was significantly larger than the effect on infarct volume. This suggests that the effects of exercise involve modulation of the response to ischaemia and effects on regeneration and repair, whereas

the beneficial effects of environmental enrichment may be limited to regeneration and repair.

Methodological limitations

Firstly, there was evidence of a substantial publication bias, and we were only able to analyse data from published literature; while we have made estimates of overall efficacy adjusted for publication bias it may be that the inclusion of unpublished data– were these available – would change some of our conclusions about the influence of study design and quality. Secondly, our assessment of study quality was based on reported measures to avoid bias; it may be that some studies took such measures but did not report them; or that studies which did report such measures did not use adequate methods of for example randomisation. This highlights the importance of improved reporting of study methodology. Thirdly, while we sought to include all relevant outcomes the meta-analysis methodology can only use parametric data, and for this reason data from two publications could not be used. Fourthly, where serial neurobehavioural data were presented we only used data from the last time point[13]. Although this approach does not capture transient improvements we believe that long term outcome is the most clinically relevant. Fifthly, for our analysis of the amount of exercise we used exercise duration; while this accounts for one facet of the amount of exercise, our analysis is not sensitive to potentially important variables such as the total distance run, the intensity of exercise, or the exercise schedule. Finally, and most importantly, our work is in essence an observational study and our findings should only be considered as hypothesis generating

Clinical Implications

While our results can only be considered as hypothesis generating we believe they may have important clinical implications. Firstly, the effects of exercise are most pronounced when it occurs before ischaemia, consistent with findings in human stroke[28]. Secondly, regarding the question of optimal timing of exercise based therapies; taken together, the animal data do not support the hypothesis that early exercise may be harmful. For neurobehavioural outcomes the delay to initiation of treatment had no significant effect, and for infarct volume the benefit was greatest with shorter delays to treatment. This predicts that clinical trials testing early mobilisation[29] are unlikely to show harm, and may indeed show benefit. Next, our findings suggest that physical exercise has beneficial effects on unrelated neurobehavioural tasks. We believe this supports exercise as a rehabilitative treatment in and of itself, in addition to task specific approaches to rehabilitation. Further high quality studies in animals testing hypotheses about the most effective type and intensity of exercise and the relative benefits of forced compared with voluntary exercise could provide important data to inform the development of human trials.

Summary

Exercise improves outcome in animal models of stroke. Reported study quality was good, but there was evidence of publication bias. The most effective intensity and timing of and motivational drive for exercise might usefully be addressed in future well conducted animal studies.

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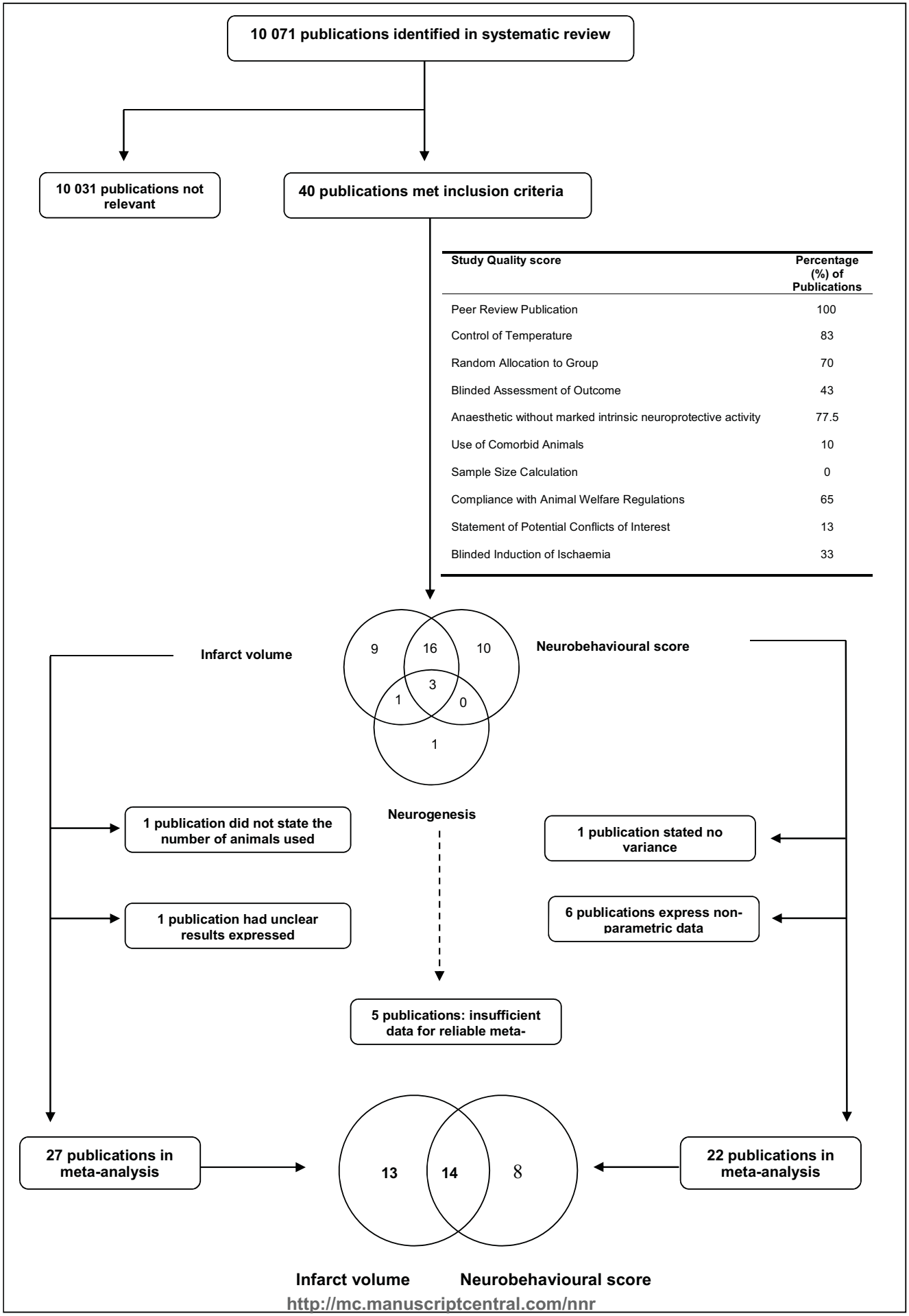
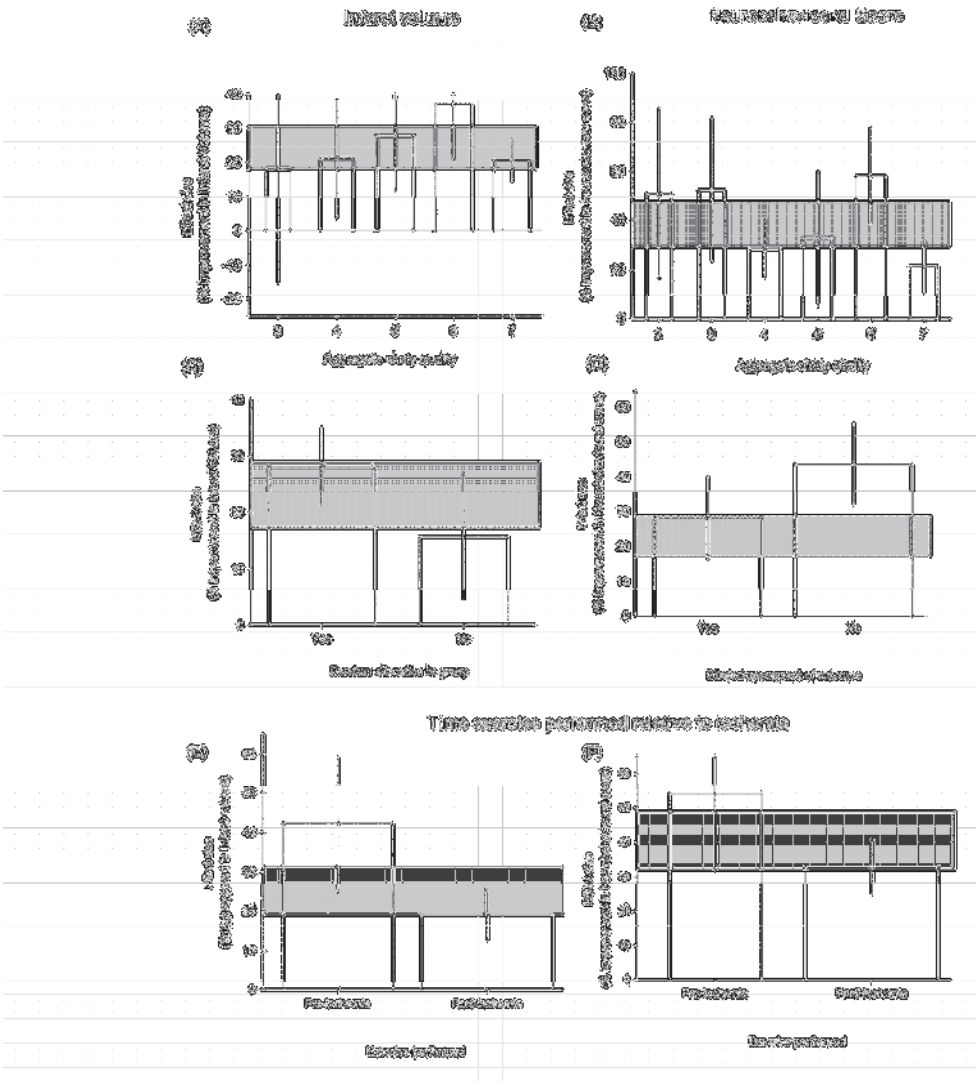

10 071 publications identified in systematic review
10 031 publications not relevant
40 publications met inclusion criteria
Study Quality score
Percentage (%) of Publications
Peer Review Publication 100
Control of Temperature 83
Random Allocation to Group 70
Blinded Assessment of Outcome 43
Anaesthetic without marked intrinsic neuroprotective activity 77.5
Use of Comorbid Animals 10
Sample Size Calculation 0
Compliance with Animal Welfare Regulations 65
Statement of Potential Conflicts of Interest 13
Blinded Induction of Ischaemia 33
Infarct volume
Neurobehavioural score
9
16
10
3
1
0
1
Neurogenesis
1 publication did not state the number of animals used
1 publication had unclear results expressed
1 publication stated no variance
6 publications express non-parametric data
5 publications: insufficient data for reliable meta-
27 publications in meta-analysis
13
14
8
22 publications in meta-analysis
Infarct volume
Neurobehavioural score



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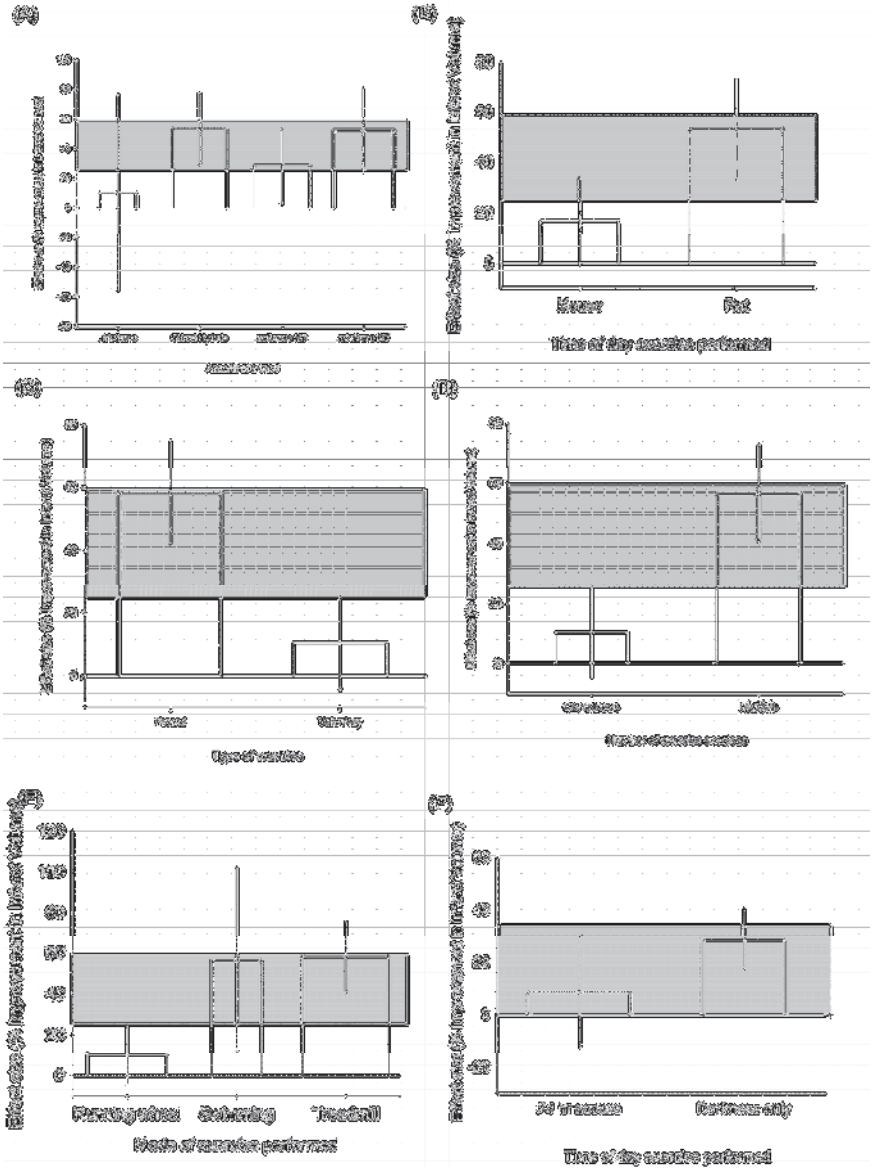

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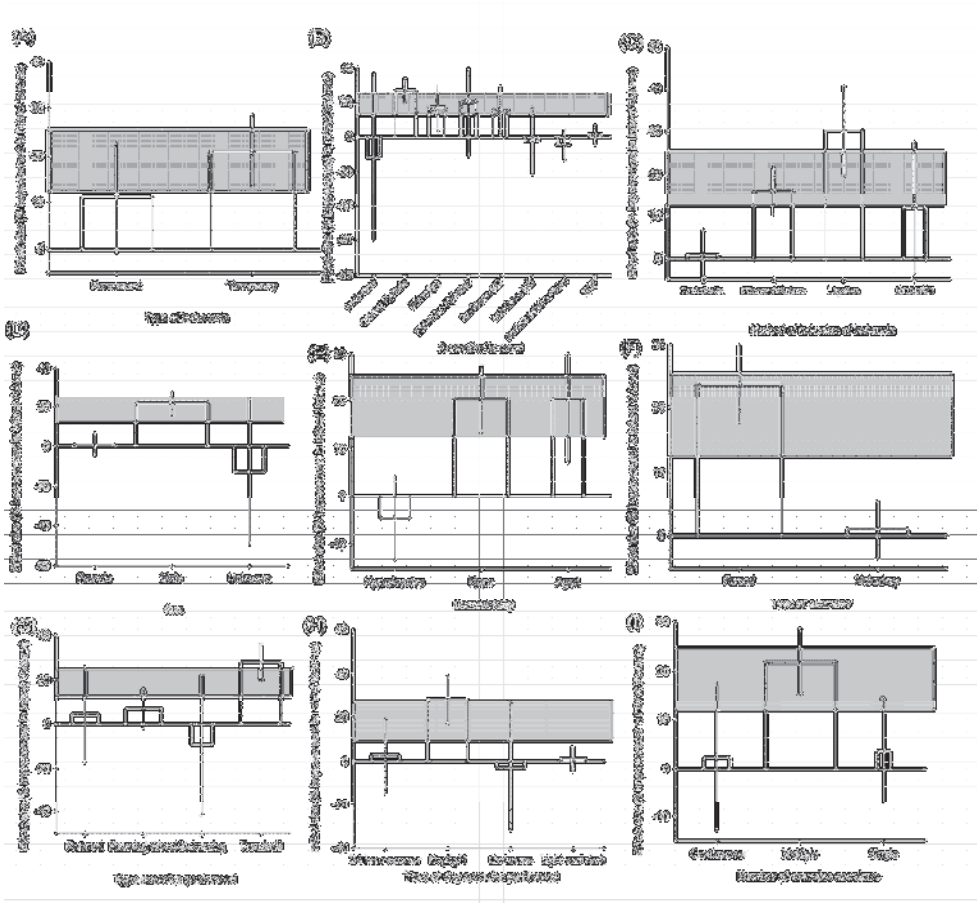

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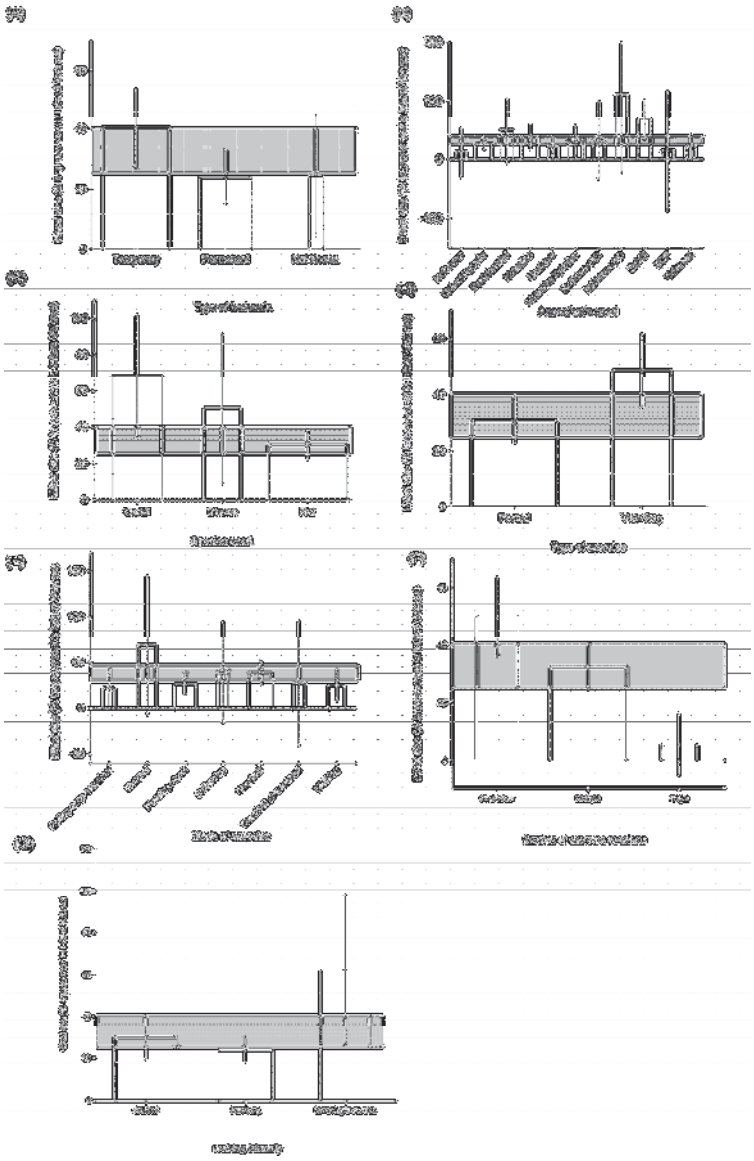

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(1.1) Infarct volume: Pre-ischemia exercise (18 outcomes in total dataset)

	Co-efficient (% Effect size)	Standard Error	t	P>|t|	Lower 95% CI	Upper 95% CI
Duration of ischemia	0.23	0.334	0.69	0.507	-0.525	0.986
Time at administration (hours)	-0.043	0.05	-0.87	0.398	-0.149	0.063
Time at assessment (hours)	-0.066	0.028	-2.33	0.033	-0.125	-0.006
Dose	0.007	0.066	0.1	0.924	-0.141	0.155
Sacrifice time	-1.252	0.732	-1.71	0.109	-2.821	0.318
Minutes per day	N.A	----	----	---	---	---

(1.2)Infarct volume: Post- ischemia exercise (47 outcomes in total dataset)

	Co-efficient (% Effect size)	Standard Error	t	P>|t|	Lower 95% CI	Upper 95% CI
Duration of ischemia	-0.427	0.176	-2.43	0.022	-0.787	-0.067
Time at administration (hours)	-0.24	0.06	-3.08	0.004	-0.36	-0.06
Time at assessment (hours)	-0.009	0.011	-0.83	0.411	-0.032	0.014
Dose	0.004	0.011	0.35	0.732	-0.018	0.026
Sacrifice time	0.691	1.109	0.62	0.536	-1.542	2.924
Minutes per day	0.17	0.366	0.46	0.645	-0.571	0.911

(1.3)Neurobehavioural Score: Post ischemia-exercise (36 outcomes in total dataset)

	Co-efficient (% Effect size)	Standard Error	t	P>|t|	Lower 95% CI	Upper 95% CI
Duration of ischemia	0.34	0.339	1	0.333	-0.387	1.067
Time at administration (hours)	0.014	0.125	0.11	0.914	-0.24	0.267
Time at assessment (hours)	0.021	0.02	1.05	0.302	-0.02	0.062
Dose	0.014	0.016	0.83	0.413	-0.02	0.047
Sacrifice time	N.A	----	----	----	---	---
Minutes per day	0.179	0.53	0.34	0.739	-0.915	1.272

Figure/Table Legends

Figure 1: The number of publications identified from the systematic search alongside the number which met inclusion criteria. The centre venn diagram demonstrates the number of publications which reported infarct volume, neurobehavioural score and neurogenesis outcomes, whereas the lower venn diagram demonstrates the number of publications included in the meta-analysis for both infarct volume and neurobehavioural score. Within figure, table summarises the percentage of studies which report study quality items as described in methods.

Figure 2: Effect size and 95% confidence intervals (CI) for effect of exercise on: infarct volume stratified by (A) aggregate study quality score and (B) presence of randomisation; and neurobehavioural score stratified by (C) aggregate quality score and (D) blinded assessment of outcome. (E) Reported effect sizes for infarct volume according to pre or post ischaemic exercise; whereas (F) shows neurobehavioural outcomes according to exercise pre or post ischaemia. Error bars represent 95% CI of individual estimates. Bar width represents the log of the number of animals, grey bar represents the 95% CI of the global estimate.

Figure 3: Effect size and 95% confidence intervals (CI) for effect of pre-stroke exercise by: (A) anaesthetic used, species used, (C) type of exercise, (D) number of exercise sessions (E) mode of exercise performed and (F) time of day exercise is performed. Bar width represents the log of the number of animals, grey bar represents the 95 CI of the global estimate.

Figure 4: Effect size and 95% confidence intervals (CI) for effect of: post stroke exercise on: (A) type of ischemia, (B) anaesthetic used, (C) method of induction of ischaemia, (D) sex, (E) comorbidity (F), type of exercise, (G) Mode of exercise, (H) time of day exercise is performed and (I) number of exercise sessions. Bar width represents the log of the number of animals, grey bar represents the 95 CI of the global estimate. MCBVAO; middle cerebral artery occlusion plus bilateral vertebral artery occlusion.

Figure 5: Effect size and 95% confidence intervals (CI) for effect of post stroke exercise by: (A) type of ischemia (B) anaesthetic used (C) species used (D) type of exercise performed, (E) mode of exercise (F) number of exercise sessions and (G) intensity of exercise. Bar width represents the log of the number of animals, grey bar represents the 95 CI of the global estimate. Equithesin/chloral hydrate/pentobarbiturate (ECP) and nitrous oxide (NO).

Table 1: Continuous data were analysed using meta-regression techniques both infarct volume and neurobehavioural score according to whether exercise was pre or post-ischemia. The time to treat and duration of ischemia for post-exercise could explain a significant portion of the improvement in infarct volume. N.A; not applicable.

Author	Year	Species	Type of Ischaemia	Method of Induction of Injury	Type of exercise	Cotreatment in both Groups	Cotreatment in Treatment Group Only	Time of Administration relative to ischemia (days)	# Days	Minutes per day
Chang	2009	Rat	Temporary	Ligation	F			1	14	30
de Araujo	2008	Gerbil	Permanent	Ligation	F			0.5	3	no data
								1	3	no data
								2	2	no data
								3	1	no data
Ding	2004	Rat	Temporary	Intraluminal filament/suture	F			-21	18	30
							Rest	-42	18	30
Ding	2004	Rat	Temporary	Intraluminal filament/suture	F			5	28	20
							Rotarod Skill	5	28	20
Endres	2003	Mouse	Temporary	Intraluminal filament/suture	F			-21	15	30
					V			-21	21	no data
Gertz	2006	Mouse	Temporary	Intraluminal filament/suture	V			-21	21	no data
								1	21	no data
						Endostatin		-21	21	no data
						L-NAME		-21	21	no data
Guo	2008	Rat	Temporary	Intraluminal filament/suture	F			-21	15	30
Guo	2008	Rat	Temporary	Intraluminal filament/suture	F			-21	15	30
Hayes	2008	Rat	Temporary	Intraluminal filament/suture	F			-21	15	30
					V			-21	21	no data
Hu	2010	Rat	Permanent	Intraluminal filament/suture	F			2	1	20
									5	20
									12	20
Ke	2011	Rat	Temporary	Intraluminal filament/suture	F			1	7	30
					V			1	7	no data
Kim	2005	Rat	Permanent	Ligation	F			4	12	30
	2007	Rat	Temporary	Intraluminal filament/suture	F			1	28	60
						Stem cells		1	28	60

Author	Year	Species	Type of Ischaemia	Method of Induction of Injury	Type of exercise	Cotreatment in both Groups	Cotreatment in Treatment Group Only	Time of Administration relative to ischemia (days)	# Days	Minutes per day
	2009	Rat	Permanent	MCBVAO	F			3	14	30
						Electro-acupuncture		3	14	30
Komitova	2005	Rat	Permanent	Ligation	V			1	7	no data
Lee	2008	Rat	Temporary	Intraluminal filament/suture	F		Rotarod Skill	3	14	40
	2009	Rat	Temporary	Intraluminal filament/suture	F			1	7	30
									14	30
Li	2004	Rat	Permanent	Intraluminal filament/suture	F			-21	21	30
			Temporary	Intraluminal filament/suture	F			-21	21	30
Luo	2007	Mouse	Temporary	Intraluminal filament/suture	V			7	42	no data
Maldonado	2008	Rat	Temporary	Endothelin	V			5	35	no data
						Reach training		5	35	no data
Marin	2003	Rat	Temporary	Intraluminal filament/suture	V			-7	15	no data
Matsuda	2011	Rat	Temporary	Intraluminal filament/suture	F			1	1	20
									3	20
									5	20
									7	20
									14	20
									28	20
Ploughman	2007	Rat	Temporary	Endothelin	F			5	25	92
						Reach training		5	25	48
	2009	Rat	Temporary	Endothelin	F		Reach training	5	23	37.5
						BLOCK BDNF	Reach training	5	23	37.5
Qin	2006	Rat	Permanent	Intraluminal filament/suture	F		Skill	1	7	40
Risedal	2002	Rat	Permanent	Ligation	V			2	28	no data
Seo	2010	Rat	Temporary	Intraluminal filament/suture	F			1	14	30
							Rotarod Skill	1	14	30

Author	Year	Species	Type of Ischaemia	Method of Induction of Injury	Type of exercise	Cotreatment in both Groups	Cotreatment in Treatment Group Only	Time of Administration relative to ischemia (days)	# Days	Minutes per day
Wang	2001	Rat	Temporary	Ligation	F			-28	20	30
								-14	10	30
								-7	5	30
	2003	Rat	Temporary	Ligation	F			-14	10	30
									10	30
	2005	Rat	Temporary	Ligation	F	Rest		1	5	30
									10	30
Yang	2003	Rat	Temporary	Ligation	F			1	5	30
	2003	Rat	Temporary	Ligation	F			1	10	30
									20	30
	2003	Rat	Temporary	Ligation	F		Rest	1	5	30
								7	5	30
	2006	Rat	Not Known	Unknown	F		Skill	5	30	40
Yu	2006	Rat	Not Known	Surgery	F		Skill	4	24	20

Supplementary Table 1: Table describes the study characteristics for those publications with infarct volume or neurobehavioural data which could be taken forward to meta-analysis stage. Table describes the author, year of publication, species used, type of ischeamia (temporary, permanent and unknown), method of induction of ischemia, the type of exercise (F=forced exercise, V=voluntary exercise) and mode of exercise. Additional columns indicate the presence of co-treatments, the time to commencement (TTC, where negative values represent pre ischemic intervention and positive represent post-ischemic). The number of days exercise is performed is also described (# days) and this is also presented in the number of minutes per day.

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Figure 1

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