Motor Learning in Stroke – Role of extrinsic feedback

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“Arise, awake and stop not till your goal is achieved”

Swami Vivekananda
DEDICATION

This thesis is dedicated to my parents. Without your support, this would not have been possible. I’m happy that I could help realize one of your longstanding dreams. I cannot express my true gratitude to you Amma and Appa in these few words, for having faith in me trusting me and supporting me in every step through the way. I also wish to express my heartfelt gratitude to my wife Shreya, for without her assistance, this monumental task would have been impossible. Thanks for being a sounding board, bouncing ideas with me, putting up with my idiosyncrasies and always encouraging me to do better. To my little baby girl Shloka, you were the major force behind the completion of this theses. Thank you, sweetheart.
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STATEMENT OF AUTHORSHIP

I certify that I am the primary author of all manuscripts contained in this thesis. I claim full responsibility for the content and style of the text here included.
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STATEMENT OF ORIGINALITY

This thesis contains no material that has been published elsewhere, except where specific references are made. He studies presented in chapters 3, 4, 5 and 6 represent original materials and contribute to the advancement of knowledge of the role of extrinsic feedback in motor learning after stroke, especially of upper limb tasks.

All data presented in this thesis were collected at the Feil & Oberfeld Research Centre, Jewish Rehabilitation Hospital Site of the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR), which is affiliated to McGill University. The protocols used in this study have been approved by the Research Ethics board of CRIR.
**PREFACE**

**Thesis format**
This thesis is manuscript-based, and is prepared according to the McGill Graduate and Postdoctoral studies guidelines of thesis preparation. In the guidelines is stated that: “Candidates have the option of including, as part of the thesis, the text of one or more papers submitted, or to be submitted, for publication, or the clearly-duplicated text (not the reprints) of one or more published papers.” In agreement with these guidelines, this thesis contains four original papers, which have been published or are in preparation for submission to peer-reviewed journals.

**Chapter 1**
Chapter 1 outlines the rationale of this thesis, including a short introduction which is followed by the objectives and hypotheses.

**Chapter 2**
Chapter 2 is a literature review composed of 9 sections. The first section describes the etiology and incidence of stroke with a focus on Canadian statistics. The second and third sections describe the motor impairments and appearance of synergies (specific to the upper limb). The fourth and fifth sections describe the cognitive deficits that occur as a result of the stroke and post-stroke depression. The sixth section addresses upper limb recovery after stroke with a focus on neuroplasticity and mechanisms of recovery versus compensation. The seventh section deals with motor learning in terms of its definition, models of motor learning and effects of stroke lesion location on motor learning. The eighth section describes the factors influencing neuoplasticity, motor learning and motor recovery including practice intensity, variability, task-specificity, motivation, environment of task practice and feedback. The terms knowledge of results and knowledge of performance feedback are introduced in this section. The ninth and last section provides an overview of virtual reality and use of virtual reality as a medium to provide feedback.
Chapter 3

Chapter 3 includes the first manuscript which is a systematic review that examines the evidence regarding provision of explicit feedback for implicit motor learning of upper limb tasks in individuals with post-stroke hemiparesis.

Chapter 4

Chapter 4 includes the second manuscript which estimates the concurrent and discriminant validity of movement pattern kinematic variables for pointing and reach-to grasp tasks in individuals with post-stroke hemiparesis.

Chapters 5 and 6

Chapters 5 and 6 include the third and fourth manuscripts. The third manuscript (Chapter 5) evaluated the effects of feedback provision through the medium of a virtual environment compared to a real world physical environment. Chapter 6 contains the fourth manuscript which addresses the objective of whether and to what extent cognitive impairments in the chronic stage post-stroke are associated with the ability to use feedback for improving upper limb motor performance and movement pattern variables in individuals with chronic post-stroke hemiparesis.

Chapter 7

This chapter presents a summary of the findings found in the previous four chapters. Following the summary is a discussion of the results obtained in the studies included in this thesis including an integration of the ideas expressed in the literature review.

Connecting texts
Preceeding each manuscript are connecting texts where the content of each manuscript is introduced and the integration between the manuscripts is undertaken.
Reference List
The references for chapters 1, 2, 7 and the connecting text are compiled at the end of this thesis.

Appendix
This appendix contains two tables on the relationship of neuropsychological outcomes to the recovery of ADL, participation and motor impairment.
CONTRIBUTION OF AUTHORS

Manuscript # 1 (Chapter 3) – The collection of materials, design of this review, PEDro scoring as well as preparation of the manuscript was done by Sandeep Subramanian under the supervision of Dr. Mindy Levin. Crystal Massie assisted with PEDro scoring and preparation of the manuscript. Dr. Mindy Levin was involved in the design of the study and literature review. She helped resolve differences in PEDro scoring, if any. Along with Dr. Matthew Malcolm, she critically reviewed and helped revise the manuscript. All authors read and approved the final version of the manuscript submitted for publication.

Manuscript # 2 (Chapter 4) – Part of the data collection, data and statistical analysis and preparation of the manuscript was done by Sandeep Subramanian. Jury Yamanaka was involved in data and statistical analysis as well as manuscript preparation. Gevorg Chilingaryan provided statistical guidance and helped with data analysis. Dr. Mindy Levin critically reviewed the manuscript and provided institutional affiliation and funding. All authors read and approved the final version of the manuscript submitted for publication.

Manuscript # 3 (Chapter 5) – Kinematic data collection, kinematic and clinical data and statistical analysis and preparation of the manuscript was done by Sandeep Subramanian. Part of the data collection and data analysis was done by Christiane Lourenco. Gevorg Chilingaryan provided statistical guidance and helped with data analysis. Dr. Mindy Levin was involved in the design of this study with Dr. Heidi Sveistrup. Dr. Levin provided provided institutional affiliation and funding and along with Dr. Svesitrup, critically reviewed the manuscript. All authors read and approved the final version of the manuscript submitted for publication.

Manuscript # 4 (Chapter 6) - Kinematic data collection, kinematic and neuropsychological data and statistical analysis and preparation of the manuscript was done by Sandeep Subramanian. Gevorg Chilingaryan provided statistical guidance and helped with data analysis. Dr. Mindy Levin was involved in the design of this study. She provided institutional affiliation and funding and critically reviewed the manuscript.
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ABSTRACT

Stroke contributes significantly to the incidence of motor and cognitive impairments which in turn impact motor learning abilities. Upper limb (UL) motor recovery can be attributed to plasticity mechanisms which are thought to be engaged by rehabilitation interventions focussing on motor learning principles. Factors identified to optimize post-stroke motor recovery and learning include practice intensity, variable- and task-specific practice and motivation, environment of task-practice and provision of feedback. Feedback is sensory information provided either during or following task performance. Feedback provision has been suggested as beneficial for improving motor recovery after a stroke. However, the role of extrinsic feedback on motor learning of UL tasks post stroke is less clear. The global aim of this thesis was to examine the role of extrinsic feedback on motor learning of the UL in stroke.

The thesis includes 4 manuscripts: 1 review paper and 3 experimental studies. The 1st manuscript systematically examines the role of extrinsic feedback on implicit motor learning after stroke for UL movements. The main finding was that provision of feedback is useful for individuals with UL hemiparesis post stroke to implicitly learn UL tasks with both sides and improve motor recovery.

The 2nd manuscript was a retrospective study of UL movement kinematics describing movement quality while performing pointing and RTG tasks in relationship to clinical performance. Study objective was to estimate the concurrent and discriminate validity of movement pattern kinematic measures for both tasks. All movement pattern kinematic variables were found to be valid outcomes of UL motor impairment and can be used as outcomes in studies involving feedback provision. The majority of the variance in FMA scores was explained by trunk displacement for both tasks, which was the only variable that distinguished between levels of motor impairment severity. Participants with mild levels of UL hemiparesis used 33-300% more trunk displacement compared to controls performing similar tasks.
The objective of the 3rd study was to evaluate the effects of feedback provision through the medium of a virtual reality environment (VE) compared to feedback provided in the real world physical environment (PE). Thirty two individuals with stroke were randomized to practice 72 pointing movements daily in either the VE or PE for 12 sessions. Participants in both groups were provided with feedback-terminal KR on error and speed and concurrent KP on trunk displacement. Assessments were carried out before, immediately after and at 3mos after task practice. VE group participants improved joint ranges of motion and increased scores on clinically measured arm use and reaching ability. The PE group improved clinical reaching ability, but also had greater trunk movement. Results suggest that there is an additional value in using VEs as media to provide feedback to enhance UL motor learning outcomes and recovery in chronic stroke.

The 4th manuscript addresses the objective of whether and to what extent cognitive impairments in the chronic stage post-stroke are associated with the ability to use feedback for improving UL motor performance and movement patterns. Data from 24 participants were analyzed. Participants training in the VE tended to make faster movements and improved more in movement pattern outcomes compared to those training in the PE. PE and VE group changes were related to memory and problem solving ability. The majority of the variance in outcomes immediately after practice and at retention was explained by single factors or by a combination of memory, problem solving, mental flexibility, attention and depression.

Results of this thesis suggest that task practice with feedback and attention to movement quality and presence of cognitive deficits may help ensure better motor learning outcomes related to recovery of UL post-stroke.
Certaines déficiences motrices et cognitives peuvent persister suite à un accident vasculaire cérébral (AVC) et avoir un impact sur les habiletés d’apprentissage moteur. La récupération motrice du membre supérieur (MS) peut être attribuée aux mécanismes de plasticité qui seront impliqués dans diverses interventions basées sur les principes d’apprentissage moteur. Les facteurs identifiés comme étant importants pour optimiser la récupération et de l’apprentissage moteur suite à un AVC sont l’intensité, la spécificité, la motivation, l’environnement et la rétroaction. La rétroaction consiste en des informations données pendant ou après l’exécution de la tâche. Cependant, le rôle de la rétroaction extrinsèque sur l’apprentissage moteur des MS suite à un AVC est moins clair. Le but de cette thèse était d’examiner le rôle de la rétroaction extrinsèque sur l’apprentissage moteur du MS suite à un AVC. Quatre papiers ont été inclus : une revue de la littérature et 3 études expérimentales.

Le premier papier consiste en une revue systématique de la littérature documentant le rôle de la rétroaction extrinsèque sur l’apprentissage moteur des MS suite à un AVC. Les résultats suggèrent que la rétroaction est utile pour permettre aux individus présentant une hémiparésie du MS suite à un AVC d’améliorer la capacité motrice des deux membres supérieurs.

Le 2ième papier est une étude rétrospective sur la cinématique du MS qui décrit la relation entre la qualité du mouvement et la performance clinique. L’objectif était de vérifier la validité concurrente et discriminante de la cinématique pour les tâches de pointage et d’atteinte avec préhension. Toutes les variables cinématiques étaient valides et peuvent être utilisées dans les études avec une rétroaction. Les participants avec une hémiparésie légère au MS utilisent de 33-300% plus le déplacement du tronc que les participants sains.

L’objectif de la troisième étude consistait à comparer les effets d’une rétroaction dans un environnement virtuel (ER) comparativement à un environnement physique (EP). 32 individus ayant subi un AVC ont effectué 72 mouvements de pointage par jour dans un ER ou dans un EP sur 12 sessions. Tous les participants ont pu bénéficier d’une rétroaction à la fin de la session sur la précision et la vitesse ainsi qu’une rétroaction sur le déplacement du tronc durant la tâche. Une amélioration de l’amplitude articulaire a été constatée dans l’EV.
permettant d’augmenter le pointage à la mesure clinique de l’utilisation du bras, ainsi qu’à la tâche d’atteinte. Les participants entrainés dans l’EP ont amélioré la tâche d’atteinte et une plus grande compensation du tronc. Les résultats de cette étude suggèrent que l’utilisation d’un EV avec rétroaction permet d’améliorer l’apprentissage et la récupération motrice du MS suite à un AVC.

L’objectif du dernier papier consistait à déterminer si la présence de déficiences cognitives est associée à l’habileté d’utiliser une rétroaction dans le but d’améliorer la performance motrice. Les participants entrainés dans l’EV ont démontré une tendance à effectuer des mouvements plus rapides et ont amélioré davantage leur patron de mouvement que les individus entrainés dans l’EP. Les changements obtenus dans les deux groupes (24 participants) étaient reliés à la mémoire et aux habiletés de résolution de problèmes. Une importante proportion de la variance au niveau des variables cinématiques mesurées immédiatement et 3 mois après la pratique était expliquée par un ou plusieurs facteurs : la mémoire, l’habileté à résoudre des problèmes, la flexibilité mentale, l’attention et la dépression.

Les résultats de cette thèse suggèrent que la pratique d’une tâche en présence d’une rétroaction appropriée et une attention particulière à la qualité du mouvement, en présence de déficits cognitifs pourraient résulter en un meilleur apprentissage moteur lié à une meilleure récupération des MS suite à un AVC.
CHAPTER 1 GENERAL INTRODUCTION

1.1 Background

Upper limb hemiparesis, the most common (Rosamond et al., 2008) and frequent disabling consequence of stroke (Prabhakaran et al., 2008) impacts performance of activities of daily living (ADL), participation in real life situations and quality of life (QOL) (Vestling et al., 2003). Upper limb sensorimotor dysfunctions persist in about half to three-quarters of individuals beyond three to six months post-stroke (Nakayama et al., 1994) and a large number of individuals with post-stroke hemiparesis are unable to successfully integrate the more-impaired upper limb into activities of daily living (Prabhakaran et al., 2008; Kwakkel et al., 2003).

The common clinical belief that beyond 6 months, rehabilitation interventions are no longer beneficial and motor recovery asymptotes (Jorgensen et al. 1995) has been challenged (Page et al. 2004). There is mounting evidence for continued functional recovery of upper limb paresis well into the chronic stages (≥6 months) post-stroke (Subramanian et al., 2013; Bolognini et al., 2011; Koganemaru et al., 2010). Recent metanalyses and systematic reviews have reported that upper-limb rehabilitation approaches (e.g. constraint induced movement therapy; CIMT, motor imagery) have resulted in impressive gains post-practice with moderate (0.73: CIMT) to large (0.84: motor imagery) effect sizes (Langhorne et al., 2011; Langhorne et al., 2009) based only on clinically assessed outcomes.

However, with the use of clinical outcome measures, the focus is often on task achievement and not on how the task was completed. This potentially confounds the interpretation of results as it is not clear whether recovery or compensation has occurred in terms of how the task was performed. Motor recovery has been defined as the ability to perform a movement in the same manner as before stroke while compensation refers to the ability to perform the movement in a manner different from before stroke (i.e. use of additional degrees of freedom, use of different end effectors; Levin et al., 2009a). Efforts at upper limb rehabilitation must focus primarily on motor recovery to channel or drive neuroplasticity.
towards re-organization that results in better long-term motor outcomes (Krakauer et al., 2012; Alaverdashvili et al., 2008).

Information on how a movement is performed can be obtained primarily with the use of kinematic analysis. Movements can be broadly described at two levels using kinematic analysis: motor performance (describing the results of the movements; measures of error, smoothness, movement time and velocity) and movement patterns (describing how the movement was performed using measures of trunk displacement and joint ranges of motion, interjoint-co-ordination). Movement pattern kinematics are probably the most useful tools to help differentiate recovery from compensation, as individuals after stroke can still improve motor performance (for example, speed) using compensatory movements (for example, the trunk) to assist in hand movements instead of elbow and shoulder movements (Michaelsen et al., 2006).

The presence of continued functional improvement observed well into the chronic stage of stroke can be attributable to plasticity in the remaining cortical and subcortical brain tissue (Warraich and Kleim, 2010). Neuroplastic mechanisms are thought to be engaged by rehabilitation interventions that focus on motor learning principles. Motor learning involves a relatively permanent change in the capability for producing movements associated with practice or experience (Schmidt and Lee, 2011). The changes that ensue at a neuronal and behavioral level as a result of motor learning and the variables influencing these changes are of particular interest for rehabilitation (Magill, 2011). Factors related to neuroplasticity that have been identified as pertinent to optimize post-stroke motor recovery and learning include practice intensity, variable- and task-specific practice and motivation (Kleim and Jones, 2008).

The presence of cognitive deficits after a stroke influence motor learning and recovery. Enhanced learning of motor performance outcomes (Cirstea et al., 2006; Dancause et al., 2002) and greater improvements of impairment levels and ADL performance with upper-limb rehabilitation interventions involving intense and variable task-specific practice were associated with fewer deficits in memory, problem solving and cognitive flexibility.
However, it is still unclear whether the presence of cognitive impairments is associated with learning and recovery of movement pattern outcomes.

Additional factors suggested as being crucial to maximize motor learning and optimal recovery post-stroke are the practice environment (Nithianantharajah and Hannan, 2006) and provision of task and performance relevant feedback (Cirstea et al., 2006). Training of reaching movements in enriched environments leads to long lasting functional recovery and changes in neuroplasticity in rodent stroke models (Murphy and Corbett, 2009). Provision of feedback results in better functional recovery with decreased compensations, retention of gains observed immediately after practice (Cirstea and Levin 2007) and modulation of neuroplasticity (increased ipsilesional activation after practice; Jang et al., 2005).

Virtual reality (VR) environments are enriched environments suitable for use in individuals post-stroke (Murphy and Corbett 2009; Bach-y-Rita et al., 2002). VR is a multisensorial experience in which a person is immersed and can interact with custom designed computer generated two- (2D) and three-dimensional (3D) virtual environments (VEs; Schultheis et al., 2002); affording high levels of control for individual practice parameters. VEs can be designed to include novel interactive games involving variable and intense task specific practice to motivate subjects. VEs can be manipulated to provide salient visual, auditory and haptic feedback to the learner. VEs thus serve as a platform to incorporate factors related to neuroplasticity to optimize motor learning and recovery of the upper limb.

Although the use of VEs may be feasible for upper limb rehabilitation post-stroke, the effectiveness and added value of using VR over other interventions has not yet been demonstrated for 3D VEs using research designs like randomized control trials (Henderson et al., 2007). Given that practice intensity is an essential factor for optimizing upper limb recovery (Han et al., 2013; Lo et al., 2010), it is still unknown if matched intensity training with feedback provision through the medium of a VE results in similar or better outcomes compared to feedback delivered in a real world physical environment (PE). Better motor learning outcomes in previous studies involving task specific intense practice with a large number of repetitions and feedback in a PE have been associated with fewer deficits in
memory, cognitive flexibility and problem solving. However, it is still unknown whether improved motor learning outcomes, after task practice in VEs are associated with deficits in cognitive functioning.

1.2 **Objectives and Hypotheses of the Thesis**

The global aim of this thesis was to examine the role of extrinsic feedback on motor learning of the upper limb in stroke.

The specific objectives of this thesis are:

1) To review the literature regarding the effectiveness of the use of feedback by patients with stroke for motor learning, specifically in relation to upper limb tasks;
2) To estimate the validity of movement pattern kinematics in subjects with post-stroke hemiparesis in order to determine which kinematics are best suited for use as motor outcome measures;
3) To estimate the effect of feedback (provided through the medium of virtual reality) for upper limb motor recovery;
4) To estimate the influence of cognitive impairments on using feedback to learn and recover motor performance and movement pattern variables (i.e. upper limb kinematics).

The first objective is addressed by the review paper in Chapter 3. The second objective is addressed by the manuscript in Chapter 4. The third objective is addressed by the manuscript in Chapter 5 and the last objective is addressed by the manuscript in Chapter 6.

In line with objective 3, the following hypotheses were tested:

1. Greater improvements in upper limb motor impairment levels will be noted after task practice in the VE compared to the PE.
2. Greater improvements in clinical measures of upper limb activity and arm use will be noted after practice in the VE compared to the PE
This doctoral thesis consists of a review of the relevant literature and includes four manuscripts, a summary of the findings and a general discussion. Finally, clinical relevance and limitations of the studies as well as a consideration of future research directions are presented.
CHAPTER 2 LITERATURE REVIEW

2.1 Etiology and Incidence of stroke

Stroke is the leading cause of adult disability and the third leading cause of death in Canada (StatsCan, 2011). Stroke costs the Canadian economy more than $2.7 billion a year (Canadian Stroke Network, para. 5). After a stroke, Canadians spend a total of 4.5 million days in facilities with residential care (Lindsay et al., 2011). Of every 100 people hospitalized for stroke, 15% die, 10% completely recover, 25% have a minor impairment, 40% have a moderate impairment or disability and 10% are severely impaired needing long-term care (Heart and Stroke Foundation Website, 2012).

A Quebec based study (Mayo et al., 2007) reported a steady decline in the incidence of cerebral infarction from 1988 to 2002 (32.5% in men, 25.5% in women). This was accompanied by a simultaneous increase in the incidence of intracerebral hemorrhage (2% in men and 1.6% in women every year). Recent reports indicate that an increasing number of stroke survivors return home after acute hospitalization (60%), with about 12% requiring long term care (as compared to 14% in 2002). About one-fifth of the total numbers of those who had a stroke (17%) were transferred to a rehabilitation facility (Lindsay et al., 2011).

Up to 77% of patients show initial upper limb sensorimotor dysfunctions that persist in 55 to 75% of patients for more than three months (Green et al., 2002; Lawrence et al., 2001). At the end of 6 months post stroke, a fairly large proportion of people (65%) had limitations in functional activities (39%) and a larger proportion in higher ADLs like shopping and housework (Mayo et al., 2002). Subjects were chronic post-stroke hemiparesis were found to be unable to incorporate their more-affected upper limb for performance of ADL (Prabhakaran et al., 2008; Kwakkel et al., 2003). Longitudinal studies of recovery after stroke have reported that only about 50% of stroke survivors with significant arm paresis recover useful arm function (French et al., 2010; Sunderland et al., 1989).
2.2 Upper limb motor impairments post-stroke

The changes occurring post-stroke at the level of the body structures/normal function are referred to as impairments under the International Classification of Functioning, Disability and Health (ICF) framework of the World Health Organization (WHO, 2001). Arm paresis on the affected side is one of the most common sequelae of stroke (Bourbonnais and Vanden Noven, 1989). In addition, changes occur in the upper limb at the level of the bones and individual muscles.

2.2.1 Bone change

Demineralization of bone occurs due to reduced use of the more-impaired side (Pang et al., 2007), with differences in bone mineral content (13.8% lower) and bone mineral density (4.5% lower; Pang and Eng, 2005). For individual bones, reductions in bone mineral density range from 1.6% (radius) to 25% (humerus; Jorgensen and Jacobsen, 2001) in people with chronic stroke.

2.2.2 Muscle changes

2.2.2.1 Changes in muscle mass

At the level of the muscles, changes occur in the i) amount of muscle mass and ii) motor unit structural and contractile properties. The total upper limb lean muscle mass differs between the less impaired and more-impaired sides (mean difference of 240 gms; English et al., 2010). Lack of differences in the diameter of the more- and less-impaired upper limbs (Sunnerhagen et al., 1999) can be attributed to the fact that muscle atrophy is accompanied by simultaneous fat deposition (Lang et al., 2010). A recent metanalysis concluded that the more-impaired side had greater fat mass compared to the less-impaired side (English et al., 2012).
2.2.2.2 Changes in motor unit numbers and properties

The structural and contractile properties of motor units change post-stroke. There is a loss of motor units on the more-impaired side. This loss begins anywhere from 4-30 hours after stroke in the hypothenar muscles (Arasaki et al., 2006) to 9 days in the thenar muscles (Hara et al., 2004). This loss continues until about 3 months (McComas et al., 1973), when it plateaus. There is a selective loss of high threshold motor units (atrophy of fast twitch type 2 fibers; Lukács et al., 2008; Young and Mayer, 1982; Edström, 1970). Greater losses in motor unit numbers have been recorded in those individuals with a higher severity of initial motor impairment (Arasaki et al., 2006; Hara et al., 2004).

In addition, motor units undergo a transformation and are converted into those with longer contraction times (compensatory hypertrophy of type 1 slow twitch fibers; Frontera et al., 1997; Dattola et al., 1993) which leads to weakness. The diameter of the type 1 fiber is smaller (difference of 8.5 µm) on the more- compared to the less-impaired side (Hachisuka et al., 1997). The reduction in numbers of motor units is also accompanied by a decrease in firing rates in motor units among individuals post-stroke. These changes occur in both intrinsic and extrinsic hand muscles (Freund et al., 1973). Reduction of motor unit synchronization is associated with slowing of alternating finger to thumb movements on the more-impaired side in individuals post-stroke (Farmer et al., 1993).

The reduction in numbers of motor units has been attributed chiefly to two mechanisms: i) dysfunction of the lateral corticospinal tract leading to a loss of the facilitatory input to the α motoneurons innervating the small muscles of the hand (Arasaki et al., 2006) and ii) alterations in metabolism and axonal transport causing trans-synaptic changes in the lower motor neurons (Li et al., 1992; Dahlöf et al., 1981) resulting in the loss of supraspinal input (Hara et al., 2004). Loss of high threshold motor units and re-innervation of existing muscle fibers by the lower threshold motor units results in lower force production against a given load on the more-impaired side. This also explains the phenomenon of increased amount of electromyographic (EMG) activity per unit of force generated (Gemperline et al., 1995; Tang and Rymer, 1981).
In the upper limb, the strength of the elbow flexors and extensors was found to be weaker by 65% and 61% respectively on the more- compared to the less-impaired side (Ploutz-Snyder et al., 2006). The weakness is accompanied by a decrease in total muscle RNA, total messenger RNA and myosin heavy chain RNA (Haddad et al., 2005). Morphological studies have also shown that there is a decrease in the capillary density, sodium potassium ATPase concentration and myosin heavy chain RNA expression in the muscle fibers (Ponten and Stal, 2007; Landin et al., 1977).

2.3 Appearance of synergies

As recovery from stroke progresses, there is emergence of spasticity and stereotypical movement patterns (Twitchell, 1951). Attempts at voluntary motion of a single joint result in stereotypical movement patterns in flexion or extension referred to as the flexor and extensor synergy respectively. For the upper limb, the flexor synergy consists of scapular elevation and retraction, shoulder abduction, extension and external rotation, elbow flexion, forearm supination and wrist and finger flexion. The extensor synergy is characterized by shoulder girdle retraction, shoulder horizontal adduction and internal rotation, elbow extension, forearm pronation and wrist and finger extension (Brunnström, 1970).

While Twitchell and Brunnström provided a qualitative description of synergies, quantitative evidence was provided by the work of Dewald, Beer and colleagues. A series of studies were conducted by them to understand torque production ability of individuals post-stroke and the relationship between deficient torque production ability and planar upper-limb movements.

Abnormal coactivation of shoulder abductors (secondary torque) or shoulder adductors (secondary torque) was found when participants were asked to generate either maximal (Dewald and Beer, 2001) or sub-maximal (5-50%) voluntary isometric elbow flexion or extension torques respectively (Dewald et al., 1995). The synergistic movement patterns are a consequence of the aforementioned torque coupling such that an intended action at a particular joint (e.g. elbow flexion) that requires the generation of a primary torque generates a synergistic movement driven by the production of secondary torques (Platz, 2004).
In addition, improved ability to produce shoulder-elbow flexion torque was noted in participants with stroke while maintaining sub-maximal (10%, 50%) shoulder abduction torque levels (Beer et al., 1999). However, a reduction in maximal elbow extension, shoulder flexion and shoulder extension torques was noted during unsupported compared to supported forward reaching tasks (Dewald et al., 2001b). Results of this and other studies (Beer et al., 2004; Takahashi and Reinkensmeyer, 2003) have indicated that participants with greater motor impairment levels exhibit a severely reduced ability to initiate reaching movements requiring elbow extension and shoulder abduction due to abnormal shoulder-elbow torque coupling. This leads to a reduction in the reaching workspace and decreased movement velocity.

The presence of the abnormal torque coupling can be explained on the basis of alterations in the descending commands and/or excitability at the level of the spinal cord. There is an increased dependence on brainstem pathways (vestibulospinal, reticulospinal and tectospinal tracts which extensively branch innervating many spinal segments) after damage to the pyramidal tracts (Colebatch et al., 1990; Kuypers, 1964). This results in co-activation in many muscles (due to the branching) and may lead to abnormal torque coupling. Increase in the excitability of the flexor reflex interneurons due to loss of descending input from the higher centres (Devanandan et al., 1969a, Devanadan et al., 1969b) also contributes to the abnormal coupling.

There is a deficit in the control of voluntary movements, with impaired ability to move a single joint selectively, without moving others (e.g. ability to flex the elbow without concomitant shoulder abduction) or stabilize isolated joint segments (e.g. ability to extend elbow while holding arm in an abducted position; Platz, 2004). This impacts the ability to temporally and spatially coordinate movements between adjacent joints (Cirstea et al., 2003b; Levin, 1996).

Deficits are also present in stretch reflex threshold regulation (Levin, 2000a; Levin and Feldman, 1994), which contributes to joint weakness and the presence of spasticity in specific joint ranges. Joint ranges are found in which i) active torque production is
impossible; ii) reciprocal organization of agonist and antagonist muscle activity is limited, iii) attempts to produce torque from positions outside the range of measured active movement can lead to excessive muscle co-activation, which typically produces no or paradoxical motion in the opposite direction (Levin et al., 2000b) and iv) impaired ability of force production, with relatively less strength produced in the shortened ranges (Ada et al., 2003).

2.4 Cognitive impairments post-stroke

2.4.1 Domains most commonly affected

In addition to motor impairments, a large number of stroke survivors (65-70%) show signs of cognitive impairments (Lesniak et al., 2008; Nys et al., 2007; Ballard et al., 2003). Domains most commonly affected include attention, memory, executive functioning, visual perception and visuoconstructional abilities and orientation (Lezak et al., 2004; Tatemichi et al., 1994). Aspects of attention such as focused, sustained and divided attention are all impaired post-stroke (Hochstenbach and Mulder, 1999; Hochstenbach et al., 1998). Memory impairments are related to intake and retrieval of information. Deficits include impairments in verbal and non-verbal memory (Hochstenbach et al., 1998) as well as prospective and retrospective memory (Kim et al., 2009).

Problems in executive functioning include deficits in decision making, planning and organization of the steps for action, initiation of goal-directed activities and in auto-evaluation of the results of actions (Gottesman and Hillis, 2010; Zinn et al., 2007). Some of the common impairments in visuospatial functioning include visual perceptual and constructional deficits (Brown et al., 2012a). Deficits in orientation may include impaired orientation of time, place and person and confusion and are generally accompanied by deficits in memory and attention (Lezak et al., 2004; Katz et al., 1999).

Donovan and colleagues identified relevant neurocognitive domains by expanding upon traditionally assessed cognitive impairments to develop an ecologically-valid measure of
functional cognition in stroke (Donovan et al., 2008). Stroke specific definitions of the various domains were suggested and component sub-domains/abilities were specified.

2.4.1.1 Attention

Attention has been defined as a variety of functions that include: selectivity, focusing, sustaining concentration or vigilance and ability to shift between different components of the same tasks or different tasks (Donovan et al., 2008). The intralaminar thalamic nuclei, cerebral hemispheres, parietal lobes, frontal lobes and nucleus basalis are part of a diffuse system that subserves attention (Van der Werf et al., 2003; Filley, 2002). Focussed attention (ability to attend to the main aspect of a task without being distracted by other stimuli) tasks mainly involve the parietal and frontal lobes (Dickenson et al., 2013). Sustained attention (ability to concentrate on a given task for long periods of time) is primarily mediated by the right frontal lobe and posterior parietal cortex (Rueckert and Grafman, 1998; 1996), while the nucleus basalis plays the primary role in divided (capacity to shift between tasks) attention (Olton et al., 1988).

2.4.1.2 Memory

Memory has been defined as the capacity to retain information for varying durations and use it for adaptive purposes (Donovan et al., 2008). The domain includes functions of encoding, storing and retrieval of information. Information is initially stored for a period of a few seconds to minutes in short-term or working memory (Magill, 2011), which is essential for decision-making and problem-solving. The structures of the medial temporal lobe are responsible for short-term memory. These structures are the posterior parietal cortex, hippocampus (dentate gyrus and subicular complex) and accompanying cortical areas including the entorhinal, perirhinal and parahippocampal cortices (Soto et al., 2012; Squire and Zola-Morgan, 1996; Zola-Morgan and Squire, 1993). Relevant information is then passed on to long-term memory. The medial thalamus, along with the medial temporal lobe, the frontal lobe and pre-frontal cortices have been implicated in the formation and sustenance of long-term memory (Vallar et al., 2005; Markowitsch and Calabrese, 1999).
2.4.1.3 Executive functioning

Executive functions comprise of a group of cognitive processes which are responsible for directing and managing cognitive, emotional, and behavioral functions during tasks such as organizing and prioritizing thoughts and activities, managing time efficiently and making decisions (Donovan et al., 2008). Executive functioning capacities include task initiation, problem-solving, perseveration, abstract reasoning, planning, organization, flexibility and information processing. These abilities enable a person to engage in successful and purposeful behavior (Burgess, 1997). They are involved in appropriately modifying behavior, adapting behavior to changing environmental conditions with the availability of new information and sequencing of complex actions (Elliott, 2003). They help in appropriately modifying and adapting behavior by influencing the ability to utilize information from one movement trial in the performance of the same movement again (in conjunction with memory) and auto-evaluation of the results of an activity.

Neuroimaging studies have indicated that the frontal, prefrontal, parietal cortices and basal ganglia play a role in mediating executive functioning capacities (Collette et al., 2006; Newman et al., 2003). On the basis of modelling studies, the right prefrontal area has been shown to be more involved in the generation of an action plan, while the left prefrontal area was primarily responsible for its execution (Newman et al., 2003). In addition, the integrity of the frontostriatal pathways plays a very important role in executive function capabilities (Elliott, 2003). The integrity of the frontal white matter (frontal areas, bodies of the lateral ventricles) and subcortical grey matter (frontal cortex) has been shown to be important for information processing speed and cognitive flexibility (Sachdev et al., 2004; Werring et al., 2004).

2.4.1.4 Visuospatial functions

Visuospatial functions have been defined as the ability to perceive and process visual information in one’s environment (Donovan et al., 2008). The domain encompasses the functions of topographical orientation, visual perception, visuospatial and visual construction
skills. Visual perception includes the ability to recognize and classify objects, faces, colors, people, shapes and forms (Benton and Tranel, 1993). Visuospatial skills involve the ability to associate oneself with object location, direction or movement in a logical manner such that the association conveys a meaning (Lezak et al., 2004). Visual constructional skills include the ability to organize component parts into a whole (two or three dimensional) structure (Neistadt, 1992). Visual perceptual and constructional skills are mediated by a widespread network including frontal, parietal, temporal and occipital areas, the basal ganglia, the thalamus and the cerebellum (Ganis et al., 2004). The non-dominant or right hemisphere has been indicated to be important for visuospatial functioning (Cooke et al., 2005; Heitnzer and Teasell, 1998). The left hemisphere has been postulated to be important for visual constructional skills, especially for reproducing drawings and block designs (Edmans and Lincoln, 1987).

2.4.2 Prevalence of cognitive deficits

2.4.2.1 Prevalence in acute stroke

A greater prevalence of cognitive deficits is found in the acute compared to the sub-acute or chronic stage post-stroke. The prevalence of attention deficits was reported to be from 50-70% in a sample of 129 individuals <1 month post stroke (Hurford et al., 2013). Deficits in memory were found in short-term (35%, sample size = 216; Hochstenbach et al., 1998) and visual (16%) and verbal (22%) memory (sample size of 111; Nys et al., 2005a), with long-term memory affected (48%; Hochstenbach et al., 1998) to a greater extent than short-term. Deficits in executive functioning range from 29 – 50% (sample size of 47), with deficits seen primarily in persistence, cognitive flexibility, motor planning and information processing (Zinn et al., 2007). Visuospatial functioning was found to be impaired in approximately 38% of subjects, with deficits primarily seen in visual perception and construction skills (sample size = 168; Nys et al., 2007).
2.4.2.2 Prevalence in sub-acute and chronic stroke

The prevalence of cognitive impairments changes in the sub-acute and chronic stages post-stroke, with recovery noted across all domains. Three months after stroke, a reduction is noted compared to the acute stage and the prevalence of cognitive impairments in the various domains (sample size = 37) was: attention (sustained) – 37%, memory – 33%, executive functioning (cognitive flexibility, motor planning and problem solving) – 16% and visual perception and constructional skills – 8.5% (Hurford et al., 2013).

In the chronic stage, though a further reduction in the prevalence of cognitive impairments is noted, cognitive impairments are still found to persist. Sustained and divided attention functions were found to be impaired in 31% and 44% respectively in a sample of 48 individuals with stroke (Hyndman and Ashburn, 2003). Prevalence of short-term and visual memory deficits was found to be 8.5%, while deficits in executive functioning (cognitive flexibility, motor planning and problem solving) was 13.5% (sample size = 111; Nys et al., 2005a). In the same study, visuospatial functioning deficits were prevalent in about 9% of people with stroke, especially in visual perception and constructional abilities.

2.4.3 Etiopathogenesis of cognitive deficits after stroke

Cognitive dysfunction resulting from acute stroke is influenced by inadequate perfusion in areas surrounding the lesion (Gottesman and Hillis, 2010). There is a mismatch between supply and demand, i.e., inadequate blood flow and increased demand for oxygen in the regions surrounding the lesion. Both gray-matter (thalamus, putamen, hippocampus and parahippocampal gyri, frontal, temporal, parietal and occipital lobes) and white matter atrophy have been reported in individuals with cognitive dysfunction post-stroke in at least one domain compared to those without any dysfunction. (Grau-Olivares et al., 2010; Stebbins et al., 2008; Grau-Olivares et al., 2007).

Periventricular white matter ischemic lesions around the lateral ventricles and the frontal subcortical areas (Jokinen et al., 2005; Prins et al., 2005; Vataja et al., 2003; de Groot et al.,
have been associated with impaired cognition, particularly in the domains of executive functioning and speed of performance of motor tests. In addition, using diffusion tensor imaging, reduced fractional anisotropy (FA; reflecting fiber density, axonal diameter, and white matter myelination) in the parietal area was found to be the strongest predictor for cognitive dysfunction with significant relationships to working memory, recall and basic attention skills (Williamson et al., 2010).

Other factors associated with the development of cognitive impairments post-stroke include i) accumulation of β-amyloid in the cerebral vessels leading to impaired perfusion (Kalaria, 2012); ii) presence of the apolipoprotein epsilon 4 (APOε4) allele, which has been shown to be independently associated with the development of cognitive dysfunction, especially in the domains of verbal learning and memory at two (Wagle et al., 2009) and 13 months post-stroke (Wagle et al., 2011); iii) elevated plasma homocysteine level which has been associated with impaired attention and executive functioning (Pavlovic et al., 2011; Sachdev et al., 2003) due to its role in causing micro-angiopathies.

2.4.4 Effect of lesion location, side and size on post-stroke cognitive deficits

2.4.4.1 Effects of lesion location on post-stroke cognitive deficits

Cognitive impairments have been shown to be related to lesion location. Executive functioning deficits were found to be higher in individuals post-stroke when the lesion involved areas supplied by the middle and anterior cerebral arteries (frontal lobes primarily; Barker-Collo et al., 2012). In addition, lesions in the areas supplied by the middle and anterior cerebral arteries (parietal lobes primarily) produced deficits in attention and working memory (Barker-Collo et al., 2012; Williamson et al., 2010; Bamford et al., 1991). Lacunar strokes in the basal ganglia and thalamus have been associated with deficits in visual perceptual and constructional abilities.

Cognitive deficits have also been linked to the presence of network dysfunction in place of explicit one-to-one mapping with lesion location. Impairments in the domains of attention
and verbal memory in 17 subjects with severe carotid stenosis (contributing to silent strokes) were found to be correlated ($r^2=0.74$) to decreased whole brain fractional anisotropy (Cheng et al., 2012). In addition, these subjects had markedly decreased inter- and intra-hemispheric functional connectivity in the frontoparietal network (involving cortical areas along the intraparietal sulcus, the inferior parietal lobe, and dorsal PMC including the frontal eye field; Ptak, 2012). In the default mode network (network of brain regions including the medial temporal lobe, medial prefrontal cortex, and the posterior cingulate cortex, ventral precuneus and the medial, lateral and inferior parietal cortex that are active when the individual is focused on the task at hand and not on the outside world; Raichel and Snyder, 2007), the intrahemispheric functional connectivity was found to be bilaterally impaired in the same subjects.

2.4.4.2 Effects of lesion side and size on post-stroke cognitive deficits

In addition to anatomical lesion location, side of the brain affected and size of the lesion influence cognitive impairments after stroke. In a series of studies, Nys and colleagues (Nys et al. 2007; Nys et al. 2005b) found that those individuals with left cortical, subcortical (basal ganglia, thalamus) and infratentorial (cerebellum, pons) strokes had more severe impairments in the domains of executive functions, abstract reasoning and verbal memory compared to right-sided strokes involving the same areas.

Their results also indicated that subjects post-stroke with cognitive impairment had three times larger lesion volumes compared to subjects without cognitive impairment. Lesion volume also was significantly correlated with impairments in executive functions, visual perception/ construction and visual memory. Similar results were reported by Elwan and colleagues (1994). Their results showed that cerebral infarctions of larger volumes (>5 cm) were related to greater impairments in memory (dementia scores and scores on Mini Mental scale) compared to lesions of medium (1.5 – 3 cm) or small (<1.5 cm) volumes. In the same study, electroencephalographic (EEG) recordings demonstrated that increased latency of the P300 event-related potential (reflecting characteristics of stimulus evaluation or categorization processes) was related to impaired performance on the Mini Mental Scale.
Examination (assessing global cognition) as well as Trail Making Test (A and B) which assesses cognitive flexibility and problem-solving abilities.

2.4.5 Relationship of post-stroke cognitive deficits to motor recovery

Cognitive impairments are presumed to be associated with and influence motor recovery post-stroke. Successful performance of physical, vocational, and social roles depends on cognitive functioning as well as the degree of motor and/or sensory deficit (Duncan et al., 2000). The presence and persistence of cognitive impairments are likely to be associated with greater difficulties in routine ADL performance and/or failure of the individuals post-stroke to adapt to a new or problematic situation (Cicerone et al., 2011; 2000). Although the exact mechanisms by which cognitive factors influence motor recovery is unknown, a few studies have begun to examine the etiological similarities between the presence of cognitive and motor deficits after stroke in order to try and better understand this relationship (Chen et al., 2013).

Small vessel disease has been postulated to be one of the main mechanisms responsible for the occurrence of cognitive deficits after stroke (Mok et al., 2004), especially in the thalamic and frontal areas. This has been shown to result in white matter hyperintensities (reflecting demyelination), especially in the frontal lobes and is known to be correlated to higher levels of cognitive and physical impairment (Mok et al., 2010). Another mechanism that has been postulated to be a common causative factor is an alteration in the levels of neurotransmitters, including serotonin. An improvement in levels of serotonin with the use of serotonin specific reuptake inhibitors (SSRIs) has been shown to result in neuroplastic changes in the hippocampus (increased proliferation of neuronal precursors in the subgranular zone of the dentate gyrus) and cerebral cortex (Santarelli et al., 2003). These changes led to improvements in both cognitive and physical functioning (Jorge et al., 2010).

Research however is scarce about the extent to which cognitive deficits occurring immediately after stroke and persisting in the long-term are associated with the motor recovery after stroke, especially with a reduction in motor impairment levels and
improvement in ADL performance (Feigin et al., 2008; Barker-Collo and Feigin, 2006). There have been only a few studies that have investigated whether the presence of cognitive deficits post-stroke influences motor recovery. Relevant details (including study authors, sample size, exposure and outcome variables and results) of studies that have explored the relationship with recovery of ADL and motor impairment are given in tables A-1 and A-2 respectively (provided in the appendix).

2.4.5.1 Relationship of post-stroke cognitive deficits to recovery of ADL

Amongst studies that have evaluated the association between cognitive impairments and recovery of ADL, a wide variety of tests was used as outcomes to assess the cognitive domains as well as recovery of ADL. Cognitive domains assessed included attention, memory, language, visual perception and visuoconstructional skills, planning abilities and cognitive flexibility. Studies either used standardised neuropsychological tests evaluating each of these domains separately (Cao et al., 2007; Hajek et al., 1997) or composite assessments including the Neurobehavioral Cognitive Status Examination (Cognistat; Kiernan et al., 1987), Mini Mental Scale Evaluation (MMSE; Folstein et al., 1975), Functional Independence Measure - Cognitive domain (FIM-C; Hobart et al., 2001) scores and Repeatable Battery for Assessment of Neuropsychological Symptoms (RBANS; Randolph, 1998), in which a score for global cognitive dysfunction was obtained. Some of the studies also used individual domain scores that contributed to a composite score.

Outcomes used to measure ADL performance included the FIM (Keith et al., 1987), Barthel Index (BI; Mahoney and Barthel, 1965), Frenchay Activities Index (FAI; Wade et al., 1985) and the modified Rankin Score (mRS; Lai and Duncan, 2001). The presence of global cognitive impairment was related to poorer recovery of ADLs and functional independence at discharge from acute care, rehabilitation and until 4 years post-stroke (Patel et al., 2002). Greater odds for poorer recovery were found for those with severe cognitive impairment (MMSE score ≤10; Odds ratios ranging from 3.76 to 15.18). The amount of variance in the ADL outcomes explained by various combinations of cognitive test scores ranged from 11.6 to 74.2%. In isolation, Cognistat was used most commonly and the amount of variance
explained by this scale ranged from 5.8 to 57.5%. Among the individual domains, those that made a significant contribution to the multiple regression models included attention, memory, orientation, visual-perception and visuoconstruction skills.

2.4.5.2 Relationship of post-stroke cognitive deficits to recovery of motor impairment

Amongst studies that have evaluated between recovery of motor impairment and cognitive impairments, deficits in individual neuropsychological domains were more commonly assessed compared to global cognitive status. Three of the studies assessed motor impairment using kinematically derived measures (Boyd et al., 2009; Cirstea et al., 2006; Dancause et al., 2002) and the other study used clinical measures (Barreca et al., 1999). Better performance in response to interventions consisting of repeated practice over one, two or ten days was seen in individuals with fewer deficits in memory, problem-solving and planning abilities. The amount of variance in the motor impairment measures explained by the cognitive deficits either in isolation or in combination with memory (verbal and non-verbal) ranged from 14 to 52%.

Thus, cognitive factors contribute to recovery of ADL and motor impairments and the assessment of cognitive impairments should be a regular feature of studies assessing the extent of spontaneous and practice-induced recovery post-stroke (Schellinger et al., 2012; Hachinski et al., 2006). The outcomes used to assess ADL are amongst those that have been most commonly used as primary outcomes in contemporary stroke trials (Quinn et al., 2009). However, in terms of motor impairment, the focus has been only on task performance outcomes and not on how the movement was performed (i.e. outcomes of movement patterns). It is essential to know whether cognitive factors are related to recovery of movement pattern measures and if so, to what extent. This is especially important, given the increasing focus on motor impairment (Krakauer et al., 2012) and the outcomes measuring impairment levels, especially those assessing movement quality.
2.5 Post-stroke depression

Depression is a mood disorder that is seen frequently after stroke and can be classified into major and minor depression (Lam et al., 2010). The prevalence of post-stroke depression (PSD) varies widely depending upon the time since stroke and the setting (hospital, rehabilitation or community) in which the data were obtained. In the acute phase (≤2 weeks - 1 month), the prevalence was found to be about 27% of a sample size of 103 individuals post-stroke, which peaked at 3-6 months (34% of a total sample of 104 subjects) and reached a plateau at about 21% (sample size = 106) at 2 years post-stroke (Whyte and Mulsant, 2002). In rehabilitation settings, the prevalence has been found to be about 27% (sample size = 150) and 21% (n = 136) at 3 months and 1 year post-stroke respectively (Herrmann et al., 1998). The highest prevalence of PSD (68%; n = 50) was found in the community setting, especially in people with sub-acute and chronic stroke (Lam et al., 2010).

2.5.1 Etiopathogenesis of post-stroke depression

Although the exact mechanisms underlying the development of PSD are still not very clear, alterations in brain function or psychological factors have been the two primary mechanisms proposed to explain the development of PSD (Gaete and Bogousslavsky, 2008).

2.5.1.1 Brain function alterations

The alterations in brain function include alterations in: i) levels of monoamines and neurotrophic factors and ii) inflammatory responses. PSD is known to be associated with alterations in the levels of monoamines – primarily serotonin and norepinephrine to a lesser extent (Gaete and Bogousslavsky, 2008). The monoamine levels are altered due to disruptions in monoamine fibers as a result of lesions in the frontal cortex and basal ganglia (Spalletta et al., 2006). The decrease in the levels of serotonin is further supported by evidence of reduced levels of 5-hydroxy-indoleacetic acid (main metabolite of serotonin) in cerebrospinal fluid (Bryer et al., 1992) and altered serotonin receptor activity in the temporal cortex (Mayberg et al., 1988).
Amongst neurotrophins (a group of molecules that promote growth and survival of neurons), brain derived neurotrophic factor (BDNF) plays an important role in PSD. A low serum level of BDNF on the first day post-stroke is related to the development of PSD (Yang et al., 2011). Individuals post-stroke diagnosed with PSD have lower levels of serum BDNF at 3-6 months, which corresponds with the peak rates of depression (Zhou et al., 2011). Recent studies have indicated that the BDNF val^{66}met (replacement of valine by methionene at allele 66) polymorphism renders the brain more susceptible to the development of PSD (Kim et al., 2012; Kim et al., 2008).

Alterations in inflammatory responses after stroke are an additional factor known to contribute to the pathophysiology of PSD (Dowlati et al., 2010). Following acute ischemia, increased levels of proinflammatory cytokines are seen including interleukin (IL)-6 and tumor necrosis factor (TNF-α; Wang et al., 2007) and higher levels of these cytokines were seen ≤1 year post-stroke in individuals with PSD (Su et al., 2012). These cytokines have a stimulatory effect on the hypothalamic-pituitary-adrenal axis leading to increased release of corticotrophin releasing hormone (Silverman et al., 2005) which contributes to increased metabolism of the monoamines (serotonin, norepinephrine) in the limbic and hypothalamic areas (Anisman et al., 2002). This results in a vicious circle with release of corticotrophin stimulating hormone promoting the release of pro-inflammatory cytokines (Miller and Pariante, 2000).

2.5.1.2 Psychological factors

While in the earlier stage after stroke, the biological changes are more influential, psychological factors have been proposed to play an important role in the later stages (≥6 months; Gaete and Bogousslavsky, 2008). Both levels of dependence in ADL performance and major life events are known to be strong psychological risk factors influencing the development of PSD (Whyte and Mulsant, 2002). The level of independent functioning and mobility in ADL performance (BI score) has been shown to be correlated to PSD at 6 months (Saxena et al., 2007) and at one and two years post-stroke (Wulsin et al., 2012). In addition, a
strong psychological risk factor is the occurrence of major life events before and around the
time of stroke (Bush, 1999; Morris et al., 1992).

Dependence in ADL performance and major life events contribute to the development of
PSD by being overwhelming for an individual’s coping skills. Those with ineffective coping
skills or inadequate social resources have been identified as more-prone to develop PSD
(Whyte and Mulsant, 2002). Other psychological factors identified include past psychiatric
history (Meroni et al., 2012; Storor and Byrne, 2006) and aphasia (Thomas and Lincoln,
2006; Kauhanen et al., 2000). Aphasia as a risk factor can be identified as a form of
impairment that impacts coping skills.

In addition to being one of the sequelae of stroke, depression has been recognized as being a
risk factor for stroke. Results from a recent metanalysis involving 17 studies and 6086
subjects with depression showed that prior depression was an independent risk factor for
stroke (relative risk of 1.34; Dong et al., 2012).

2.5.2 Influence of lesion location, side and size on post-stroke depression

Lesion location, side and size are factors known to influence PSD. Lesions in cortical and
subcortical regions of the frontal and temporal lobes, basal ganglia and the internal capsule
(anterior and posterior limbs, genu) are known to be more common in those with PSD at 3
months post-stroke (Zhang et al., 2012). Subjects with PSD were also found to have greater
grey matter hyperintensities, especially in the region of the putamen (Tupler et al., 2002).
Although no differences were found between subjects with right and left hemispheric lesions,
irrespective of dominance, strokes in the anterior areas have been shown to be more closely
related to PSD compared to the posterior areas (Narushima et al., 2003; Sinyor et al., 1986).
Larger lesion volumes were present in individuals post-stroke with compared to those
without PSD (Nys et al., 2005c).
2.5.3 Association of post-stroke depression with recovery of motor impairment and ADL performance

Presence of PSD is associated with recovery of motor impairment and ADL performance (Ayerbe et al., 2013; Chen et al., 2013). This association is influenced by factors including time post-stroke, participation in rehabilitation interventions and use of anti-depressant medication. Although an earlier review (Hadidi et al., 2009) was inconclusive whether PSD affects motor recovery, seven recently published studies (since 2005) have provided evidence supporting the association. A brief overview of these studies is provided below.

PSD was diagnosed using a variety of scales including the Hamilton Depression Rating Scale (Hamilton, 1960); Geriatric Depression Scale (Montorio and Izal, 1996); Montgomery-Asberg Depression Rating Scale (Montgomery and Asberg, 1979); Patient Health Questionnaire – 9 (Williams et al., 2005) and the Center for Epidemiological Studies Depression Scale (Irwin et al., 1999). The Fugl-Meyer Assessment (FMA; Fugl-Meyer et al., 1975) and the Scandinavian Stroke Scale (SSS; Scandinavian Stroke Study Group, 1985) were used to assess impairment levels. Levels of function and ADL performance were measured by the mRS; Action Research Arm Test (ARAT; Lyle, 1981) and BI. Subjects with PSD scored lower on impairment measures at baseline, 1 month and 3 months post-stroke (Bilge et al., 2008; Nannetti et al., 2005) compared to those without depression.

Provision of anti-depressant medication (Serotonin Specific Reuptake Inhibitors; SSRIs) resulted in a reduction in motor impairment levels (Bilge et al., 2008) at 6 months post-stroke. No differences were found between subjects with PSD and those without it. Presence of PSD however did not influence the rate of improvement of motor impairment and upper limb activity performance. No difference was found in the amount of improvement in subjects with and without PSD in the acute, sub-acute (measured using FMA; Nannetti et al., 2005) and chronic stages (measured using ARAT; Skidmore et al., 2012).

Presence of PSD resulted in lower scores on measures of independence in ADL at 9 days (mRS and BI scores; Nys et al., 2005c), 3 months (mRS score; Wulsin et al., 2012; Schmid et
al., 2011), 6 months (BI score; (Bilge et al., 2008; Saxena et al., 2007), 12 months (BI Score; Wulsin et al., 2012; Willey et al., 2010) and 2 years (Willey et al., 2010) post-stroke. Subjects with moderate-to-severe PSD also had concomitant cognitive impairments in the domains of memory and visuoperception (Nys et al., 2005c). Higher levels of depression were associated with less independence at 3 months (OR = 2.42), one (OR = 3.31) and 2 years (OR=3.72) post-stroke (Wulsin et al., 2012; Willey et al., 2010). Greater magnitude of improvement in BI scores was associated with a reduction in depression scores (β = -0.31; Saxena et al., 2007).

Similar results in terms of improvements in BI scores in those with lower depression scores were reported in other studies (Schmid et al., 2011; Bilge et al., 2008). However, since both scores (depression and BI) were obtained at the same time points (baseline and after 12 weeks), the directionality of the association could not be estimated. In addition, in both studies, subjects received concomitant antidepressant medications (SSRIs; citalopram and fluoxetine). This could be an additional confounding factor, as use of SSRIs has been shown to result in improved motor and cognitive recovery in individuals post-stroke (Jorge et al., 2010; Zittel et al., 2008; Pariente et al., 2001; Dam et al., 1996).

2.5.4 Post-stroke depression and motor learning

Compared to placebo and before drug administration, fluoxetine administration resulted in improved motor performance of the more-affected side on the finger tapping test and grip strength in subjects with acute stroke (Pariente et al., 2001). This improvement in performance was accompanied by increased activation in the ipsilesional motor cortex area. Citalopram improved performance on the nine hole peg test in subjects with chronic stroke (Zittel et al., 2008). Administration of fluoxetine resulted in an increase in the size of the cortical motor representation of the abductor pollicis brevis (APB) muscle (measured using transcranial magnetic stimulation; TMS) and improved motor learning of performance outcomes on a task involving co-contraction of the deltoid and APB muscles (Pleger et al., 2004).
While the use of SSRIs improves motor function (assessed using clinical outcomes in individuals post-stroke) and motor learning in controls, it is still unclear if the use of SSRIs can help improve motor performance and movement quality outcomes post-stroke. In addition, it is still relatively unknown if the presence of PSD affects movement execution. A study involving individuals diagnosed with schizophrenia (Sabbe et al., 1997) found that movement performance on a simple computer assisted line drawing task (in terms of movement amplitude and speed) was decreased in those with depression compared to controls. Treatment with fluoxetine for 6 weeks helped improve performance in the depressed group, but differences still existed compared to controls. Thus, the presence of depression influences movement performance in individuals with schizophrenia. However, the influence of depression on movement quality outcomes in individuals with stroke has not yet been investigated.

2.6 Recovery from stroke

The common clinical belief that beyond 6 months, rehabilitation interventions are no longer beneficial and motor recovery asymptotes (Jorgensen et al., 1995) has been challenged (Page et al., 2004). There is mounting evidence for continued functional recovery of upper limb paresis well into the chronic stage post-stroke (Subramanian et al., 2013; Bolognini et al., 2011; Koganemaru et al., 2010). Continued functional improvement can be attributable to neural plasticity in the remaining cortical and subcortical brain tissue (Warraich and Kleim, 2010; Nudo, 2003).

2.6.1 Neuroplasticity

Neuroplasticity can be defined as the capacity for structural and functional adaptation in neurons to reorganize neural circuits in response to changes in the environment or lesions (Sharma et al., 2013; Kleim, 2011). The term neuroplasticity encompasses mechanisms of neuronal reorganisation including recruitment of latent pathways (e.g., non-pyramidal corticospinal pathways), formation of new synapses, dendritic arborisation (branching) and
reinforcement of existing synaptic connections with long-term potentiation (LTP) mechanisms (Rossini et al., 2003).

Neuroplasticity can be modulated by performing repetitive movements leading to motor skill improvement with the upper (Jang et al., 2005; Pascual-Leone et al., 1995) and lower limbs (You et al., 2005; Perez et al., 2004). Understanding the role of neuroplasticity in the functional recovery process post-stroke is essential as it can assist in the development of interventions designed to engage mechanisms of plasticity to aid recovery after a stroke (Sharma et al., 2013). The presence of neuroplasticity presents an opportunity to train the injured brain to improve motor recovery and reacquire skilled movement.

Initial studies from animal (rodent and primate) models demonstrated the presence of neuroplasticity and its association with improved functional performance after stroke. Rats trained on reaching tasks demonstrated increased dendritic arborisation, synaptogenesis and alterations in cortical motor maps compared to control animals (Monfils et al., 2004; Kleim et al., 2002; Biernaskie and Corbett, 2001). Similar results have been found in primate (squirrel monkey) models where training led to an improvement in reach performance and an increase in the cortical motor map area (Nudo et al., 1996b).

2.6.2 Recovery and Compensation

Improvements in motor performance post-stroke (which may be associated with regulation of neuroplasticity) can be achieved by the use of two mechanisms: recovery and compensation. Recovery refers to the capacity of an individual to perform a task in the same manner as before injury (i.e. use of the same motor patterns as in the pre-morbid state). Compensation refers to the performance of a movement involving use of a different motor pattern compared to the pre-morbid state (Levin et al., 2009a). Both recovery and compensation can occur at two levels each: neuronal and behavioral (table 2-1). For neurorehabilitation purposes, it is useful to understand the distinction between recovery and compensation at the Neuronal, Body Structure and Function (impairment) and Activity levels (Figure 2-1) of the ICF (Levin et al., 2009a). This distinction is pertinent to the understanding of the relationship between
neuroplasticity and improvements in performance in people post-stroke following or as a result of rehabilitation interventions.

Table 2-1 Distinction between recovery and compensation at neuronal and behavioral levels

<table>
<thead>
<tr>
<th>Term</th>
<th>Neuronal level</th>
<th>Behavioral level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>Restoration of neuronal activity in the same area as the lesion.</td>
<td>Recovery of pre-morbid movement patterns.</td>
</tr>
<tr>
<td>Compensation</td>
<td>Restoration of neuronal activity in areas remote from the lesion but serving the same function. This primarily refers to activity in the contralesional hemisphere.</td>
<td>Use of trunk or other degrees of freedom to compensate the loss of movement in the target joints to perform a task.</td>
</tr>
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Figure 2-1-- The ICF Model in the context of a health condition (Stroke, reproduced with permission from Dr. Mindy Levin).

2.6.2.1 Recovery and compensation at the neuronal level

At the neuronal level, strategies employed to improve functional performance include
restitution/restoration and recruitment of new areas (Kleim, 2011; Levin et al., 2009a). Restoration is characterized by re-engagement of brain areas which were previously not active due to the injury. Factors including changes in metabolism and blood flow, edema, inflammation and neuronal excitability contribute to the loss of activation (Dirnagl et al., 1999). Resolution of these factors enables the return of the motor cortex to a functional state which begins contributing to motor improvement (Keiner et al., 2008; Ward, 2007).

2.6.2.1a Restitution and recruitment of new brain areas

Restitution in neuronal recovery may be characterized by the activation of cortical and subcortical areas in zones surrounding the lesion (penumbra) and in the area of diaschisis in animal (Kleim et al., 2003) and human models of stroke (Cramer et al., 1997). Recruitment may also play a role in neuronal recovery. Recruitment refers to the engagement of new areas that contribute to successful performance of a motor function after injury but which did not play a role prior to injury. The activation of these new areas contributes to recovery at the neuronal level if these areas are contained in the same hemisphere as the lesion (Levin et al., 2009a).

An example of recruitment contributing to recovery is the activation of the premotor cortex (PMC) on the ipsilesional side while extending the index finger of the more-affected side is (Gerloff et al., 2006). Disrupting the functioning of the ipsilesional PMC using TMS in individuals with stroke results in impaired performance on a sequence learning task (Fridman et al., 2004) using the more-affected upper limb. This suggests that the activation of the ipsilesional PMC plays an important role in successful task performance using the more-affected upper limb. Similar results have been obtained from monkey models of stroke where the PMC in the injured hemisphere plays an important role in recovery of hand dexterity (Liu and Rouiller, 1999).

Recruitment contributes not only to recovery, but also to compensation (at the neuronal level), especially if new areas, which normally do not contribute to the motor function, are recruited in the contralesional hemisphere. Neuroimaging studies have indicated greater
activations in the contralesional sensorimotor cortex (SM1), PMC, cerebellum, parietal
cortex and supplementary motor areas (SMA; Bradnam et al., 2012; Ward and Cohen, 2004;
Cao et al., 1998). Greater activations, especially in the contralesional PMC have been seen in
subjects with greater levels of motor impairment and/or extensive damage to the pyramidal
tracts (Bestmann et al., 2010; Ward et al., 2006; Zemke et al., 2003).

2.6.2.2 Recovery and compensation at the behavioral level

Successful task performance post-stroke can be achieved either by the use of movement
patterns similar to those used before stroke or by the use of new movement patterns (i.e. use
of additional degrees of freedom and/or new end effectors). The former refers to behavioral
recovery while the latter refers to behavioral compensation (table 2-1). Behavioral
compensation can be further divided into two types: adaptive and substitutive (Levin et al.,
2009a).

2.6.2.2a Adaptive Compensation

Adaptive compensation refers to task achievement by using the same end effector (i.e. limb),
but by incorporating additional degrees of freedom. An example of adaptive compensation
would be to use the more-impaired upper limb to reach for an object and substitute for the
lack of elbow extension by using more trunk displacement (Cirstea and Levin, 2000). While
the use of adaptive compensations may help in successful task accomplishment in the short
term, it has been linked to long term issues such as the development of pain and contractures
(Ada et al., 1994), learned non-use (Taub et al., 1993) and learned bad-use (Alaverdashvili et
al., 2008). The use of adaptive compensations (e.g. use of shoulder abduction movement in a
simulated eating task) has been linked to altered cortical activations (Lee et al., 2009).
Increase in shoulder abduction angle (to assist in bringing the hand closer to the mouth due to
inadequate range of elbow flexion) was related to greater activations in the contralesional
compared to ipsilesional SM1 and bilateral SMA.
2.6.2.2b Substitutive compensation

Substitutive compensation refers to task achievement by using a different end effector (i.e. limb). An example of substitutive compensation would be to use the less-impaired upper limb to bring a glass of water to the mouth to for people with severe grasping problems after stroke. Studies on animal (rodent) models have elegantly described the maladaptive effects of promotion of substitutive compensatory approaches. In a series of experiments by Allred and colleagues, rats were trained on a skilled reaching task (single pellet retrieval task). After the preferential limb had been identified, strokes were induced in the SM1 opposite to the preferred limb causing pronounced impairments in the contra-lesional forelimb. While one group of rats was encouraged to train on the reaching task using their non-affected side (experimental group; EG), the other was given control procedures (control group; CG). After 10 days, both the groups were trained on the same skilled reaching task, with the impaired/preferred forelimb. The performance of the rats in the EG on the skilled reaching task was significantly worse as compared to the rats in the CG. There was also a more permanent decreased usage of the impaired forelimb in the EG for postural support behaviors (Allred et al., 2005). It seemed that the training conducted with the ipsilesional forelimb in focus, contributed to a long lasting disuse of the impaired forelimb and led to learned non-use.

Training the more-impaired side led to an increased expression of the transcription factor FosB/ΔFosB in the remaining cortex (Allred and Jones, 2008). FosB and Delta FosB are present immediately after an injury and they stimulate neuronal growth and repair (McClung et al., 2004). In a further experiment, along with the lesions in the SM1, the transcallosal connections were also severed. Severing the transcallosal connections in addition to the SM1 lesions did not result in worse performance in the EG. This indicated that the impaired performance in reaching performance and postural support behaviors noted in the earlier two studies was mediated by the intra-hemispheric connections (Allred et al., 2010). Thus promotion of a substitutive compensatory approach led to a decrease in neuronal recovery.
2.6.3 Measurement of recovery and compensation

Motor recovery after a stroke is most commonly measured with clinical outcome measures at both the impairment and activity levels of the ICF. Assessment of impairments using clinical scales provides an appreciation of the underlying deficits and ability of patients to complete particular tasks. However, the focus is chiefly on goal achievement (for example, FMA, Chedoke McMaster (CM) Assessment; Gowland et al., 1993; etc.) and not on how the task was completed, which only a handful of scales entirely focus upon (example: Reaching Performance Scale in Stroke, RPSS; Levin et al., 2004 and Motor Evaluation Scale for Upper Externity in Stroke Patients, MESUPES; van de Winckel et al., 2006).

Information on how the movement is performed, the motor patterns used and the quality of movement can be obtained primarily with the use of kinematic analysis. Kinematic measures can provide detailed spatial, temporal and spatio-temporal descriptions of the movement performance at two levels: motor performance (descriptions of the results of the movements, measures of error, smoothness, movement time and velocity) and movement patterns (trunk and joint ranges of motion, interjoint-co-ordination).

At the impairment level, recovery is characterized by the return of pre-morbid movement patterns and measures used to assess recovery include electromyography and kinematics. Use of kinematic analysis has been shown to more sensitive in identifying deficits even in those individuals who are considered well recovered (CM arm scores of 6-7/7; Banina et al., 2010 or have mild levels of upper limb hemiparesis (FMA scores of ≥50/66, Cirstea et al., 2003; upper limb strength score of ≥4/5 on the Medical Research Council scale, Platz et al., 1999). For example, the use of kinematic analysis revealed deficits such as slower speed of movements and greater error in tasks such as tapping on a screen using a stylus (requiring wrist flexion/extension) and pointing to an object placed in front in the above mentioned studies.

However, the use of only motor performance variables may also prove to be inadequate, as individuals with stroke may still continue to use compensatory movement patterns.
Individuals with stroke can still perform precise movements with the use of additional degrees of freedom such as trunk displacement, even for reaching and pointing movements to objects placed within or at arm’s length (Michaelsen et al., 2006; Levin et al., 2002; Cirstea and Levin, 2000). Thus, measurement of only motor performance variables may provide an incomplete assessment of motor abilities of individuals post stroke and it is suggested to use movement pattern variables in addition to motor performance variables in order to gain all relevant information regarding the underlying motor impairments in movement production.

At the activity level, again the focus is on the ability of the subjects to complete the intended tasks. The majority of the assessments at this level (e.g. ARAT, FIM, BI, mRS, etc.) are used as primary and/or secondary outcomes measuring change in functional task performance in intervention studies (Simpson and Eng, 2013; Quinn et al., 2009). The focus on task completion ability makes the interpretation of results difficult since it is not clear whether recovery or compensation has occurred at this level. The use of outcomes such as the Wolf Motor Function Test (WMFT; Wolf et al., 2001) and the Chedoke Arm and Hand Inventory (CAHAI; Barreca et al., 2005) that incorporate measures of task success as well as the use of compensatory movement patterns in scoring should be encouraged to better distinguish between recovery and compensation at this level (Levin et al., 2009a).

2.6.4 Use of rehabilitation approaches promoting recovery versus compensation

The use of compensatory movements can affect the potential for further recovery and result in long term sequelae like pain and contractures. Thus, these approaches must generally be avoided. However, consensus panels (Foley et al., 2012; Barreca et al., 2002) have opined that teaching the individuals to use compensatory (substitutive and/or adaptive) movements may be appropriate in those with a poor prognosis (severe levels of clinically measured impairments and functional limitations; CM Arm Subscale score of ≤2 out of 7). Individuals with stroke who have an upper limb impairment level of ≥4 (measured using the CM Arm Subscale score; good prognosis; Barreca et al., 2002) should be encouraged to work towards motor recovery and avoid compensations. Thus, use of approaches promoting recovery or
compensation may depend on the level of the individual’s motor impairment and functional limitations.

The use of neuroimaging information (if available) may further help in determining the best approaches to be used for individuals post-stroke. For example, individuals in the chronic stages post-stroke with the presence of a motor evoked potential (MEP - an electrical potential recorded from the muscle after nervous system stimulation using TMS) in the extensor carpi radialis muscle were found to have good ability to recover (Stinear et al., 2007) and be encouraged to work towards achieving behavioral recovery. In those subjects with no MEP present, the fractional anisotropy values can be used to determine the potential for motor recovery. A fractional anisotropy value of $\leq 0.25$ (indicating poor white matter connectivity in the pyramidal tract) denotes poor recovery. Thus, information available from neuroimaging resources have the potential to help in appropriate clinical decision making about the appropriate type of rehabilitation approaches to be employed.

Rehabilitation has been described to be a process where the subjects relearn how to successfully move, in order to carry out their basic daily needs (Carr and Shepherd, 1987). However, relearning how to move could involve use of compensation or recovery mechanisms. Thus the manner in which the patients learn to move and the changes that occur in their capability to respond to rehabilitation interventions needs to be examined more closely. Knowledge on what kind of motor learning is occurring is essential.

2.7. Motor Learning

Motor learning is defined as “a set of internal processes associated with practice or experience leading to a relatively permanent change in the capability for movement” (Schmidt and Lee, 2011). The movements which are learnt require minimal effort with repeated practice and environmental interactions (Doyon and Benali, 2005). The capacity of (re)learning and retaining new motor skills is essential for performance of daily activities (Doyon et al., 2009) in both healthy subjects and individuals with stroke. The changes that
occur at the neuronal and behavioral levels due to motor recovery and learning and the variables influencing these changes are of particular interest for rehabilitation (Magill, 2011).

2.7.1 Models of motor learning

One of the most predominating and influential theories of motor learning is the Schema theory by Schmidt. Schmidt’s schema theory of motor learning (Schmidt, 1975) was developed from a theory of motor control—the concept of the generalized motor programs, which had been described earlier by Bernstein (1967). Schmidt modified the generalized motor program concept in response to the then prevailing theory of closed-loop control. In the theory of closed-loop control (Adams, 1971), movement was considered to evolve as a series of related reactions. These reactions used afferent proprioceptive feedback as the stimulus for generating the next efferent signal in the movement sequence (Adams, 1976; Adams, 1971).

2.7.1.1 Adams’ Closed Loop Theory

In Adams’ theory, to learn a movement, two components are required: the memory trace and perceptual trace. The memory trace initiates the movement, choses the initial direction and determines the earliest parts of the movement (e.g. initial movement trajectory). The perceptual trace is postulated to be involved in guiding the limb to the correct position along a trajectory. When an error occurs, the limb is adjusted until the movement is appropriate to the task goal of the action. The greater the movement accuracy, the more useful is the perceptual trace which was collected and retained. The major weakness in Adams’ closed-loop theory is the requirement of one-to-one mapping between stored traces and movement production (Sherwood and Lee, 2003; Schmidt, 1975). This creates an issue relating to the storage capacity of the central nervous system; a vast collection of movements would require an equally large storehouse of motor programs and this would require a lot of space in the central nervous system (CNS). In addition, this theory cannot be used to explain how motor programs for novel movements are formed.
2.7.1.2 Schema Theory

In the schema theory, the motor program is generalized, i.e. it could involve a multitude of ways to perform the same movement and do not involve explicit one-on-one mapping, as proposed in Adams’ theory. Schmidt proposed the existence of two constructs: the generalized motor program (GMP) that defined the form of the movement and the schema that allowed scaling of the action in response to the environmental demands and constraints. The schema was designated as a rule developed by practice which described the relationship between outcomes achieved while performing movements and the parameters chosen on those attempts. Basically two types of schemas were postulated to be developed – a recall schema and a recognition schema (Schmidt, 2003; Schmidt, 1975).

2.7.1.2a Recall and Recognition schema

The recall schema refers to the association between parameters chosen for the GMP for performance of movement on that particular trial and the outcome obtained. The recognition schema refers to the association between past sensory consequences generated by employing the GMP and the outcome obtained. The recall schema is used to indicate a specific response depending upon the conditions. Throughout the performance of a particular movement, the recognition schema is compared to the expected sensory information (e.g., proprioceptive and exteroceptive) from the ongoing movement to evaluate the effectiveness of the response. If an error is detected, an error signal is sent upon finalizing the movement, where the schema is then modified based on the sensory feedback and knowledge of results (see motor learning). Motor learning was envisaged by Schmidt as the update of the schemas with practice and experience (Schmidt, 2003).

The generalized rule allows the production of new movements within the classes of movements for which the schema/s are established. Thus, when learning novel movements an individual may generate a new GMP based on the selection of parameters (addressing the novel movement production issue in the closed loop theory), or modify an existing GMP.
(addressing the storage problem), depending on prior experience with movement and the context in which the task is performed.

2.7.1.2b Schema theory and feedback

The schema theory incorporates feedback into motor learning. The ongoing sensory consequences to movement were used in a closed-loop error detection and correction framework. The greater the amount of information available from sensory channels (i.e. proprioceptive and exteroceptive), the stronger and more representative was the development of the recognition schema. This led to a better performance during both acquisition trials (feedback provided) and later in test and retention trials (no feedback provided; Schmidt and Wrisberg, 2008; Newell, 1991). Augmented feedback was also useful in the formation of the recall schema. The capability of specifying the correct program parameters was posited to be obtained by the formation of the recall schema, with practice involving different program parameters (e.g., force, duration) and initial conditions using augmented feedback (Sherwood and Lee, 2003).

2.7.1.2c Role of cognitive processes in Schema theory

Cognitive processes are involved in the learning process proposed by the schema theory. Cognition is an essential component of the learning process, as the people learning tasks are required to make decisions. For example, the correct parameters need to be selected to achieve the movement goal. Detection of movement errors requires auto-evaluation of the feedback produced by the movement (Sherwood and Lee, 2003; Schmidt, 1975). It is also essential to be able to incorporate the result of the current movement to be able to adjust the schema for successful goal-achievement in the next attempt.

2.7.1.3 Internal Model framework

The internal model (IM) framework is a recent postulation of motor control, which has also been used as a theory to address motor learning. According to the internal model theory,
motor learning is thought to involve the formation of an internal model representing the exact matching between the sensory and motor information of the task performed (Wolpert and Kawato, 1998). IMs are thought of as neural representations of the body and the interacting environment produced by the nervous system and these evolve continuously during learning (Shadmehr and Mussa-Ivaldi, 1994; Craik, 1943). The sensory information from the periphery is transformed into desired motor actions. Support for IMs was obtained from electrophysiological recordings of Purkinje (P) cells in the ventral paraflocculus region of the cerebellum during ocular following responses in monkeys (Gomi et al., 1998).

The simple spike firing of the P cells was reconstructed with mathematical modeling using an inverse dynamics approach. The eye movements were represented with a combination of position and its derivatives, velocity and acceleration. When the various dynamic, viscous and inertial forces needed to control the eye muscles were accounted for, the model was a good fit and high correlations were obtained; r² > 0.75. The ability of humans to interact with and adjust their movements to a wide variety of environmental conditions, switch between conditions and produce remarkably similar and accurate movements in all the conditions has been interpreted as meaning that the nervous system learns and maintains IMs of the kinematics and dynamics (Flanagan et al., 1999). These interpretations however, have largely been based on correlational analyses which do not necessarily indicate causality.

2.7.1.4 The Equilibrium Point Theory

An alternate theory of motor control not involving complex calculations and which also addresses motor learning, is the equilibrium point (EP) theory (Feldman, 1986; Feldman, 1974), has been used as a theory to explain. The EP theory was posited by Feldman around the same time as the Schema theory. The EP theory assumes that the referent configuration or the posture of the limb is shifted to a new configuration or position. This is achieved by shifting the thresholds of muscle activity by the CNS to produce movement to a new position. The previous starting position then becomes a divergence from the newly specified position and posture stabilizing mechanisms generate forces to move the joint to the new position (Feldman and Latash, 2005). The EP is a point between the effector (e.g. limb) and
external environment at which the internal and external forces are balanced (Levin, 2000). The EP theory resulted from experiments in cats (Feldman and Orlovsky, 1972) and human subjects (Asatryan and Feldman, 1965).

2.7.1.4a Components of the Equilibrium Point theory

Important components of the EP theory include threshold length (λ), R command and C command. The R command, C command and λ are control variables (CVs) that are specified by the central structures independently of the current environmental conditions (Feldman and Levin, 1995; Feldman and Levin, 1993). The R and C commands are considered CVs at the joint level, while λ is considered a CV at the muscle level (Levin, 2000). Lambda (λ) is the threshold value beyond which active muscle recruitment begins and below which the muscles are in a sub-threshold state (Levin and Dimov, 1997). It refers to a component of the tonic stretch reflex threshold.

2.7.1.4b R and C commands

The command specifying the movement of the joint from one position to another is called the R or reciprocal command (Feldman, 2006). The R command defines the position of the characteristic relating the static net muscle torque and the actual joint angle. This characteristic is known as the invariant characteristic or IC (Figure 2-2, bottom panel, dashed line; Crago et al., 1976; Asatryan and Feldman, 1965). The R command results in joint motion from one position to another by shifting λs of both the flexor and extensor group of muscles in the same direction (Figure 2-2, top panel).

The C command does not produce movement. It changes the thresholds of the muscle groups in opposite directions and surrounds the same joint position with a zone in which muscles are co-activated, thus increasing the stiffness of the joint (Feldman, 1966; Figure 1, bottom panel). The C-command contributes to speed of movement to the new position (Feldman and Latash, 2005) and increases the damping of the system (controls terminal oscillations by increasing joint stiffness; Feldman and Levin, 1995).
Fig. 2-2 – Explanation of the functions of the R and C commands in altering muscle thresholds. The dark bars refer to flexor muscles and the light bars to extensor muscles, the dotted line refers to the IC. (Figure obtained from Levin MF, Hum Movt Sci 2000;19:107-137).

2.7.1.5 Association between Schema Theory, Internal Models Framework and Equilibrium Point Theory

According to the schema theory, the CNS integrates in the schema rules that predict the effects of a motor command/GMP in a given environment. Motor learning consists of an alteration or enhancement of the schema with repeated practice and experience. The schema can be postulated to be represented by the ‘forward model’ in the IM theory and by CVs according to the EP theory (Dancause et al., 2002). Thus the schema theory is associated with the currently more-prevalent motor learning theories.

2.7.2 Classification of motor learning

Motor learning can be explicit or implicit. Explicit learning is the attainment of accessible declarative knowledge of components of a motor action through cognitive processes (Gentile, 1998) and can be tested by recall or memory for factual knowledge. On the other hand, implicit learning is an unintended and unconscious form of learning characterized by behavioral improvement (Halsband and Lange, 2006). It demands less attention (Cleermans
et al., 1998) and is fundamental to learning most everyday skills (Howard et al., 2004). For example, learning to ride a bicycle occurs after a few errors and falls while the learner does not remember the exact components of the motor actions that led to success.

2.7.3 Central Nervous System areas associated with motor learning

Explicit learning and memory systems are distributed over the medial temporal lobe (MTL; e.g., hippocampus), the dorsolateral prefrontal cortex (DLPFC), premotor area (PMA) and posterior parietal cortex (PPC; Sanes, 2008; Honda et al., 1998; Reber and Squire, 1998; Nissan and Bullemar, 1987). The implicit learning and memory systems are distributed over the basal ganglia (BG), cerebellum, SM1, SMA, ventral PMA and PPC areas in addition to the DLPFC and MTL (Forkstam and Petersson, 2005; Seidler et al., 2002; Honda et al., 1998; Doyon et al., 1998; Pascual-Leone et al., 1995a). Hence the capacity to learn implicitly is usually not completely lost post-stroke (Pohl et al., 2001; Weinstein et al., 1999), given the extensive distribution of the learning networks in the CNS.

2.7.4 Influence of stroke lesion location on motor learning ability

The influence of stroke on motor learning has been addressed by considering the effects of lesions in various locations mentioned above. Studies have mainly considered the effects of lesions in the territory supplied by the middle cerebral artery (MCA), basal ganglia, PFC, SMA, thalamus and cerebellum. Implicit sequence learning ability has been shown be unaffected by lesions in the MCA area when subjects used their less-affected or ipsilesional upper limb (Boyd and Weinstein, 2004b; Weinstein et al., 1999). For the basal ganglia, lesions involving the putamen do not have an effect on implicit sequence learning using either the less-impaired upper limb (Boyd et al., 2009; Boyd and Weinstein, 2004a) or both the less- and more-impaired upper limbs (Ell et al., 2006). Similarly, subjects with lesions involving only the striatal and pallidal areas of the basal ganglia also retain the ability to learn implicitly using both the less- and more-impaired arms (Shin et al., 2005).
Focal thalamic lesions (Exner et al., 2001) and lesions in the left SMA (Ackermann et al., 1996) impair short-term motor adaptation and learning abilities. In addition, lesions in the PFC also impact motor learning. Motor sequence learning abilities as assessed by the serial reaction time task (SRTT) are impaired in subjects with PFC lesions using both the more- and less-affected sides. Greater impairment was noted when the more-affected side was used for learning the sequence (Beldarrain et al., 1999).

Results of a recent study by Meehan and colleagues (2011) further emphasize the role of the PFC in implicit sequence learning in subjects with stroke and healthy controls. Individuals with subcortical stroke involving the right hemisphere and controls (age- and sex-matched; n=9/group) were tested with functional magnetic resonance imaging (fMRI) before and after practicing a sequence tracking task using their more-affected upper limb for three days. The fMRI data analyses revealed increased activation in the DLPFC in the early practice period. While this activation decreased after practice in the healthy group, no such changes were noted in the stroke group. After practice, there was additional activation in the prefrontal areas involved with working memory and attention (Broadman’s area 8 and 9).

Results of studies involving patients with cerebellar lesions are mixed. Subjects with focal cerebellar lesions involving only one hemisphere demonstrated impaired implicit learning on the SRTT, irrespective of whether the more- or less-affected side was used (Molinari et al., 1997). Subjects with unilateral lesions of the cerebellum in the areas involving the posterior inferior cerebellar artery and superior inferior cerebellar artery circulation retained the ability to learn implicitly with the more-affected side, but not with the less-affected side (Beldarrain et al., 1999; Pascual-Leone et al., 1995a) on the SRTT. When a sequence tracking task was used, subjects with cerebellar lesions involving the dentate nucleus implicitly learnt only the spatial and not temporal part of the task (Boyd and Weinstein, 2004b). A combination of lesions in the cerebellum and brainstem also affected motor learning abilities, with no sequence learning demonstrated in those with combined lesions (Daum et al., 1993).

The results of the above studies indicate that while lesions in the MCA territory or basal ganglia do not influence implicit motor learning abilities, lesions in the PFC, SMA and
thalamus seem to impair this ability. The results of studies involving lesions in the cerebellum are mixed and there is very little information available on brainstem strokes (Kruger et al., 2007). Thus, the presence of focal lesions in the brainstem and cerebellum are likely to confound the results of implicit motor learning studies.

2.8 Factors influencing neuroplasticity, motor recovery and motor learning

Factors considered as pertinent to influencing neuroplasticity and motor learning and recovery include practice intensity, variability, specificity, motivation, environment in which the task is practiced and feedback (Levin et al., 2010; Kleim and Jones, 2008). In the following section, a brief discussion about each of these elements will be provided.

2.8.1 Intensity of practice

A standardized definition of intensity of task practice was recently provided by Page and colleagues (Page et al., 2012). Intensity has been defined as the amount of effort (physical and/or psychological) invested by the client in a single movement or series of movements during a defined period of time. The authors mention that the amount of effort should be measured using assessments like the Borg scale or heart rate. However, the heart rate can be affected by other factors and the Borg scale is a subjective rather than an objective assessment. Hence, a definition of intensity based only on effort may not be the best choice applicable to all situations (Kwakkel et al., 2006).

For stroke rehabilitation purposes, a definition that involves the frequency (in terms of number of repetitions) may be more suitable. Intensity can also be defined as the duration and frequency of the task practiced, within a given time span like a day or week (Keith, 1997). Task practice at moderate to high intensities has been linked to better outcomes after stroke. In animals, moderate intensity exercise (motorized wheel running for 30-60 min) resulted in increased levels of BDNF, insulin like growth factor (IGF) and synapsin1 in a rat model of focal ischemia (Ploughman et al., 2005). BDNF and IGF support neuronal survival and promote dendritic spine branching while Synapsin1 is a downstream mediator of the
effects of BDNF on synaptic transmission. Enhanced BDNF, IGF and synapsin1 levels have been postulated as factors contributing to the synaptic changes underlying motor learning after a stroke (Ding et al., 2006; Vaynman et al., 2003).

High intensity exercises are beneficial for stroke recovery in humans as well. In a meta-analysis of 17 studies on the effects of high compared to low intensity exercise training in subjects ≤6 months post-stroke, higher exercise intensity was associated with greater improvements in the performance of ADL (summary effect size = 0.23; 95% CI: 0.13- 0.33; Kwakkel et al., 2004). The subjects in the higher intensity group received therapy on average for 16 more hours compared to the control group. Training for a minimum of two hours/day was found to result in greater improvements in clinical measures of upper limb impairment (FMA scores) and ADL performance (ARAT, BI scores) compared to one hour/day (Han et al., 2013). However, people with post-stroke hemiparesis used their more and less-impaired side for 3.3 and 6 hours respectively compared to control subjects who used their dominant and non-dominant upper limbs for an average of 8-9 hours/day (Lang et al., 2007). Thus, there is a need to increase the duration of use of the more-impaired side in people with post-stroke hemiparesis.

In terms of frequency, the average number of repetitions involving functional activities performed with the upper limbs in clinical care at acute and sub-acute phase (inpatient and outpatient rehabilitation) was found to be 32 per session (Lang et al., 2009). Animal models of stroke have demonstrated that large numbers of repetitions are essential for motor learning and recovery (Kleim et al., 1998; Nudo et al., 1996a). In a recent proof of concept study, individuals with chronic upper limb post-stroke hemiparesis were able to practice an average of 322 repetitions in every session of functional tasks involving the upper limb without fatigue and improve ADL performance (measured using ARAT scores; Birkenmeier et al., 2010). While the exact number of repetitions is currently unknown, a minimum of 72 per session have been found to be essential for motor recovery (measured using clinical assessments and kinematics), especially in the chronic stage of stroke (Subramanian et al., 2013; Cirstea and Levin, 2007).
2.8.2 Variability of practice

Variability in task practice is an important factor in motor learning. Tasks can be practiced on a blocked (constant) or random (variable) schedule. In a blocked schedule, each task is practiced in a series of consecutive trials in the same condition. In contrast, under a random schedule, the task varies in every trial without advance knowledge of the task to be practiced (Proteau et al., 1994). Random scheduling is beneficial since every movement is akin to a new problem to be solved (allowing the system to take advantage of its inherent redundancy), rather than the repetition of the same set of movements (Yang et al., 2007; Bernstein, 1967).

Variable task practice results in greater improvements in task performance compared to constant practice. Variable task practice results in better outcomes (for example, decreased error) in retention tests in controls, though the task performance in the actual acquisition phase may be worse, compared to constant practice (Song et al., 2012; Proteau et al., 1994). Similar results have been reported in individuals post-stroke (Schweighofer et al., 2011; Hanlon, 1996). Changes seen after blocked and random practice schedules are thought to be mediated by connections between different brain areas. Blocked practice results in increased white matter connectivity between the two homologous prefrontal cortices (PFC) and between the lateral PFC and anterior putamen through the corticospinal tract. Random practice results in better white matter connectivity between the left sensorimotor cortex and the posterior putamen though the corticospinal tract (Song et al., 2012).

2.8.3 Task specific practice

While practice intensity and variability are important, it is essential that the practice is specific and salient. The task being practiced should be relevant to the needs of the participant. Task specific practice is an essential component for motor learning and motor recovery to occur (Schmidt and Wrisberg, 2008). In primate models of stroke, it has been demonstrated that only participation in task-specific exercises (retrieving pellets from a small diameter well, key turning task; Nudo et al., 1996a) and not generalized upper limb training (retrieving pellets from a large diameter well; Plautz et al., 2000) led to changes in cortical
M1 representations. Similarly, results from a study involving playing the piano in controls demonstrated that motor cortical maps (measured using TMS) for finger flexors and extensors increased only in those subjects (n=6) who were trained on a specific sequence compared to those with no training (n=6) or those who played the piano randomly (n=6; Pascual-Leone et al., 1995).

 Provision of inadequate amounts of task-specific training had been postulated as one of the reasons for low efficacy of post-stroke motor rehabilitation (Bütefisch et al., 1995). Results of a meta-analysis involving 8 studies and data from 412 participants with stroke revealed that task-specific training regimens (for example, activities practiced using CIMT approach) are beneficial for upper limb function, with a standard mean difference of 0.24; 95% CI: 0.06 - 0.42; French et al., 2008). With the availability of recent evidence regarding the effectiveness of task specific training, it has been recommended that task specific training be routinely applied in physical and occupational therapy sessions, especially for upper extremity training (Hubbard et al., 2009).

2.8.4 Motivation

Motivation is another factor that plays a key role in motor recovery and determining outcome post-stroke (MacLean et al., 2000; Kaufman and Becker, 1986). It has been shown that unless the animal (rodent) is motivated enough, improvements in performance on a radial maze task indicating recovery and learning will not occur (Schaar et al., 2010). Being motivated contributes to post-stroke recovery in humans as well. In a qualitative study conducted on 19 individuals post-stroke and their spouses, participants with stroke reported that they ‘kept a door open’, continued to hope for and worked towards better improvement while adjusting to life post stroke. They did this by being motivated to persist, drawing support from others and finding out how to keep moving ahead to maximize upper limb recovery (Barker and Brauer, 2005).

In a follow up study (Barker et al., 2007), the same group of authors found that self-reported upper limb recovery in 220 individuals with stroke was positively correlated with factors
such as ‘being hopeful of recovery’, ‘getting going and continuing with exercises’ and ‘using the arm in everyday tasks’. These factors were associated with motivation and were derived as questions from the results of the earlier qualitative study published in 2005. Another study (Ostir et al., 2008) found that higher levels of positive emotion (a surrogate marker for motivation) were associated with better motor (β=0.37), cognitive (β=0.37) and functional (β=0.70) recovery (measured using the motor, cognitive and total FIM scores) in 823 individuals post-stroke.

2.8.5 Environment of task practice

An additional factor suggested as being crucial to maximize recovery and motor learning post-stroke is the environment in which the task is practiced. Training in enriched environments has been found to be beneficial in ischemic (Biernaskie and Corbett, 2001) and hemorrhagic (Auriat et al., 2010; Auriat and Colbourne, 2009) rodent models of stroke. Long lasting behavioral recovery was seen in rats housed in an environment providing enriched rehabilitation (ER) compared to rats housed in standard conditions. ER consisted of a combination of skilled reach training and housing in an enriched environment. An enriched environment provides abundant possibilities of physical and social stimulation/interaction and contain different objects like ladders, running wheels, chains, cups, etc. that are changed daily.

The rats that experienced the enriched rehabilitation improved in the skilled use of their affected forelimbs and long lasting recovery was noted (5 – 6 weeks after stroke induction). Recovery in reaching performance was accompanied by an increase in basilar dendritic growth in the striatum and ipsilesional (Auriat et al., 2010) or contralesional motor cortex (Biernaskie and Corbett, 2001). This might contribute to functional improvements and neuroplasticity by formation of new synaptic connections or by unmasking latent tracts.

A review by Will and colleagues (Will et al., 2004) indicated that exposure to enriched environments caused an increase in the rate of protein synthesis and the amount of proteins (nerve growth factor, BDNF and growth derived neurotrophic factor) in the motor cortex.
Protein synthesis is an essential component for the formation of long-term memories during or after training. Enriched environments may foster plastic changes in areas not directly affected by the stroke as well. Pyramidal neurons in layers II / III had significantly more dendritic spines in the contralesional hemisphere in rats that were exposed to enriched environments, after a stroke had been induced. Those neurons have extensive intracortical connections that may play a role in modulating neuronal plasticity.

Voluntary exercises have been known to cause increased thickness of the motor cortices, expression of trophic factors such as BDNF and nerve growth factor and increased angiogenesis in the cortical areas in rats (Will et al., 2004). Thus a combination of enriched environments and voluntary exercises can be expected to lead to better recovery of impairment and reaching performance post stroke. It is still relatively unknown as to which enriched environments are best suited for human subjects with stroke related brain damage. The use of virtual reality has been suggested as one of the emerging contenders in this area (Murphy and Corbett, 2009; Bach-y-Rita et al., 2002).

2.8.6 Feedback

Task practice which includes only the elements described above as relevant to post-stroke recovery and learning can be insufficient for optimal motor recovery. As mentioned above, individuals post-stroke may still continue to achieve successful task performance by using compensatory movement patterns without the provision of feedback (Cirstea and Levin, 2007; Cirstea et al., 2003). Task practice should ideally include appropriate feedback. This may help ensure that the right kind of motor (re) learning ensues leading to optimal recovery of the upper limb after a stroke (Winstein et al., 1999).

Feedback is sensory information provided either during or following task performance in the form of intrinsic or extrinsic information. Intrinsic feedback refers to somatic information (e.g., tactile, proprioceptive, kinesthetic, etc.) obtained during performance of the task itself. Extrinsic or augmented feedback is related to the environment, such as verbal or nonverbal
information provided by an external source (Winstein, 1991). Extrinsic feedback can be used to substitute for or enhance intrinsic feedback (Magill, 2011).

2.8.6.1 Knowledge of results and knowledge of performance feedback

Extrinsic feedback related to the goal of the task is called knowledge of results (KR). Knowledge of performance (KP) is extrinsic feedback on the nature of the movement pattern used for goal achievement. For example, when picking up objects, feedback about task success or failure is KR (i.e., “that movement was correct”), whereas that related to movement quality is KP (i.e., “move your trunk less” or “bend your elbow more”). KP is used predominantly in rehabilitation settings. KP or KR delivery schedules can be continuous (every trial), summary (after a fixed trial number), or faded (initially every trial, then after several trials). Although motor learning may occur without it, feedback provision results in better retention of learned skills (Cirstea and Levin, 2007; Bedard and Proteau, 2004).

2.8.6.2 Effectiveness of feedback provision for upper limb motor learning and recovery

Two previous reviews (one systematic, van Dijk et al., 2005, and one narrative, van Vliet and Wulf, 2006) concluded that provision of feedback enhances motor learning and motor recovery. However, while the systematic review included studies in populations with heterogeneous diagnoses (stroke, cerebral palsy, traumatic brain injury, spinal cord injury, Parkinson’s disease), the stroke-specific narrative review, considered both upper limb and lower limb tasks. Several questions emerged from the narrative review regarding feedback type, frequency and provision medium. Given the importance of the use of the upper limb in daily life activities and lower levels of recovery of the upper limb, a systematic review focusing solely on the upper limb in patients with stroke help will help in enhanced understanding of the currently available evidence regarding the effectiveness of feedback for motor learning. It may also assist in making recommendations regarding use of type, frequency and medium of feedback provision to enhance arm motor recovery in individuals with post-stroke upper limb hemiparesis.
2.9 Virtual Reality

The use of Virtual Reality (VR) technology is gaining prominence for post-stroke motor rehabilitation. It is a technical assembly that allows users to interact in a virtual environment (VE; computer software generated simulation), with objects or events in a manner similar to the physical environment (PE; Wilson et al., 1997). A variety of hardware and software devices may be used to create VR simulations of varying degrees of complexity and immersion. The equipment used in studies involving VR usually consists of a visual display, a motion tracking device and augmented feedback.

With the use of VR, therapy can be provided within a functional, purposeful and motivating context. Salient tasks can be practiced in a manner just as interesting as the real world with the ability to easily adjust task difficulty levels as a means of progression in therapy (Crosbie et al., 2007). Interaction is present not only with the environment, but also with the objects in it. VR enables the combination of tasks that have varying difficulty levels with guidance that has been known to be a key factor in causing improvement in the functional abilities of patients (Piron et al., 2009).

2.9.1 Virtual environments and factors influencing neuroplasticity and motor learning

VR presents a platform that can combine factors pertinent to optimize neuroplasticity and motor learning post-stroke mentioned previously (Levin et al., 2009; Holden, 2005). VR environments (VEs) can be designed to include novel interactive games involving variable and intense task specific practice to motivate subjects. Intense task-specific practice (5 days/week, 1 hours daily, 4 weeks) of upper limb tasks such as putting an envelope into a slot, practising a basketball shot, reaching to grasp a rubber ball and polystyrene cube is possible in VEs for individuals with upper limb hemiparesis post-stroke (Piron et al., 2010, Piron et al., 2005). VEs can be designed to provide variable practice of a task of catching sphere-like objects (Cameirão et al., 2012), playing soccer as a goalkeeper to try and block goals, reaching for colored balls appearing at different workspace locations in a motivating gaming like context (Levin et al., 2012).
VEs can also be designed to resemble ecologically valid settings such as a shopping mall (Rand et al., 2009) to help promote functional independence and community participation. Training in VR has been reported to be interactive and enjoyable like a game, rather than just repetitive exercise (Sveistrup, 2004). Thus, the participants are likely to be more motivated (Lourenco et al., 2008; Holden and Dyar, 2002). These factors can serve to limit fatigue, loss of enthusiasm and co-operation, factors that have been known to negatively influence participation in rehabilitation interventions and recovery (Lang et al., 2009; Tinson, 1989). Control over VEs is more precise compared to the real world. VR provides an opportunity to study movement production in situations that may be considered dangerous in the real world (for example: trying to reach for a can of soda in a virtual shelf before a door closes; Banina et al., 2010 or crossing the road on a green light before the signal turns red; Fung et al., 2006).

VEs can be used to present multimodal sensory information to the user (Riva et al., 2006). Feedback can be integrated into a VE. VEs can be suitable manipulated to provide both KR and KP feedback (Subramanian et al., 2007). Feedback provision through the medium of VEs is known to modulate neuroplasticity. Increased ipsilesional activity in the SM1 has been noted after task practice in VEs with feedback involving upper (Merians et al., 2009; Jang et al., 2005) and lower limbs (You et al., 2005). The same areas are recruited after task practice in a PE (Carey et al., 2002). Training in VEs with feedback also results in an increase in amplitude and decreased latency in the MEP produced by TMS recorded from the flexor carpi radialis (FCR) muscle (Kang et al., 2012) in subjects with stroke and controls. A brief review of studies that have used VR as a medium to provide feedback is provided at the end of this section (section 2.9.5).

Before reviewing the studies of the effects of feedback provision in VEs, it is essential to know whether the movements performed in various types of VEs are valid, i.e. how similar or different are the movements performed in a VE compared to the real world. The performance of movements in VEs are known to be influenced by factors such as the type of VE (immersive vs. non immersive; Knaut et al., 2009; Viau et al., 2004) and by the display medium used to view the VEs (Subramanian and Levin, 2011). In the following paragraphs,
information is provided about two important technical aspects of VR (immersion and presence), types of VEs, comparison of movement performance in VEs to PEs and the influence of the display media.

2.9.2 Immersion and Presence

Immersion is a psychological state in which the person feels that he/she is surrounded by, is a part of and communicates with an environment that provides a constant flow of experiences and stimuli (Witmer and Singer, 1998). Immersion has also been used to refer to the technical capability of the system to deliver a surrounding and convincing environment with which the participant can interact (Sanchez-Vives and Slater, 2005). Information about a greater number of sensory systems (auditory, visual, proprioceptive/haptic, exteroceptive) can be included in more-compared to less-extensive VEs. Immersive systems are inclusive to the extent to which all external sensory data (from physical reality) is shut out. Finally, a match between the participant's proprioceptive feedback about body movements, and information generated on the displays is necessary for immersion (Slater and Wilbur, 1997).

This matching between proprioceptive information and body movements may be achieved through real-time tracking of head and body motion, such that, a turn of the head results in a corresponding change in the visual display (Sanchez-Vives and Slater, 2005). Immersion is intended to encourage the belief that one has left the real world and is now "present" in the VE. The sense of presence has been defined as the feeling of being in an environment i.e. being immersed in it. The sense of “being there” in a VE is closely linked to the ability of performing actions in it (Sanchez-Vives and Slater, 2005).

If a subject feels present in a VE, the resulting behavior is then consistent with the subject’s behavior in a similar environment in the physical world (Witmer and Singer, 1998). The sense of presence has been suggested to be a key factor for use of VEs as a treatment modality for rehabilitation. A positive correlation has been reported between the sense of presence and control and successful task performance in VEs for upper (reaching and
retrieving objects, practising isolated wrist extension movements; Crosbie et al., 2004) and lower limb (walking in parks, corridors and street crossing; Fung et al., 2006) tasks.

2.9.3 Types of virtual environments

VEs can be classified into two broad types: immersive and non-immersive. Fully-immersive VEs generally use large screen projection systems (SPS), Head-Mounted Displays (HMD) or cave systems, where the sense of immersion is created by projecting the VE on a (concave) surface. Immersive systems may also include the use of video capture systems (for example, Integrated Rehabilitation Exercises; IREX; SensAble Technologies Inc.), where the users can view themselves (first person view) or an avatar (representation of the whole body or just a part; third person view) in the scene using appropriate display media. Interface devices such as computer mice, haptic devices such as Cybergloves/ Cybergrasps, joysticks or force sensors may be used by the participants to interact at different levels with the VE in both immersive and non-immersive environments. The use of haptics can be used to increase the sense of immersion, as they can provide sensory feedback similar to what is obtained during real world task performance (Adamovich et al., 2009, Levin et al., 2009b).

2.9.4 Movement patterns in virtual environments

Patterns of the movements made in the VE should be taken into consideration as the quality of the viewing environment can influence the production of movements (Liebermann et al., 2012; Ustinova et al., 2010; Marathe et al., 2008). This information helps to better understanding whether: i) the patterns of movements performed in a VE are the same as those made in a PE and ii) transfer of training to the real world occurs after task practice in a VE. In addition, little information is available whether impairments after central nervous system injury (for example, stroke) influence the performance of movements in the VE in a manner similar to the PE (Edmans et al., 2006).

The kinematics of pointing, reaching and grasping movements made in 2D and 3D VEs have been compared to those made in PEs by participants with chronic post-stroke upper limb
hemiparesis and control subjects in a series of studies (Liebermann et al., 2012; Magdalon et al., 2011; Cameirão et al., 2010; Knaut et al., 2009; Levin et al., 2008; Viau et al., 2004). Results of these studies helped to answer the question regarding similarities and differences in patterns of movements produced in PE and VE.

2.9.4.1 Comparison of movements performed in physical and virtual environments

2.9.4.1a Reaching and Grasping movements

Viau et al. (2004) compared reaching, grasping, transport and release movements made by the individuals post-stroke with or to virtual objects in VE to the movements made with or to real objects in a PE in a non-immersive 2D VE viewed on a computer monitor. In both environments, participants used similar movement patterns while grasping and placing the ball. However, in the VE, participants with stroke made slower reaching movements and used a greater range of elbow extension and lesser range of wrist extension compared to the real world. The authors suggest that this might have been due to the absence of tactile feedback at the end of the reach and depth perception in the 2D VE.

Reaching and grasping movements of participants with chronic post-stroke hemiparesis and controls of real and virtual objects were compared by Magdalon and colleagues (Magdalon et al., 2011; Levin et al., 2009). Participants wore a Cyberglove with a Cybergrasp (exoskeleton) which provided haptic feedback and reached to three objects of different sizes (can, pen and screwdriver) placed in the midline in both PE and VE. The VE was 3D fully immersive (with depth perception) and viewed using an HMD. The virtual objects had the same shape and size dimensions as the real objects. Participants with stroke and controls had slower movements in the VE and used more elbow extension and shoulder horizontal adduction compared to the PE. Subjects also tended to use less trunk displacement in the VE. Overall, subjects could scale the hand aperture to object size in both environments and hand orientation parameters were preserved in VE.
2.9.4.1b Pointing movements

Cameirão and colleagues compared pointing movements made in a PE on a table top and in a similar non immersive 2D VE by subjects with chronic post-stroke hemiparesis and healthy controls (Cameirão et al., 2010). The 2D VE was viewed using a computer monitor. The pointing task was performed by using both upper limbs by controls (dominant and non-dominant) and subjects with stroke (more-impaired and less-impaired arms). Overall, the movement speed was slower in the VE compared to the PE. In the stroke group, the movements were slower with the more- compared to less-impaired upper limb. No other differences in terms of trajectory shape and elbow and shoulder ranges were noted between the more- and less-impaired sides in subjects with stroke and between the dominant and non-dominant sides in controls. Thus, participants had similar movement pattern variables and endpoint trajectories in both environments. The authors however do not provide any reasons to explain the differences in movement speed noted between the two environments.

Pointing movements made by subjects with chronic post-stroke hemiparesis and controls to three targets in a 2D immersive VE (viewed on a large TV screen) were compared to similar movements made in a PE (Liebermann et al., 2012). Movement patterns differed between environments. In the VE movements were less accurate, slower, more curved and involved smaller elbow and shoulder ranges compared to the PE. However, both groups of participants used less trunk displacement in the VE compared to PE. The authors attribute these differences to factors including probable lack of depth perception in the 2D VE and viewing a 3D scene on a planar 2D VE.

Pointing movements made by subjects with chronic post-stroke hemiparesis in a 3D fully immersive VE (viewed using a HMD) were compared to movements made in a similarly designed PE in the real world (Knaut et al., 2009). Similar characteristics at movement pattern level in terms of joint ranges of motion (elbow extension, shoulder flexion and horizontal adduction) were noted in both environments. However, subjects used less forward trunk displacement (compensation) in the VE as compared to the PE, and differed at the motor performance level (less precise movements and more curved trajectories in the VE).
2.9.4.1c Role of the display media

In all 5 studies described above, participants had slower speeds of movements in the VE compared to the PE. In addition, in 3 of 5 studies (Liebermann et al., 2012; Knaut et al., 2009; Levin et al., 2008) participants with stroke used less trunk displacement in the VE. One possible explanation for these findings is the influence of viewing medium used. Viewing the 2D VE using a TV screen (Liebermann et al., 2012) may have been unable to provide information about the physical limit of the environment which was available in the PE. This may have changed their judgement on the target affordance (Wagman and Carello, 2001) and led to misjudgement on the actual location of the targets, thus limiting the amount of trunk movement. Thus participants may have perceived the target to be closer than it actually was and probably moved forward to a smaller extent, thus producing a movement pattern that did not require a large amount of forward trunk movement for task completion.

In studies with 3D fully immersive VEs (Knaut et al., 2009; Levin et al., 2008), subjects viewed the VEs using an HMD. Wearing an HMD may have limited the amount of trunk movement because of: i) its weight (Knight and Baber, 2007) or ii) the need to keep the head straight due to the reduced field of view (extent of the world observed that is seen at any given moment; FOV) of about 50° with an HMD compared to 160° in the physical world (Creem-Regehr et al., 2005), since too much head motion may have resulted in the loss of view of the environment.

To examine the effects of the HMD on movement production, pointing movements made by subjects with post-stroke hemiparesis and controls were compared while a VE was viewed using a HMD or SPS (Subramanian and Levin, 2011). Results indicated that viewing a VE through an HMD influenced movement production. In controls, movements were slower and less precise (vertical and sagittal directions) and subjects used less elbow extension when the VE was viewed with the HMD compared to the SPS. Similarly, in the stroke subjects, movements were less precise and there was a greater vertical directional error using the HMD. Thus the differences seen in the earlier studies could be attributed to the use of the
HMD. These results also suggest that SPS can be used as a comfortable and effective medium to view VEs for stroke rehabilitation.

2.9.4.2 Transfer of training from virtual environments to the real world

Wilson and colleagues (Wilson et al., 1996) conducted a study with severely disabled children (n = 10), who explored a scaled computer simulation of a real building. Following the exploration, children were asked to locate a fire extinguisher in the real environment. A control group did the same task, without the opportunity of VR exploration. The children were far superior in the correctly identifying the location of the fire extinguisher than the control group. This indicated good transfer of the spatial knowledge into the real world. The children had also found the route properly, providing further support for transfer of spatial skills.

In a recent study (Rand et al., 2009), 6 participants with chronic post-stroke upper limb hemiparesis underwent 10 sessions of training over 3 weeks in a VE simulation of a supermarket (VMall). The VMall was viewed using a video capture VR system and encouraged functional upper limb reaching tasks. Immediately after training, all subjects had improved scores on the UL part of the FMA, mean WMFT Functional Assessment scores (WMFT-FAS) and performed the timed tasks on the WMFT faster. These changes were retained at follow-up (2 weeks from end of intervention).

Similar results were reported for lower limb rehabilitation in a single-blind RCT (Mirelman et al., 2009). Compared with ankle training using a robotic device alone, dose-matched practice on a robotic device coupled with a VE for 4 weeks resulted in greater improvements in gait velocity and walking distance (on the 6-minute walk test) and number of steps in the community (measured using accelerometers). Changes were retained at 3 months follow-up. The results of the above two studies indicate the transfer of both spatial and temporal (decreased time on WMFT, increase in gait velocity and walking distance) skills and provide encouraging results for the use of VR as an effective training modality for upper and lower limb rehabilitation post-stroke.
2.9.5 Virtual reality and feedback provision

As mentioned previously, VEs serve as one of the mediums for feedback provision. One of the earliest studies on the effects of feedback provision in a VE was conducted by Todorov and colleagues (Todorov et al., 1997). Healthy subjects (n = 52) were divided into three groups and received training in either the real world (n = 20), or in the VR simulator. Those training in the VR simulator were divided into either the training group (n = 19) or the pilot group (n = 13). They were trained to execute a table-tennis shot with their left hand.

Those in the real world group were coached by an experienced player. The coaching provided included information on errors, demonstrations of correct techniques to successfully execute the shots and extra practice trials. The VE consisted of a 3D simulation of the real environment, viewed on a computer screen. Both KR (score) and KP feedback (movement trajectory of the participants moving in the environment) were displayed after every trial. After 10 minutes of training, the performance of those in the VR group was superior to those in the real world group.

The effects of task practice accompanied by provision of KR and KP feedback on motor learning and recovery has been addressed by 5 studies with individuals with post-stroke upper limb hemiparesis (Kang et al., 2012; Hwang et al., 2012; Piron et al., 2010; Merians et al., 2009; Jang et al., 2005). The studies involved games to practice upper limb tasks including reaching, grasping and lifting skills and hand functions like individual finger movements and hand opening and closing.

All studies involved individuals with chronic post-stroke hemiparesis with either no control group (Merians et al., 2006), a control group with no intervention provided (Jang et al., 2005), a control group of age and sex-matched healthy individuals (Kang et al., 2012), control group with traditional therapy (based on the Bobath concept; Piron et al., 2010) or a control group with therapy provided at half the intensity of the intervention group (Hwang et al., 2012).
For all studies, visual KR and/or KP feedback was provided. In addition, KP feedback was verbally provided by the therapist in one of the studies (Piron et al., 2010). Primary outcomes included clinical assessments of upper limb impairment and ADL performance and kinematic measures of motor performance and movement pattern outcomes. In addition, levels of activation in the ipsilesional SM1 and amplitude and latency of the muscle evoked potential in the FCR muscle were also measured.

Task practice in the VE resulted in faster movements, better ability to move the fingers individually and increased range of motion of the fingers. Clinical assessments revealed an improvement in impairment levels (measured using grip strength, FMA and Motor Function Test), hand function (measured using the Jebsen Taylor and Box and Blocks Test) and ADL performance (measured using FIM). In addition, increased activation in the ipsilesional SM1 and an increase in amplitude and decrease in the FCR MEP (using TMS) were noted. The improvements in finger range of motion and performance on the Jebsen Taylor test were retained at follow-up.

Feedback was provided either on a continuous (Hwang et al., 2012; Merians et al., 2009) or a faded schedule (Piron et al., 2010; Jang et al., 2005). Only one study (Kang et al., 2012) compared feedback provision on a continuous and intermittent schedule of presentation of KP (mirror feedback). Better effects were found (lower MEP latency and higher amplitudes) on an intermittent compared to a continuous schedule of feedback delivery. However, the average amount and type of feedback for each individual over the training period was not specified in the studies that did not use continuous feedback.

Improvements in clinical outcomes, endpoint motor performance measures and hand movement pattern measures have been noted after training in VEs with feedback. However, the effects of feedback provision and task-practice in VEs on shoulder and elbow ranges of motion have not yet been investigated. Previous study results have indicated that movement speed and precision can be improved by use of a compensatory movement pattern (e.g. trunk displacement) instead of using elbow extension and shoulder flexion (Michaelsen et al., 2006, Cirstea and Levin, 2000). Thus it is still unclear whether training in VEs with feedback
leads to improvements in motor performance through behavioral recovery or use of compensations. An additional issue is that the amount of training between the groups in the above mentioned studies was not matched and there is no mention about the exact number of repetitions employed. As exercise intensity is known to be a key factor for motor improvements after stroke (Lo et al., 2010; Kwakkel et al., 1997), it can be a confounding factor and should be accounted for.

The use of VEs as a medium to provide feedback for stroke rehabilitation is gaining prominence. However, it is still unknown if matched intensity training between a PE and a similarly designed VE leads to similar or better outcomes. Whether feedback provided through the medium of a VE is more effective is additionally also unknown. Better motor learning outcomes in previous studies involving task specific intense practice with a large number of repetitions and feedback in a PE have been associated with fewer deficits in memory, cognitive flexibility and problem solving. However, it is still unknown whether improved motor learning outcomes after practice in VEs are associated with cognitive functioning. In particular, guidelines about the cognitive abilities required for individuals to benefit from different types of feedback delivery in VEs for motor learning need to be established for better individualized treatment prescription (Fluet and Deutsch, 2013; Levin et al. 2009).
CHAPTER 3

3.1 Preface

The global aim of this thesis was to examine the role of extrinsic feedback on motor learning in stroke. As the first part of this thesis, a systematic review of the literature was conducted to examine the level of evidence for the effectiveness of feedback provision for learning upper limb tasks in individuals with post-stroke hemiparesis.

The review focussed on the effectiveness of provision of extrinsic feedback for implicit motor learning with the upper limb in individuals with post-stroke hemiparesis. We concluded that provision of explicit feedback is beneficial for implicit motor learning using both the less- and more-impaired upper limbs and that provision of KP feedback may result in better motor learning outcomes. Visual and auditory feedback provided through media such as videotapes, VEs as well as robotic systems can be beneficial, but there is still no consensus regarding the best medium for feedback provision as well as the frequency of feedback provision. The presence of cognitive deficits was found to influence the ability to use feedback for motor learning, with better learning outcomes seen in those individuals post-stroke who had fewer deficits in verbal memory, problem solving and cognitive flexibility. Questions that emerged from the review were the need to identify advantages/disadvantages of using different media for feedback delivery and the optimal type and schedule of feedback to enhance motor learning in people with stroke. Answers to these questions can help provide a better understanding of the role of feedback in motor learning after a stroke.
Manuscript 1: Does provision of extrinsic feedback result in improved motor learning in the upper limb post stroke? A systematic review of the evidence

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Does provision of extrinsic feedback result in improved motor learning in the upper limb post stroke? A systematic review of the evidence

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3.2 Abstract

Background: Recovery of the upper limb (UL) after a stroke occurs well into the chronic stage. Stroke survivors can benefit from adaptive plasticity to improve UL movement through motor relearning. The provision of feedback has been shown to decrease the use of compensatory UL movement patterns. However, the effectiveness of feedback in improving UL motor recovery after a stroke has not yet been systematically reviewed.

Objective: The objective of this review was to systematically examine the role of extrinsic feedback on implicit motor learning after stroke, focusing on UL movement and functional recovery.

Results: Nine studies were retrieved that examined the role of feedback on UL motor recovery. Of these, 6 were Randomized Controlled Trials (RCTs), one was a single subject design, one was a pre-post design and one was a cohort study. The studies were rated on the basis of Sackett’s levels of evidence and PEDro scores for RCTs. Levels of evidence were limited (Level 2b) for UL motor learning of the less affected extremity and strong (Level 1a) for the more affected extremity.

Discussion and Conclusions: The results suggest that people with stroke may be capable of using extrinsic feedback for implicit motor learning and improving UL motor recovery. Emergent questions regarding the advantages of using different media for feedback delivery and the optimal type and schedule of feedback to enhance motor learning in patient populations still need to be addressed.
3.3 Introduction

Stroke is one of the leading causes of death and disability worldwide. The prevalence of patients with incomplete recovery has been estimated at 460/100,000\textsuperscript{1} with differing recovery rates for upper (UL) and lower limbs. UL recovery may extend beyond the time of usual cessation of rehabilitation.\textsuperscript{2} Indeed, there is mounting evidence for continued functional recovery of arm paresis well into the chronic stage of stroke.\textsuperscript{3,4} This may be attributable to sensorimotor learning and adaptive plasticity in the remaining cortical and subcortical brain tissue.\textsuperscript{5} Adaptive plasticity may be defined as reorganization of movement representations in motor and other cortical regions (e.g., supplementary motor area, SMA; pre-motor cortex, PMC; somatosensory cortex) resulting from learning or experience and involving physiological changes (e.g., synaptic efficacy and neurotransmitter systems), as well as long-term structural changes (e.g., remodeling the dendritic spines\textsuperscript{6}).

Intensive rehabilitation can engage adaptive plasticity mechanisms post-stroke to improve motor recovery through motor learning. Adaptive plasticity linked to rehabilitation is predicated on the hypothesis that short duration connections achieved through fast Hebbian learning facilitate the establishment of more durable connections occurring with repeated practice.\textsuperscript{7} Motor learning can occur via functional reorganization in relevant cortical areas, presumably through movement-related afferent processing.\textsuperscript{8} Motor skill reacquisition can occur, however, through restitution of pre-morbid movement patterns and/or adaptation of remaining motor elements by substitution or compensation (for recent review, see\textsuperscript{9}).

Motor learning is commonly divided into explicit and implicit learning systems. Explicit learning is the attainment of accessible declarative knowledge of components of a motor action through cognitive processes\textsuperscript{10} which can be tested by component recall or recognition. On the other hand, implicit learning is inadvertent, unconscious, characterized by behavioral improvement\textsuperscript{11}, demands less attention\textsuperscript{12} and is fundamental to relearning most everyday skills.\textsuperscript{13} For example, learning to ride a bicycle occurs after repeated errors and falls while the learner does not remember the exact motor components that led to success. Explicit learning and memory systems are distributed over the medial temporal lobe and the
dorsolateral prefrontal cortex. Implicit learning and memory systems also engage these two areas in addition to the cerebellum, basal ganglia and sensorimotor cortex (SM1). Hence, due to its widespread distribution, the capacity to learn implicitly is usually not completely lost following stroke.

Factors related to experience-dependant plasticity identified as pertinent to optimize post-stroke motor rehabilitation and recovery include intensity of practice, repetition, variable and task-specific practice and motivation. However, subjects may still use inefficient or ineffective movement patterns that are considered compensatory if task- or performance-relevant feedback is not provided. Feedback is sensory information provided either during or following task performance in the form of intrinsic or extrinsic information. Intrinsic feedback refers to somatic information (e.g., tactile, proprioceptive, kinesthetic, etc.) obtained during performance of the task itself. Extrinsic or augmented feedback is related to the environment such as verbal or non-verbal information provided by an external source. Extrinsic feedback can enhance or substitute for intrinsic feedback.

Goal-related extrinsic feedback is known as knowledge of results (KR). Knowledge of performance (KP) is extrinsic feedback on the nature of the movement pattern used for goal achievement. For example, for picking up objects, feedback about task success or failure is KR (i.e., ‘that movement was correct’) while that related to movement quality is KP (i.e., ‘move your trunk less’ or ‘bend your elbow more’). KP is used predominantly in rehabilitation settings. KP or KR delivery schedules can be continuous (every trial), summary (after a fixed trial number) or faded (initially every trial, then after several trials). While motor learning may occur without it, feedback provision results in better retention of learned skills.

In a recent review of extrinsic feedback for post-stroke motor learning, Van Vliet and Wulf concluded that feedback was useful for improving balance and sit-to-stand tasks and that <100% feedback or summary feedback may enhance learning. Questions remaining were whether a) KR or KP was better for stroke survivors; b) video or kinematic feedback could enhance learning; c) greater benefits could result from a reduced feedback frequency; and d)
reduced frequency feedback improved retention. Our objective addresses some of these questions by systematically examining the role of extrinsic feedback on implicit motor learning post-stroke, focusing on UL motor recovery. The question guiding our review, presented in Population, Intervention, Comparison and Outcome (PICO) format was: “In participants with post-stroke hemiparesis, does provision of extrinsic feedback benefit implicit motor learning as compared to no feedback?”

3.4 Methods

3.4.1 Systematic Literature Review

An extensive review of the scientific literature published in English was performed by two investigators (SKS, MFL). Randomized controlled trials (RCTs) and pre-post studies focusing on feedback provision for UL motor learning in adult survivors of ischemic or hemorrhagic stroke were identified. Studies having an element of motor learning were retained. MEDLINE, EMBASE, CINAHL, PEDro, OT seeker, PsycINFO, Cochrane Database, the Cochrane Central Register of Controlled Trials (CENTRAL) and NARIC databases were searched from January 1998 to September 2008. Publications in the area of motor learning in rehabilitation were identified using the ISI Web of Science database. Databases were searched using the following keywords: cerebrovascular accident, stroke, upper limb, motor learning, implicit and explicit feedback, extrinsic feedback, rehabilitation, treatment, and brain damage. In addition, reference lists of retrieved articles were reviewed to identify other relevant articles.

3.4.2 Data Abstraction and Analysis

Retrieved articles were grouped according to whether the less- or more-affected arm was studied. Study details were summarized according to author, research design, feedback type, outcomes and results.
RCTs and quasi-RCTs were evaluated using the valid and reliable (inter-rater 0.56-0.91) PEDro (Physiotherapy Evidence Database) Scale developed by the Centre for Evidence Based Practice in Australia. This 10-item scale is based on core-criteria generated by expert consensus for assessment of RCT quality. Each item is rated as present (1) or absent (0) with the score out of 10 reflecting internal validity. Points are allocated for blinding methods (three points; subjects, therapists evaluators), randomization (two points; random and concealed allocation), data reporting (three points; baseline similarity of groups, between-group statistical comparison for at least one key outcome, point and variability estimates), data analysis (one point; intention to treat) and adequacy of follow-up (one point).

Scoring was completed by two authors (SKS, CLM) with discrepancies resolved by a third (MFL). Foley et al’s assessment was used to interpret RCT quality. Studies were rated from excellent to poor based on PEDro classification: 9-10 “excellent”; 6-8 “good”; 4-5 “fair”; <4 “poor”. Sackett’s Levels of Evidence adapted to include PEDro ratings were used to estimate the effectiveness rating. A level of evidence rating of 1a was allotted if two or more good-to-excellent quality RCTs (PEDro ≥6) reported evidence of intervention effectiveness. If one good-to-excellent RCT was found, a 1b level of evidence was given. A rating of 2a indicated effectiveness based on one or more fair quality RCTs (PEDro = 4-5). RCTs receiving a PEDro score ≤3 and non-randomized trials were rated 2b. If several pre-post design studies showed similar results or there was consensus by an expert panel, a level of 3 was given. Finally, a level of 4 indicated conflicting results of two or more studies with similar study designs and quality, and a level 5 denoted the absence of experimental studies.

3.4.3 Data Retrieved

Of 114 citations retrieved in MEDLINE, six RCTs, two pre-post studies and one cohort study met inclusion criteria. No new citations were retrieved from the remaining databases or reference lists of retrieved studies. In the following section, conclusions are made regarding evidence levels and brief summaries of the studies focus on effectiveness of extrinsic feedback for implicit motor learning.
3.5 Results

Study details are listed in Table 3-1 with salient features outlined in the text. Detailed explanations on the assigned PEDro scores are listed in Table 3-2.

3.5.1 Effectiveness of Feedback on Implicit Motor Learning Using Less-Affected UL

There is level 2b evidence on the effectiveness of feedback provision for motor learning from one RCT using the less-affected UL. Motor learning tasks were accomplished with the ipsilesional (less-affected) limb, based on the assumption that some aspects of learning are not lateralized and to avoid confounding factors related to motor performance deficits of the more-affected arm.

Two groups (healthy, stroke, n=40 each) practiced blocks of a planar flexion-extension elbow movement by moving the handle of a lever. The stroke group had infarcts in the anterior circulatory system mainly in the middle cerebral artery (MCA) region. Two subgroups received either 67% (n=20) or 100% feedback (n=20) in each trial block. ANOVAs assessed the effects of feedback, group and trial block on two main outcome measures (random and variable errors). Performance improved in both groups but movements in the stroke group were consistently less accurate and more variable. For both groups, there was only a tendency for more accurate movements in those who received 100% compared to 67% feedback.

Insert Table 3-1 near here

This study showed that motor learning was relatively preserved in chronic post-stroke subjects. However, underlying deficits in control or execution of motor skills remained even in the less-affected arm. Secondly, there was no differential effect of the two augmented feedback schedules on the main outcome measures (errors). Based on this observation, the authors suggested that motor learning principles derived for healthy populations may be generalized to stroke survivors.
3.5.2 Effectiveness of Feedback on Implicit Motor Learning Using More-Affected UL

There is level 1a evidence from four good quality RCTs\textsuperscript{26,35-37} on the effectiveness of feedback for motor learning using the more-affected UL. Feedback was provided via various media including verbal, virtual environments, videotape, robotic haptic interface, audition and vision. Note that none of the studies specifically analyzed the effects of lesion location on feedback utilization for motor learning.

Insert Table 3-2 near here

Levin and colleagues analyzed the effects of different types of feedback on UL motor recovery compared to no feedback on movement outcome (precision, speed, variability\textsuperscript{26}) and motor performance (movement quality\textsuperscript{35}) variables. In both studies, the lesion type was cortical, subcortical or combined. In the first study, 26 participants were randomly assigned to three groups – KP (n=14), KR (n=14) and Control (n=9). KP and KR groups practiced a reaching task while the control group practiced a non-reaching task. The KP group received faded feedback regarding joint motions, including information about excessive compensatory trunk displacement (~27%). The KR group received summary feedback on movement precision (20%). Clinical assessments (UL motor impairment and function) and kinematic analysis of a pointing task were done before, after and one month following practice. Cognitive domains of memory, attention, planning and mental flexibility were also evaluated pre-intervention. Data were analyzed using between-group comparisons with mixed model ANOVAs and multiple regressions. While the KR group improved movement precision post-intervention, the KP group made faster, less variable and less segmented movements compared to pre-intervention. Changes were retained at follow-up in both groups. Larger clinical improvements in arm impairment and function occurred in subjects with fewer deficits in memory and executive functioning.

In the second study,\textsuperscript{35} chronic post-stroke survivors were randomly assigned to two groups – KP (n=14) and KR (n=14). Feedback type, task practice, kinematic and clinical assessments were similar to the first study. Mixed-model ANOVAs, Pearson correlation and multiple
regression were used for data analysis. Immediately post-intervention, the KP group increased the range of shoulder movements and improved elbow and shoulder temporal interjoint coordination (IJC) compared to the KR group. A trend towards improvement in elbow and trunk motion was noted with all changes being retained at follow-up. There were no immediate post-intervention changes in the KR group but temporal IJC improved at follow up.

Based on the above studies comparing KP and KR, there is Level 1b evidence that provision of KP in chronic stroke survivors may result in better motor learning outcomes and retention of learned movement patterns, compared to provision of KR. These studies also showed that improvement depended on feedback type (KR or KP).

Piron and colleagues\textsuperscript{38} assessed whether rehabilitative therapy combined with enhanced KP and KR feedback in a computer-displayed 2D virtual reality environment (VE) was useful for chronic stroke survivors with MCA lesions. Fifty subjects practiced UL activities involving object transport in the VE and received unspecified KP about arm movements and post-movement KR about endpoint trajectory. Clinical assessments (UL motor impairment and function) and movement analyses were done before and after task practice. Data were analyzed using non-parametric statistics. After training, subjects had significantly higher scores on all outcome measures. However, this study (level 5 evidence) had no control group and assessed only performance outcome and not movement quality variables. Thus, it cannot be determined whether improvements were due to the intervention or to participation alone. In addition, the medium used to provide KP (i.e. visual or verbal) was unclear.

Effects of feedback delivery in another 2D VE based on video-capture technology (IREX) on arm motor function in chronic stroke survivors with cortical, thalamic and corona radiata lesions were investigated by Jang et al\textsuperscript{36} (level 1b). Ten participants were randomly assigned to a VE therapy group (n=5) who played UL skills games or to a no-treatment control group (n=5). Initially, a high (>90%) frequency of augmented feedback was provided as KR or KP which was then gradually reduced. FMRI and clinical motor impairment and function assessments were done before and after training. Data were analyzed with Wilcoxon signed-
rank tests. Post-training, the VE group had increased ipsilesional activation in primary SM1 and improved clinical outcome measures compared to controls. Although feedback frequency was indicated, the average amount and type of feedback for each individual over the training period was not specified.

Based on these two studies, there is Level 1b evidence that training in a VE with feedback benefits arm motor recovery by reducing impairment and improving function. Still unknown is whether VE training leads to improvements in movement quality and whether effects of such training are similar or superior to those in a real-world (conventional therapy) environment.

The effect of a combined intervention using occupational therapy and videotape feedback (OTV) on skill learning involving donning socks and shoes as compared to occupational therapy (OT) alone was estimated by Gilmore and Spaulding. Subjects were randomly allocated to one of two groups (OTV/OT, n=5 each) receiving verbal KR and KP. Though all subjects were videotaped during the intervention, only OTV participants received additional videotape feedback. Main outcomes were the socks and shoes sub-tests of the Klein-Bell ADL test and the Canadian Occupational Performance Measure (COPM). The Klein-Bell ADL test was performed pre-intervention and after each of the 10 sessions while COPM was done only pre- and post-intervention. Outcome measures, analyzed using a split-plot ANOVA, improved in both groups with the OTV group reporting better performance and increased satisfaction in their ability to don shoes on the COPM. The authors concluded that using videotape feedback may increase satisfaction, motivation and effort in therapy. In this study, details of potential effect modifiers such as the type and delivery of KP and KR and the duration of videotape feedback in the OTV group were not provided. This study suggests that provision of videotape feedback in addition to KP and KR may be beneficial in promoting arm motor recovery in acute stroke survivors (level 1b). However, it is unknown whether provision of videotape feedback alone leads to better post-stroke arm motor recovery.
Maulucci and Eckhouse\textsuperscript{39} investigated whether provision of auditory feedback could augment arm motor recovery in chronic stroke survivors compared to practice alone. Subjects were randomized into two groups (n=8 each) receiving a combination of KP and KR feedback or only KR feedback. They made pointing movements in a randomized order to three targets, placed in ipsilateral, contralateral and central arm workspaces. The feedback group received both KP (auditory signal) and KR (light switching off) in the middle 24 trials of a 42-trial block. Kinematics of the pointing movements were recorded and outcomes defined at various levels of motor performance and movement quality which were compared across groups using ANOVAs. Improvements occurred in both groups on various outcomes, though improved path trajectory straightness only occurred in the feedback group.

In this study (level 2b), subjects were not evaluated on any clinical outcome measures of UL impairment and/or function. The investigators reported that UL elevation angles improved in the group receiving feedback. However, it is difficult to compare these measures to standard kinematic outcomes to determine intervention effectiveness. The choice of the 42-trial intervention was not supported by evidence.

The effect of robot-mediated therapy (RMT) on arm impairment and activity limitation levels post-stroke was evaluated by Coote et al\textsuperscript{40} in a series of single-case studies using a multiple randomized baseline design. Subjects with sub-acute to chronic post-stroke hemiparesis were assigned to two groups (n=10 each) and received either RMT or sling suspension. Following 8-10 baseline assessments, both groups received both interventions for three weeks. The RMT system consisted of a haptic interface arm with three degrees-of-freedom. Subjects practiced exercises like hand-to-mouth movements and reaching at table and shoulder height while excessive trunk displacement was restricted by a harness.

Feedback was provided on a screen about the desired movement direction and task accomplishment. In the RMT group, KP about trajectory straightness was provided as increased haptic resistance when the hand strayed from the programmed trajectory path. In the sling suspension group, elbow and shoulder exercises were practiced with the more-affected arm suspended in a sling. UL motor impairment and activity limitation levels were
measured before and after practice, in addition to shoulder flexion range via goniometry. Rate of recovery was analyzed using a Wilcoxon sign-ranked test and a linear regression. Overall, trends for higher recovery rates on all outcomes occurred in the RMT compared to sling suspension group.

In this study (level 2b), the authors concluded that a greater improvement for the RMT group was due to haptic and visual feedback. However, it is difficult to ascertain whether the improvements were due to practice with the robotic device alone or practice with the device combined with feedback. Although feedback was given about the required movement and exercise completion, operational definitions of the type and schedule of feedback were unclear. Whether subjects had to follow a specific movement direction to receive the feedback or whether this was a form of instruction was also not mentioned.

Dancause et al\textsuperscript{41} analyzed short-term motor learning strategies in chronic stroke survivors (n=10) compared to healthy age-matched controls (n=6). In the stroke group, the lesion type was either cortical, subcortical or a combination of both. Clinical physical (UL impairment) and cognitive (memory, attention, executive functioning) evaluations were performed. All participants made 50° elbow flexions from an initial to a final target at self-selected speeds using a horizontal manipulandum with or without a load. They were provided with KR about movement accuracy and KP (visual feedback of arm) on each trial. Additional feedback about movement speed was provided. Subjects practiced making rapid movements without a load and then, in random trial blocks, a load was suddenly introduced. Participants were instructed to correct movement errors. The number of trials in each block varied from 7-10 per block for a total of 150 trials in 12-15 blocks. Kinematic performance variables were defined. Data were analyzed using t-tests, 2-way ANOVAs and logistic non-linear regression analysis. Movements made by the stroke group were slower than controls, especially for loaded trials. Correction strategies used by participants with mild hemiparesis were similar to those used by healthy subjects, but differed for those with moderate and severe hemiparesis. Correction strategies highly correlated with the level of arm impairment (r = 0.79) and moderately correlated with cognitive executive function (r = 0.58).
This study (level 2b) demonstrated that chronic stroke survivors could learn implicitly based on short-term motor learning testing in the more-affected UL. This study also provided evidence that motor learning strategies were correlated with levels of cognitive functioning and arm impairment suggesting that these factors should be considered when assessing motor learning in chronic stroke survivors. However, the application of these results is limited by the small sample size.

3.6 Discussion

We found strong evidence supporting the provision of explicit feedback for implicit motor learning in the UL of stroke survivors. Our results suggest that stroke survivors are able to use explicit feedback and preserve motor learning abilities despite having underlying UL motor control deficits. An important consideration is that the ability to use explicit feedback applies to both the less- and more-affected sides.\textsuperscript{20,41} Based on these findings, some motor learning principles derived for normal populations can be generalized to a stroke population, but further research is needed to clarify this relationship.

3.6.1 Feedback Delivery Type: KP and KR

Three studies\textsuperscript{26,35,39} examined differences between provision of KR and KP and found that KP may lead to greater improvements in arm motor performance and movement quality. Provision of KR led to immediate improvements in motor performance variables, while improvements in movement quality were only evident at retention. KP, on the other hand, resulted in improvements in both motor performance and movement quality immediately and for up to one month post-training. On the basis of these studies, it can be suggested that stroke survivors are able to use the complex information provided in KR and KP. The more lasting benefits of KP may be related to the focus on improving recovery by addressing movement quality\textsuperscript{9}, decreasing compensatory trunk movement\textsuperscript{26,35} or maintaining a particular endpoint path.\textsuperscript{39}
3.6.2 Feedback Delivery Medium

Precise feedback about movement parameters has recently been incorporated into new technologies such as robotics and virtual reality. Studies included in this review showed that stroke survivors can use feedback from various sources including videotape\textsuperscript{37}, VE\textsuperscript{36,38} and robotic\textsuperscript{40} systems which may provide precise information more consistently than individual therapists (i.e., detailed information on movement parameters). Incorporation of such technologies as adjunctive therapies may augment motor learning and outcomes in stroke survivors and lead to higher patient satisfaction.\textsuperscript{37} However, based on current studies, there is still no consensus on the best delivery medium for feedback.

3.6.3 Feedback Delivery Schedule

Limited evidence exists for how feedback delivery should be scheduled for optimal results in stroke survivors. Winstein and colleagues\textsuperscript{20} have suggested that providing feedback on a faded compared to a continuous schedule may be more beneficial for stroke survivors. However, whether all stroke survivors may benefit equally from a reduced feedback frequency is unknown. One possibility is that feedback frequency may need to be altered depending upon levels of arm and/or cognitive impairment. More research is needed to clearly understand the relationship between motor learning and feedback types (KR or KP) and delivery schedule. For example, should KP and KR be delivered using the same schedule, and should the schedule change according to levels of cognitive impairments?

3.6.4 Effect of Lesion Location and Level of Motor Impairment on Learning

In the nine studies reviewed, lesion location and motor impairment levels did not affect the ability of stroke-survivors to use feedback. Participants had lesions in only MCA areas (homogenous groups\textsuperscript{20,38}) or cortical and/or subcortical areas (heterogeneous groups\textsuperscript{26,35,36,41}). In three studies, lesion location information was not provided.\textsuperscript{37,39,40} Feedback provision was found to be beneficial for implicit learning irrespective of lesion location.
However, it is possible that learning in general may be influenced by lesion location. In studies in which feedback was not provided, stroke survivors with MCA, basal ganglia or cerebellar lesions retained the capacity for implicit learning. However, implicit sequence learning after short-term practice was impaired in subjects with focal thalamic lesions. In these studies, either no information or explicit information (instructions) was provided prior to task practice.

Reviewed studies did not specifically address the impact of lesion side (left or right) and dominance on implicit motor learning. In healthy individuals, the left PMC and SMA are implicated in implicit sequence learning for both sides. In one reviewed study, only activation in the ipsilesional SM1 after training in a non-sequence task was associated with learning. Future research focusing on task practice with a specific arm and side of lesion may help clarify the role of hemispheric specialization on motor learning post-stroke.

In terms of level of arm motor impairment, despite a wide variation of severity from mild to severe, all subjects could learn implicitly after practice with feedback. In one study, arm impairment affected the ability to maintain stable arm positions but implicit learning was preserved.

3.6.5 Adaptive Plasticity, Learning and Recovery

Task practice with feedback may facilitate cortical plasticity. After UL task practice in a VE with feedback, there was more ipsilesional SM1 activation compared to pre-practice activation in SM1 bilaterally, contralesional PMC, and contralesional or ipsilesional SMA and participants improved clinical arm motor impairment and function scores. Improvement in task performance may be mediated by increased activity in the subcortical circuit consisting of cerebellum, thalamus and putamen occurring after short-term learning and in the cortical-basal ganglia loop including the putamen after long-term learning.
3.6.6 Impact of Cognitive Function

Many stroke survivors have cognitive impairments in the domains of attention, memory and executive functioning.\(^{50}\) Attention plays a major role in skill reacquisition. Attention deficits can lead to decreased mental flexibility, impaired concentration and deficits in dual-tasking. Memory problems impact intake and storage of information as well as its retrieval such as the ability to use information and feedback from one movement in a subsequent similar movement. Problems in executive function include deficits in planning and initiation of goal-directed activities and in auto-evaluation of activity outcomes. Although cognitive impairment (memory and executive functioning) can be correlated with arm motor impairment and function levels,\(^{26,41}\) better motor learning ability was found in those with higher cognitive ability. Higher cognitive ability may be related to the capacity to store and retrieve information from previous trials for use in subsequent movements.\(^{41}\) This suggests that the ability to use feedback for motor learning may not be entirely lost in post-stroke patients with cognitive impairments.

3.6.7 Limitations

Overall, interpretations of the reviewed studies are limited by 1) low to moderate outcome measure effect sizes\(^{35,36,38}\) or lack of information about effect sizes;\(^{20,26,37,40}\) 2) inadequate information on type and/or frequency of feedback;\(^{36,37,38,40}\) and 3) absence of adequate control groups.\(^{36,38}\)

3.7 Conclusion

There is evidence to conclude that extrinsic feedback is useful for implicit motor learning in stroke survivors. Newer questions that have emerged from this review are 1) whether training in a VE with enhanced feedback results in similar or better arm motor recovery compared to real-world training; 2) whether provision of videotape feedback leads to better arm motor recovery in sub-acute and chronic stroke; 3) how the feedback delivery medium impacts motor learning; and 4) whether provision of faded feedback results in better arm motor
recovery compared to 100% feedback. Further research should also elucidate the role of different types, amounts and delivery schedules of feedback on motor learning in patients with lesions in specific brain areas. Feedback is one element essential to maximize experience-dependant plasticity and learning.21 Kleim and Jones21 described 10 basic elements including intensity, variability, repetition, specificity, motivation and salience of the tasks to be practiced. Incorporation of these basic elements into task practice with appropriate feedback and adequate attention to movement quality9 may help ensure best recovery of post-stroke arm-motor impairment and function.

3.8 Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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3.10 References


Table 3.1 – Details of all reviewed studies

<table>
<thead>
<tr>
<th>Reference Number</th>
<th>Side involved</th>
<th>Sample size</th>
<th>Type of study</th>
<th>Intervention</th>
<th>Feedback provided</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>20, PEDro = 3</td>
<td>Less affected</td>
<td>40 stroke</td>
<td>RCT</td>
<td>Two groups (healthy, stroke). Two subgroups per group receiving 100% or 67% faded feedback.</td>
<td>Elbow motion trace superimposed on the target movement trace using a graphical interface.</td>
<td>Stroke group less accurate and more variable than controls. Stroke group less accurate and more variable than controls.</td>
</tr>
<tr>
<td>PEDro = 3</td>
<td>chronic</td>
<td>40 healthy controls</td>
<td>Discrete elbow flexion-extension task practiced on a horizontal surface. Two 99 trial practice sessions and two 18 trial no feedback retention sessions.</td>
<td>Numeric error score.</td>
<td>100% feedback group tended to be more accurate than the 67% feedback group.</td>
<td>100% feedback group tended to be more accurate than the 67% feedback group.</td>
</tr>
<tr>
<td>PEDro</td>
<td>RCT</td>
<td>Subjects</td>
<td>Strokes</td>
<td>Level</td>
<td>Groups</td>
<td>Task</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>----------</td>
<td>---------</td>
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</tr>
<tr>
<td>26, 7</td>
<td>37</td>
<td>More</td>
<td>Chronic</td>
<td>1b</td>
<td>3 groups (KR, KP, control).</td>
<td>Three groups (KR, KP, control).</td>
</tr>
<tr>
<td>35, 8</td>
<td>28</td>
<td>More</td>
<td>Chronic</td>
<td>1b</td>
<td>2 groups (KR, KP).</td>
<td>Two groups (KR, KP).</td>
</tr>
</tbody>
</table>
| PEDro | More affected | 50 stroke subjects | Pre-post Training in VE on activities like putting a letter into an envelope and a ball into a basket. Daily 1-hr sessions, 5 days/ wk for 4 wks. | KP - about arm movementsKR - trajectory of the endpoint transporting the object compared to desired trajectory | Kinematic- Mean movement duration and movement velocity. Clinical – FMA and FIM. After training, mean movement duration and movement velocity, FMA and FIM scores +++.
| PEDro | More affected | 10 stroke subjects | RCT | Two groups, VR therapy vs. no-treatment control group.VR therapy- games focused on development of reaching, grasping, and lifting skills. Daily 1-hr sessions, 5 days/ wk for 4 wks. | KP or KR provided verbally. Initially high frequency (> 90%) and then gradually reduced. | Clinical – FMA, BBT and MFT, Radiological – fMRI scanning. VR group - All clinical scores +++; Increased ipsilesional activation in the primary SM1
<p>| PEDro | More affected | 10 stroke subjects | RCT | Two groups, videotape feedback and OT (OTV group) or OT alone. Skill of donning socks and shoes practiced for 10 sessions by both groups. | Verbal KP and KR – both groups Additional videotape replay feedback to OTV group. | Socks and shoes subtests of KB-ADL test and COPM. Both groups improved on both tests. OTV group reported better performance and more satisfaction in their ability to don shoes on the COPM. |</p>
<table>
<thead>
<tr>
<th>PEDro Score</th>
<th>More affected subjects, chronic</th>
<th>RCT</th>
<th>Two groups: practice with KR and KP feedback (n=8) and practice with KR only (n=8). 42 trials per session; total of 18 sessions; 3 times/ wk.</th>
<th>Kinematic outcomes at various levels including arm and hand orientation and displacement and linearity of the end effector. Both groups improved, though improved trajectory path straightness noted only in feedback group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 2b</td>
<td>16 stroke</td>
<td>Pre-post, sub-acute baseline and chronic single subject design</td>
<td>KP – auditory signal about endpoint trajectory. KR – visual feedback on touching the target (accuracy)</td>
<td></td>
</tr>
<tr>
<td>Score Level 2b.</td>
<td>20 stroke</td>
<td></td>
<td>Clinical – FMA, shoulder flexion range (goniometry) and spasticity (MAS). Trend for higher recovery rates for all 3 outcomes after robot mediated compared to sling suspension therapy. Spasticity: +++ in Group 1 and ++ in group 2 - after robot therapy.</td>
<td></td>
</tr>
</tbody>
</table>
Score Level 2b

More affected 10 stroke subjects, study chronic. 6 healthy controls

50° elbow flexion movement using a horizontal manipulandum.

Participants asked to correct movement errors caused by sudden introduction or removal of a load.

KP - visual feedback of the arm,
KR - about movement accuracy.
Feedback about movement speed also provided

Kinematic-Movement errors and speed.

Final position of 1st trial in changed load condition, 2nd and 3rd trials (P1, P2) and control trials (C) in same load condition recorded.

Load introduced - undershoot error; Load removed - overshoot error.

Stroke group – slower movement speeds; final positions for P1, P2 and C in the loaded condition -- compared to no load condition.

Subjects with mild hemiparesis - similar correction strategies to healthy participants.

(FMA – Fugl Meyer Assessment for the upper limb; CSI – Composite Spasticity Index; TEMPA – Upper Extremity Performance Test for the Elderly; FIM – Functional Independence Measure; BBT – Box and Blocks Test; MFT – Manual Function Test; KB ADL – Klein Bell Activities of Daily Living Test; COPM – Canadian Occupational Performance Measure; MAS – Modified Ashworth Scale; SM1 – Sensorimotor cortex; +++ – statistically significant improvement; ++ – tendency to improve; -- – significantly lower)
<table>
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<th>Eligibility criteria</th>
<th>Yes</th>
<th>Yes</th>
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<td>Random allocation</td>
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<td>Concealed allocation</td>
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<td>Similar at baseline</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Subjects blinded</td>
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<td>No</td>
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<td>No</td>
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<td>Evaluator blinded</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Outcomes obtained from 85%</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Intention to treat</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Between group comparison</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td><strong>Total score</strong></td>
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<td>8</td>
<td>8</td>
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</table>
CHAPTER 4

4.1 Preface

Inherent to the design and conduct of any study is the selection of appropriate outcome measures. Factors including established psychometric properties of reliability and validity have to be considered when selecting an outcome measure (Fitzpatrick et al., 1998). The measure should preferably be condition-specific or its psychometric properties should be tested and established for the specific condition (stroke, in this case). Scores obtained on reliable and valid clinical assessments are most commonly used as primary outcomes measures in studies involving subjects post-stroke.

The majority of the studies reviewed in Chapter 3 used clinical assessments to measure change in levels of upper limb motor impairment and performance of ADL. Clinical outcomes often focus on task-accomplishment (i.e. whether the task was completed or not) and not on how the movement is performed. Information on how a movement is performed can be obtained primarily with the use of kinematic analysis that broadly describe movements at two levels: motor performance and movement patterns.

Motor performance kinematic variables have been shown to be sensitive in identifying deficits, even in those individuals who are considered well recovered. However, the use of only motor performance variables as kinematic outcomes may provide an incomplete assessment of motor abilities of individuals post stroke, as they may still continue to use compensatory movement patterns (for example, use of forward trunk displacement to overcome deficits in shoulder and elbow ranges) to achieve better performance outcomes. It is suggested to use movement pattern variables in addition to motor performance variables in order to gain all relevant information regarding the underlying motor impairments in movement production.

Previously, only the test-retest reliability and known-groups validity have been estimated for motor performance and movement pattern outcomes. Concurrent (performance of the new measure against the established gold/silver standard) and discriminant (ability to distinguish
between different severity levels) validity have not yet been established for movement pattern kinematic variables. Such information on concurrent and discriminant validity is essential to help make informed choices about the most appropriate measures to be used in studies involving provision of feedback.

This study estimated the concurrent and discriminant validity of movement patterns as measures of motor impairment for upper limb pointing and reach-to-grasp tasks using multiple regression analyses. The Fugl-Meyer Assessment, arguably the gold standard for assessment of upper limb motor impairment was used as the dependant measure and movement pattern kinematic outcomes of trunk displacement, shoulder horizontal adduction, shoulder flexion and elbow extension were used as predictors.
Validity of movement pattern kinematics as measures of arm motor impairment post-stroke

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Validity of movement pattern kinematics as measures of arm motor impairment post-stroke

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4.2 Abstract

Background and Purpose: Upper limb (UL) motor impairment post-stroke is commonly evaluated using clinical outcome measures such as the Fugl-Meyer Assessment (FMA). However, most clinical measures provide little information about motor patterns and compensations (e.g., trunk displacement) used for task performance. Such information is obtained using movement quality kinematic variables (joint ranges, trunk displacement). Evaluation of movement quality may also help distinguish between levels of motor impairment severity in individuals post-stroke. Our objective was to estimate concurrent and discriminant validity of movement quality kinematic variables for pointing and reach-to-grasp tasks.

Methods: A retrospective study of kinematic data (sagittal trunk displacement, shoulder flexion, shoulder horizontal adduction, elbow extension) and FMA scores from 86 subjects (sub-acute to chronic stroke) performing pointing and reaching tasks was done. Multiple and logistic regression analyses were used to estimate concurrent and discriminant validity respectively. Cut-off points for distinguishing between levels of UL motor impairment severity (mild, moderate-to-severe) were estimated using sensitivity/specificity decision plots. The criterion measure used was the FMA (UL section).

Results: The majority of variance in FMA scores was explained by a combination of trunk displacement and shoulder flexion (51%) for the pointing task and by trunk displacement alone (52%) for reach-to-grasp task. Trunk displacement was the only variable that distinguished between levels of motor impairment severity. Cut-off points were 4.8cm for pointing and 10.2cm for reach-to-grasp movements.

Conclusion: Movement quality kinematic variables are valid measures of arm motor impairment levels post-stroke. Their use in regular clinical practice and research is justified.

Keywords: Stroke, Pointing, Reach-to-grasp, Measurement, Movement quality
4.3 Introduction

Descriptions of motor patterns used for task performance can help better quantify impairment levels in individuals post-stroke. Kinematic variables provide detailed measures at two levels: motor performance (endpoint error, velocity, etc.) and movement quality (joint ranges, trunk movement). Both levels of movement description are increasingly being used as outcomes in studies involving upper limb (UL) movement re-education in individuals post-stroke. Kinematic measurement has revealed differences in arm movement patterns during reaching tasks between i) healthy controls (dominant arm) and individuals with stroke (more-affected arm) and ii) individuals with stroke (more-affected vs. less-affected arms). For example, motor performance measures revealed that tapping with a stylus, requiring wrist flexion/extension, and 3D pointing movements were less precise and slower in the hemiparetic arm compared to healthy controls despite clinically assessed mild levels of arm motor impairment (strength ≥4/5 on the Medical Research Council Scale or ≥50/66 on UL Fugl-Meyer Assessment (FMA). This suggests that motor performance variables may better identify motor control deficits than clinical outcome measures.

In addition to motor performance measures, movement quality measures also identify and quantify motor compensations used for task accomplishment. During UL reaching tasks, children and adults with hemiparesis use excessive trunk displacement, compared to controls, to assist arm endpoint displacement when they have a restricted range of voluntary elbow extension and/or disrupted elbow/shoulder interjoint coordination. Thus, measurement of only motor performance variables may provide an incomplete assessment of motor abilities of individuals post-stroke.

Test-retest reliability and minimal detectable change (MDC95) of 3D kinematic variables of a midline reaching task have recently been investigated in 13 individuals with chronic stroke. Only two trials were recorded for each reaching task. Motor performance (endpoint error, peak-velocity, movement time, reach extent) and movement quality variables (ranges of shoulder flexion, shoulder abduction, elbow extension, and elbow-shoulder cross-correlation) had moderate to excellent reliability (ICCs≥0.6). MDC95 values differed, with
lowest variability for reach-path ratio (7.9-20.9%) and elbow-shoulder cross-correlation (10.2-18.2%) and highest (~44-99%) for temporal measures.

Previous studies have not investigated concurrent validity of kinematic measures and their ability to detect UL impairment severity levels, including compensatory movement patterns in individuals with stroke. Our goal was to estimate the concurrent and discriminant validity of movement quality kinematic measures for UL pointing and reach-to-grasp tasks. The UL part of FMA, with well-known psychometric properties, was used as the criterion measure. Arguably the gold standard for UL impairment measurement, it is widely used as the criterion measure to estimate concurrent validity of other outcome measures.

4.4 Methods

Kinematic data were available from subjects with sub-acute to chronic post-stroke hemiparesis from four previous studies conducted by our group between 2001-2008 of either a pointing task: Study 1 (Cirstea and Levin); Study 2 (Subramanian et al.) or a reach-to-grasp task: Study 3 (Michaelsen et al.); Study 4 (Magdalon et al.). The four study samples ranged from 12 to 28 subjects recruited according to common inclusion criteria: i) first ischemic/hemorrhagic stroke ii) >three months post-stroke; iii) score of ≥two out of seven on the Arm and Hand section of the Chedoke-McMaster Stroke Assessment; iv) ability to communicate in French and/or English. Subjects were excluded if they had an (a) occipital, brainstem or cerebellar lesion, (b) other neurological or orthopedic conditions; (c) major cognitive deficits assessed by standard tests; (d) sitting balance or trunk stability deficits; and (e) problems with wearing a head-mounted display (for Study 2, 4). All participants signed informed consent forms approved by the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR).

Study designs were cross-sectional (Study 4) or randomized clinical trials (RCT, Study 1-3). Although the three RCTs included specific practice regimens, only movement quality measures and UL FMA scores from the initial pre-practice assessment were considered for analysis. In Study 1 and 2, pointing tasks consisted of repetitive pointing motions with the
more-affected arm to a shoulder-height target placed at functional arm’s length (i.e., within reach; Fig. 4-1A). Since initial arm positions varied between studies, only angular values at the end of movement (end position angles) were used. Subjects were instructed to “point to the target quickly and precisely in one smooth movement”. The subjects performed 12-25 movements with 10sec breaks between trials. For the grasping tasks (Study 3,4; Fig. 4-1B), participants reached and grasped a cylinder (diameter 35mm, height 95mm) using a whole-hand grasp at a self-paced speed for 10 trials. The cylinder was placed at xiphoid process height at a distance of 80% of the arm length. For all studies, a sound signaled movement start.

4.4.1 Kinematic Data Acquisition

Marker placement (infrared emitting diodes; IREDs) had common anatomical locations as follows: index fingertip, distal ulnar head (wrist), lateral epicondyle (elbow), ipsilateral and contralateral acromion processes (shoulders) and sternal angle. Kinematic data were recorded for 2-5s at 100-120Hz with a 3D optical tracking system (Optotrak, Northern Digital, Waterloo, Canada). Kinematic data collected included trunk displacement, shoulder flexion, shoulder horizontal adduction and elbow extension. Arm and trunk displacement were measured as the sagittal distance (mm) moved by the sternal or fingertip marker between movement beginning and end. These were defined as times at which the fingertip/sternal marker tangential velocity rose above or fell below 10% of the peak tangential velocity respectively.

Shoulder flexion was defined as the angle between vectors formed by elbow and ipsilateral shoulder IREDs, and the vertical through the ipsilateral shoulder (arm alongside body = 0°). Shoulder horizontal adduction was measured as the angle between two vectors defined by ipsilateral shoulder-elbow IREDs and contralateral-ipsilateral shoulder IREDs projected horizontally, where the full abduction in line with the shoulders was 0°. Elbow extension was measured as the angle between vectors formed by wrist and elbow IREDs and elbow and ipsilateral shoulder IREDs (full elbow extension = 180°). Angular data were low-pass filtered
at 20Hz. Definitions of beginning and end for angles measurement was based on endpoint peak velocity defined above.

4.4.2 Statistical Analysis

Preliminary analysis involved grouping data into two sets according to the task (pointing, reach-to-grasp) and ensuring that requirements of linearity, normality and homogeneity were met. The strength of correlation amongst predictors (trunk displacement, shoulder flexion, shoulder horizontal adduction, elbow extension) and with the UL FMA scores was estimated with Pearson’s correlations. Wrist movements were not included in the analysis. Correlations were defined as strong (≥0.7), moderate (0.4-0.69) or mild (≤0.39). Strong correlation between any two predictors indicates measurement of the same construct, which does not allow the amount of variance predicted to be attributed uniquely to one variable. Thus, in cases of high correlations between predictors, one predictor is substituted for another.

Concurrent validity of kinematic measures (predictors) was estimated against FMA scores (dependant variable). To determine which predictor or combination thereof (trunk displacement, shoulder flexion, shoulder horizontal adduction or elbow extension) explained the greatest amount of FMA score variance, the best fit model (BFM) was obtained using multiple linear regression analysis. Adjusted $r^2$ values were used since they consider multicollinearity. The most parsimonious model sought using various combinations of predictors was verified using robust regression procedure.

Discriminant validity of kinematic measures (predictors) was estimated against FMA scores (dependant variable) using logistic regression analysis. The cut-off score of 50/66 on FMA was used to discriminate between subjects with mild (Group 0) or moderate-to-severe (Group 1) hemiparesis. Logistic regression estimated which predictor(s) contributed most to the probability of a subject moving between groups. Using receiver operating characteristic (ROC) curves we calculated area under the curve and sensitivity and specificity values for predictor(s). Sensitivity/specificity decision (SSD) plots were constructed to estimate cut-off
values for transition between levels of severity for each predictor. Data was analyzed using SPSS© (version 17) and SAS© (version 9.3.1) with significance levels of α<0.05.

4.5 Results

Data from 44 and 42 participants respectively were available for analysis of pointing and reach-to-grasp tasks (Table 4-1). Both datasets met assumptions of linearity, normality and homogeneity.

4.5.1 Pointing Data Set

4.5.1.1 Correlations Between Predictors

All correlations were significant (p<0.05) except for shoulder horizontal adduction and trunk displacement. Correlations between FMA and individual predictors ranged from low to moderate (Table 4-2A) and were highly significant (p<0.005), except for those between FMA and shoulder horizontal adduction. Between predictors, correlations were low to moderate (Table 4-2A) except for shoulder flexion and elbow extension (r=0.71).

4.5.1.2 Multiple Regression Analyses

The best four models explaining the maximum amount of variance in FMA scores are shown in Table 2B along with amounts of variance explained by individual predictors. Trunk movement alone explained 46% of the variance. Two BFMs were identified (Table 4-2B, bold). One consisted of a combination of trunk displacement, shoulder flexion and shoulder horizontal adduction, explaining 55% of the variance in FMA (ANOVA F(3,40)=16.06, p<0.001; adjusted r²=0.51) and the other included trunk displacement and shoulder flexion, explaining 51% of the variance (ANOVA F(2, 41)=21.32, p<0.001; adjusted r²=0.49). Robust regression revealed that shoulder horizontal adduction did not contribute significantly to the variance. Thus, the final BFM consisted of trunk displacement and shoulder flexion.
4.5.1.3 Logistic Regression Analysis

Logistic regression revealed that trunk displacement was the only variable discriminating between mild and moderate-to-severe motor impairment levels (Table 4-2C). The final logistic regression equation was: Logit P (mild impairment for pointing) = −3.972 − 0.040(trunk displacement) + 0.024(shoulder flexion) + 0.005(shoulder horizontal adduction) + 0.043(elbow extension). The odds of a subject moving from Group 0 (mild hemiparesis) to Group 1 (moderate-to-severe hemiparesis) increased by 96% with one unit increase in trunk displacement. The area under the curve was 0.86 (p<0.001; 95% confidence interval 0.76-0.97). The cut-off value for transition between groups estimated by the SSD plot was 4.8cm (Fig. 4-2). Thus, subjects with mild and moderate-to-severe hemiparesis used ≤4.8cm or >4.8cm of trunk displacement respectively for the pointing task.

4.5.2 Reach–to-Grasp Data Set

4.5.2.1 Correlations Between Predictors

For the reach-to-grasp task, there were low-to-moderate correlations between FMA and shoulder flexion, shoulder horizontal adduction and elbow extension while FMA and trunk displacement were highly inversely correlated (r=−0.72; Table 4-3A). Between predictors, shoulder horizontal adduction, trunk displacement and elbow extension were moderately correlated while the other predictors were highly correlated. All correlations were highly significant (p<0.005).

4.5.2.2 Multiple Regression Analyses

Trunk movement alone explained 52% of the variance in FMA scores (ANOVA F(1,40) = 42.91, p<0.001; adjusted r²=0.51) and accounted for one BFM (Table 4-3B, bold). The other BFM consisted of a combination of trunk displacement and shoulder horizontal adduction, which also explained 52% of the variance (ANOVA F(2,39)=21.02; p <0.001; adjusted
$r^2=0.49)$. However, robust regression revealed that shoulder horizontal adduction did not significantly contribute to the model. Thus the best model was one involving only trunk.

4.5.2.3 Logistic Regression Analysis

The results for the reach-to-grasp dataset were similar to the pointing dataset. Trunk displacement was again the only variable able to discriminate between levels of impairment (Table 4-3C). The final logistic regression equation was: Logit P (mild level of severity for reach-to-grasp) = $6.093 - 0.049$(trunk displacement) + $0.081$(shoulder flexion) – $0.053$(shoulder horizontal adduction) – $0.018$(elbow extension). Thus, the odds of a subject moving from Group 0 to Group 1 were increased by 95% with one unit increase in trunk displacement. The area under the curve was 0.95 ($p<0.001$; 95% confidence interval 0.80–1.00) and the cut-off point was estimated at 10.2cm (SSD plot; Fig.4-3). Thus for the reach-to-grasp task, subjects with mild and moderate-to-severe hemiparesis used ≤10.2cm or >10.2cm of trunk displacement respectively.

4.6 Discussion

Concurrent and discriminant validity of movement quality kinematic variables as measures of UL impairment for pointing and reach-to-grasp tasks were investigated. We found that variability in FMA scores across subjects and datasets was explained by different combinations of kinematic variables for each task. A combination of trunk displacement and shoulder flexion best explained majority of the variance (51%) in FMA scores for pointing, with 46% attributed to trunk movement alone. For the reach-to-grasp task, trunk displacement was the most significant contributor to the variance (52%). Addition of other predictors in the model did not significantly change the amount of variance explained. Indeed, there were high autocorrelations between many of the predictors (Table 4-3B) which may be due to coupling between adjacent joints.

Trunk displacement was the only variable that discriminated between mild and moderate-to-severe UL impairment for both tasks. One unit increase in trunk displacement was associated
with a 96% (pointing) or 95% (reach-to-grasp) increase in the odds of having a lower score on FMA (greater impairment level). The SSD curve analysis indicated that cutoff points of 4.8cm (pointing) and 10.2cm (reach-to-grasp) for trunk displacement discriminated between different UL impairment severity levels. The cutoff point for pointing is consistent with previously reported values of trunk displacement in individuals post-stroke with mild (5.1cm) and moderate-to-severe (10.3-13.9cm) UL impairment performing comparable reaching tasks.4 Additionally, the cutoff point for the reach-to-grasp task is similar to that characterizing this task in individuals with mild UL impairment (10.2cm) compared to 1.7-2.5cm in healthy age-matched subjects.3,23 This indicates that subjects with clinically estimated mild arm motor impairment could still use as much as 33% (pointing) to 300% (reach-to-grasp) more trunk displacement compared to age-matched controls. Thus, improvement in FMA scores may not necessarily indicate that test items are accomplished without using compensatory movement patterns. Our results are also consistent with findings that trunk displacement is used to assist arm extension during reaching and hand orientation during grasping3,24

Our results suggest that movement quality variables are more sensitive in identifying UL deficits, even in well-recovered patients as compared to clinical scales. Such information may be used to complement clinical assessment. Our results also demonstrate that movement quality kinematic variables are valid measures of arm motor impairment levels and can be used to distinguish between arm motor recovery and compensation.

Measuring movement kinematics in the clinical setting is difficult, given the cost and specialization of recording and analysis technology. Alternatively, objective quantification of movement quality during task performance may be better estimated using multiple clinical outcomes25 including measures at two levels of the International Classification of Functioning (ICF).26 Thus, outcome measures can include clinical scales that focus on direct observation of movement patterns (e.g. Reaching Performance Scale for Stroke;27 ICF level: Impairment) to be combined with those of motor function (e.g., Wolf Motor Function Scale;13 ICF level: Activity).
Our kinematic assessments included only two UL joint movements, namely shoulder and elbow motion. Actions scored with FMA also include wrist movements, grasp types and coordination. Inclusion of kinematic representations of these additional variables in the model may potentially alter the percentage of variance explained by the predictors. In addition, we only considered end position static angles. It remains to be determined if the relationships between FMA and predictors would be altered when considering dynamic movement patterns.

### 4.7 References


Figures

Figure 4-1. Experimental set-up

Experimental set-up for Study 1 and 2 (A), and Study 3 and 4 (B). In A, subjects pointed to a target placed at arm’s length. In B, subjects reached for and grasped a cylinder placed at 80% of arm’s length. Initial arm position - thick lines; final arm position – thin lines.
Figure 4-2. Sensitivity/specificity decision plots for pointing dataset.

Sensitivity (grey circles) and specificity (black circles) values were plotted against trunk displacement (mm). The dashed line indicates cut-off value for trunk displacement for transition between groups.
Figure 4-3. Sensitivity/specificity decision plots for reach-to-grasp dataset.

Sensitivity (grey circles) and specificity (black circles) values were plotted against trunk displacement (mm). The dashed line indicates cut-off value for trunk displacement for transition between groups.
Table 4-1. Participant characteristics. For categorical variables, the first number is the number of subjects in that category and the second is percentage. For continuous variables, means and standard deviations (SD) are indicated. FMA=Fugl-Meyer Assessment.

<table>
<thead>
<tr>
<th></th>
<th>Number of participants/Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pointing (n=44)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29(66%)</td>
</tr>
<tr>
<td>Female</td>
<td>15(34%)</td>
</tr>
<tr>
<td>Side of hemiparesis</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>35(75%)</td>
</tr>
<tr>
<td>Left</td>
<td>11(25%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.8±13.9</td>
</tr>
<tr>
<td>FMA score ≥50</td>
<td>26/57.6±4.6</td>
</tr>
<tr>
<td>FMA score ≤49</td>
<td>18/29.6±13.6</td>
</tr>
</tbody>
</table>
Table 4-2. Results for the pointing dataset.

A. Correlations between predictors (r values and 95% confidence intervals) based on Pearson’s correlations. FMA=Fugl-Meyer Assessment.

<table>
<thead>
<tr>
<th></th>
<th>Trunk Displacement (95% CI)</th>
<th>Shoulder Flexion (95% CI)</th>
<th>Shoulder Horizontal Adduction (95% CI)</th>
<th>Elbow Extension (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMA</td>
<td>-0.676† (-1.13,-0.52)</td>
<td>0.509† (0.25,0.88)</td>
<td>0.107 (-0.40,0.42)</td>
<td>0.386† (0.10,0.73)</td>
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<tr>
<td>Trunk Displacement</td>
<td>(-0.80,-0.17)</td>
<td>-0.450† (-0.43,0.20)</td>
<td>0.651† (-0.65,0.05)</td>
<td>0.718†</td>
</tr>
<tr>
<td>Shoulder Flexion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder Horizontal Adduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk + Sh Fl + Sh Hor + Elb Ext</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Multiple Regression Analysis.

<table>
<thead>
<tr>
<th>Dependant Variable</th>
<th>Model</th>
<th>r²</th>
<th>Adjusted r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMA</td>
<td>Trunk Displacement</td>
<td>0.457</td>
<td>0.444</td>
</tr>
<tr>
<td></td>
<td>Shoulder Flexion (Sh Fl)</td>
<td>0.241</td>
<td>0.223</td>
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<td></td>
<td>Elbow Extension (Elb Ext)</td>
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<td></td>
<td>Shoulder Horizontal Adduction (Sh Hor)</td>
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<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Trunk + Sh Fl + Sh Hor + Elb Ext</td>
<td>0.549</td>
<td>0.503</td>
</tr>
<tr>
<td><strong>Trunk + Sh Fl + Sh Hor</strong></td>
<td></td>
<td><strong>0.546</strong></td>
<td><strong>0.512</strong></td>
</tr>
<tr>
<td><strong>Trunk + Sh Fl</strong></td>
<td></td>
<td><strong>0.510</strong></td>
<td><strong>0.486</strong></td>
</tr>
<tr>
<td>Trunk + Elb Ext + Sh Hor</td>
<td></td>
<td>0.485</td>
<td>0.446</td>
</tr>
</tbody>
</table>

C. Logistic Regression Analysis with 95% confidence intervals for odds ratio, Exp(B)

<table>
<thead>
<tr>
<th></th>
<th>Exp(B)</th>
<th>SE</th>
<th>P</th>
<th>95% CI for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Trunk</td>
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<td>0.017</td>
<td>0.016†</td>
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<tr>
<td>Elb Ext</td>
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<td>0.046</td>
<td>0.349</td>
<td>0.954</td>
</tr>
<tr>
<td>Sh Fl</td>
<td>1.024</td>
<td>0.065</td>
<td>0.715</td>
<td>0.901</td>
</tr>
<tr>
<td>Sh Hor</td>
<td>1.005</td>
<td>0.035</td>
<td>0.887</td>
<td>0.938</td>
</tr>
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</table>

Best fit models are identified in bold font. *p<0.05, †p<0.005.
Table 4-3. Results for the reach-to-grasp dataset.

A. Correlations between predictors (r values and 95% confidence intervals) based on Pearson’s correlations. FMA = Fugl-Meyer Assessment.

<table>
<thead>
<tr>
<th></th>
<th>Trunk Displacement (95% CI)</th>
<th>Shoulder Flexion (95% CI)</th>
<th>Shoulder Horizontal Adduction (95% CI)</th>
<th>Elbow Extension (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMA</td>
<td>-0.719†</td>
<td>0.563†</td>
<td>0.392†</td>
<td>0.678†</td>
</tr>
<tr>
<td></td>
<td>(-1.22,-0.60)</td>
<td>(0.32,0.94)</td>
<td>(0.11,0.73)</td>
<td>(0.50,1.12)</td>
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<tr>
<td>Trunk Displacement</td>
<td>-0.716†</td>
<td>-0.585†</td>
<td>-0.807†</td>
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<tr>
<td></td>
<td>(-1.22,-0.60)</td>
<td>(-0.99,-0.37)</td>
<td>(-1.44,-0.82)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>(0.78,1.40)</td>
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<tr>
<td>Shoulder Horizontal</td>
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<td>0.666§</td>
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<td></td>
</tr>
<tr>
<td>Trunk + Sh Fl + Sh Hor + Elb Ext</td>
<td>0.562</td>
<td>0.515</td>
<td>0.557</td>
<td>0.519</td>
</tr>
<tr>
<td>Trunk + Elb Ext</td>
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<td>0.544</td>
<td>0.521</td>
<td>0.519</td>
</tr>
<tr>
<td><strong>Trunk + Sh Hor</strong></td>
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<td>0.024</td>
<td>0.039</td>
<td>0.098</td>
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<tr>
<td>Elb Ext</td>
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<td>0.063</td>
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<td>0.069</td>
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</table>

B. Multiple Regression Analysis

<table>
<thead>
<tr>
<th>Dependant Variable</th>
<th>Model</th>
<th>r²</th>
<th>Adjusted r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMA</td>
<td><strong>Trunk Displacement (Trunk)</strong></td>
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<td>0.505</td>
</tr>
<tr>
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<td>Shoulder Flexion (Sh Fl)</td>
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<td>Elbow Extension (Elb Ext)</td>
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<td>Shoulder Horizontal Adduction (Sh Hor)</td>
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<td>0.133</td>
</tr>
<tr>
<td></td>
<td>Trunk + Sh Fl + Sh Hor + Elb Ext</td>
<td>0.562</td>
<td>0.515</td>
</tr>
<tr>
<td></td>
<td>Trunk + Sh Hor + Elb Ext</td>
<td>0.557</td>
<td>0.522</td>
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<td>Trunk + Elb Ext</td>
<td>0.544</td>
<td>0.521</td>
</tr>
<tr>
<td></td>
<td><strong>Trunk + Sh Hor</strong></td>
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<td>0.998</td>
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C. Logistic Regression Analysis with 95% confidence intervals for the odds ratio, Exp (B)

<table>
<thead>
<tr>
<th></th>
<th>Exp(B)</th>
<th>SE</th>
<th>P</th>
<th>95% CI for Exp(B)</th>
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<td></td>
<td>Lower</td>
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<tr>
<td>Trunk</td>
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<td>0.039§</td>
<td>0.908</td>
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<td>0.063</td>
<td>0.771</td>
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<td>0.086</td>
<td>0.343</td>
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<td>Sh Hor</td>
<td>0.948</td>
<td>0.069</td>
<td>0.440</td>
<td>0.829</td>
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</table>

Best fit models are identified in bold font. *p<0.05, †p<0.005.
CHAPTER 5

5.1 Preface

As seen in Chapter 3, individuals with stroke can use feedback from various sources, including videotapes, VR and robotic systems. The advantage of using these media is that they may provide precise information more consistently than individual therapists (i.e., with regard to detailed information on movement parameters). VR serves as a platform to incorporate the factors such as intensity of practice, repetition, variable- and task-specific practice, motivation and feedback identified as pertinent to improve recovery and enhance motor learning (sections 2.8 and 2.9.1).

The use of VR as mediums to provide feedback for stroke rehabilitation is gaining prominence. As seen in Chapter 3, previous study results (Jang et al., 2005, Piron et al., 2005) have shown that task practice in VEs with enhanced explicit feedback leads to recovery of motor impairment and increased activity levels (measured using motor performance kinematic outcomes of endpoint speed and movement duration along with clinical outcomes) in those with chronic upper limb hemiparesis post-stroke. However, these studies had control groups receiving no (Jang et al., 2005) or conventional treatment (Piron et al., 2005). It is still unknown if matched intensity training between a PE and a similarly designed VE leads to similar or better outcomes. In addition, it is still unclear whether training in VEs with feedback leads to improvements in motor performance through recovery (i.e. return to pre-morbid movement patterns) or use of compensations.

A VE was developed that was matched to a similar physical environment (PE) in terms of intensity and type of practice and feedback provision. This was used to address the question of whether and to what extent feedback provision through the medium of a VE results in similar or better arm motor recovery compared to a PE in individuals with chronic post-stroke upper limb hemiparesis. Kinematic and clinical assessments were used to assess the changes. Kinematic outcomes included both motor performance and movement pattern variables (whose validity was estimated in Chapter 4). Clinical assessments measured change at both impairment (FMA, RPSS) and activity (WMFT, Motor Activity Log) levels of the
ICF. Clinical assessments included previously suggested measures (section 2.6.3) that evaluate the presence of compensatory movement patterns at both levels of the ICF.
Manuscript 3: Arm-motor recovery using a virtual reality intervention in chronic stroke: randomized control trial

This manuscript was accepted for publication in the journal Neurorehabilitation and Neural Repair in April 2012, published online on July 10, 2012 and was published in print form in January 2013. According to the rules of the journal for re-use, (re-publish the whole or any part of the Contribution in a printed work written, edited or compiled by you provided reference is made to first publication by SAGE/SOCIETY) , the article has been included here with appropriate bibliographic citation

Arm Motor Recovery Using a Virtual Reality Intervention in Chronic Stroke:
Randomized Control Trial
Sandeep K. Subramanian, Christiane B. Lourenço, Gevorg Chilingaryan, Heidi Sveistrup and Mindy F. Levin
Neurorehabil Neural Repair 2013; 27:13-23. originally published online Jul 10, 2012; DOI: 10.1177/1545968312449695

The online version of this article can be found at:
http://nnr.sagepub.com/content/early/2012/07/09/1545968312449695

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Arm-motor recovery using a virtual reality intervention in chronic stroke: randomized control trial
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5.2 Abstract

Introduction: Despite interest in virtual environments (VEs) for post-stroke arm motor rehabilitation, advantages over physical (PE) training have not been established.
Objective: We compared kinematic/clinical outcomes of dose-matched upper-limb training between a 3D-VE and a PE in chronic stroke.

Methods: Participants (n=32) were randomized to 3D-VE or PE training environments. They pointed to 6 workspace targets (72 trials, 12 trials/target, randomized) for 12 sessions over 4wks with similar feedback on precision, movement speed and trunk displacement. Primary (kinematics, clinical arm-motor impairment) and secondary (activity, arm use) outcomes were compared by time (PRE, POST, follow-up, RET), training environment and impairment severity (mild, moderate-to-severe) using mixed-model ANOVAs.

Results: Endpoint speed, overall performance on a reach-to-grasp task and activity levels increased in both groups. Only participants in the VE group improved shoulder horizontal adduction at POST (9.5°) and flexion at both POST (6.3°) and RET (13°). Impairment level affected outcomes. After VE training, the mild group increased elbow extension (RET: 25.5°). The moderate-to-severe group in VE increased arm use at POST (0.5pts) and reaching ability at RET (2.2pts). The moderate-to-severe group training in PE increased reaching ability earlier (POST: 1.7pts), and both elbow extension (10.7°) and arm use (0.4pts) at RET, but these changes were accompanied by increased compensatory trunk displacement (RET: 30.2mm).

Conclusion: VE training led to more changes in the mild group and a motor recovery pattern in the moderate-to-severe group indicative of less compensation, possibly due to better use of feedback.

Clinical Trial Registration number: ACTRN12611000858998

Keywords: feedback, recovery, rehabilitation, kinematics, upper-limb
5.3 Introduction

Upper limb impairment, a frequent disabling consequence of stroke, affects participation and quality of life. Improvements in upper limb impairment can be attributed to sensorimotor learning and adaptive plasticity in the nervous system that extends well past the acute stages. A promising new rehabilitation approach uses virtual reality technology, a multisensorial experience that permits feedback-based motor learning in a computer generated virtual environment (VE). Virtual reality technology permits individualization of training environments, combining intensity, variability, specificity, motivation and interactivity of practice. These factors enhance experience-dependent neuroplasticity, influence motor learning and improve rehabilitation outcomes.

VEs can be manipulated to provide meaningful visual, auditory and haptic/tactile feedback to the learner. Feedback can be delivered as enhanced information about knowledge of results (KR) and of performance (KP). Task practice in VEs with feedback increases activation in the ipsilesional hemisphere. VEs can thus incorporate important attributes linked to maximizing post-stroke motor recovery and learning. While authors concur that using virtual reality for stroke rehabilitation is feasible, the effectiveness and added value of using this over other interventions need to be documented using rigorous research designs such as randomized control trials (RCTs).

Studies have compared virtual reality intervention effectiveness to no or conventional treatment. However, since exercise intensity is a critical factor in motor recovery, it needs to be controlled for when comparing treatment effectiveness between different training environments. We addressed the question of whether and to what extent intensity-matched training in a VE results in similar or better outcomes than training in a physical environment (PE). This was addressed by creating a VE that was equivalent to a PE in terms of type of practice, practice intensity and feedback. Training environments only differed in that the VE had an additional visual effect (target size increased to indicate a successful trial), encouraged movement in a functional context (shopping task) and included a game score for monitoring success. We investigated the effectiveness of these additional VE attributes on upper limb recovery in chronic stroke. We hypothesized that upper limb impairment, activity
and use would improve more after VE compared to PE training. Preliminary results have appeared in abstract form.\textsuperscript{18}

5.4 Methods

Participants were included in this double-blind RCT if they: 1) were between 40-80yrs; 2) sustained a single ischemic or hemorrhagic stroke 6-60mos previously; 3) scored 3-6/7 on Chedoke-McMaster Stroke Assessment\textsuperscript{19} arm subscale; 4) had no other neurological, neuromuscular/orthopaedic problems affecting the upper limb and trunk. Subjects were excluded if they had: 1) brainstem/cerebellar lesions; 2) comprehension difficulties; 3) marked apraxia, attention or visual field deficits. Subjects signed informed consent forms approved by the institutional review board of Center for Interdisciplinary Research in Rehabilitation of Greater Montreal.

Subjects were stratified at baseline by severity (Fugl-Meyer Stroke Assessment-upper limb Score; FMA ±5pts)\textsuperscript{20} and age (±5yrs) and block randomized to VE or PE. Randomization, clinical evaluations, training and data analysis were done by different individuals uninvolved with and blinded to other study aspects.

5.4.1 Intervention

Subjects in both groups (PE, VE) repetitively pointed towards six targets placed just beyond arm’s length, without physically touching the target in either environment. Earlier work by Cirstea et al.\textsuperscript{21} showed that reaching training-based improvement in movement variables (e.g., error) asymptoted only after 30-35 repetitions depending upon arm motor impairment level. This number was doubled to ensure high practice intensity. The total number, 72 trials, was divided into 3 blocks of 24, with 5min inter-block intervals. A pre-recorded verbal randomized target sequence was played back on the computer instructing subjects to point to the next target. Each training session averaged 45mins in both environments. The acquisition phase was 12 days spaced over 4wks (3 times/wk).
For both environments, subjects sat with back supported and hips and knees flexed to 90°, shoulder abducted (20°) and internally rotated, elbow slightly flexed, forearm pronated and wrist in neutral. Prior to movement, the index finger was placed ipsilaterally on a 41.5cm high platform, 10cm lateral to the hip (starting position, Fig.5-1A). This position was chosen to encourage full range shoulder and elbow movement during pointing. A research assistant seated behind the subject ensured that the arm starting position was similar before each trial during interventions and kinematic assessments. Subjects were instructed to point as fast and as accurately as possible.

5.4.2 Physical Environment

In the PE, six square (6x6 cm) numbered targets were mounted on a wooden frame and arranged in a 2-row by 3-column grid numbered 1 to 6 (Fig.5-1B) which was placed just beyond arm’s length (measured from the medial axilla to index fingertip) for each participant. This ensured that there was no contact between the finger and the target (no haptic feedback). Target collision was detected by the Computer Assisted Rehabilitation Environment (CAREN) software (Motek BV, Amsterdam) when the index fingertip approached a critical distance from the target centre defined as ±4cm³ for the initial condition (but see progression below). Grid midpoint, the centre of the CAREN-Optotrak global axis system, was aligned with the sternum at a height of 90° shoulder flexion. Targets were located in middle (T2-upper,T5-lower), ipsilateral (T3-upper,T6-lower) and contralateral (T1-upper,T4-lower) arm workspaces separated by a 20cm edge-to-edge distance (Fig. 5-1A). During practice, arm and trunk position were tracked using electromagnetic sensors (Fastrak, Colchester, VT) on the fingertip, ipsilateral acromion and mid-sternum. Positional data were used to generate feedback about movement precision, speed and trunk displacement by the CAREN software.

Feedback was provided to facilitate motor learning. It consisted of terminal (end of movement) auditory plus visual KR about movement precision and speed, and concurrent auditory KP about compensatory trunk use. Positive KR (‘ping’ sound) was delivered if movement met accuracy and speed criteria without excessive trunk displacement (≤5cm). A buzzer sounded (negative KR) if subjects were unable to point to the correct target within
allotted time. If trunk movement exceeded 5cm, a “whoosh” sound was heard (KP) regardless of whether movement was within accuracy and speed constraints. During practice, individual accuracy and speed criteria were progressed from low to high (accuracy: 4 to 1cm3 from target center; speed: 6-1s) when participants were successful ≥75% of the time.

Figure 5-1 near here

5.4.3 Virtual Environment

A 3D-VE (CAREN) simulated a supermarket scene. To provide a context for the shopping task, the VE scene initially depicted a supermarket aisle filled with products viewed from one end (Fig.5-1C). An animation sequence then simulated the participant moving through the aisle. At the end of the aisle, the scene stopped moving and participants saw six consumer products – 2 soda cans, water, juice, ice cream and peas - arranged on two shelves (Fig.5-1D). The objects on the shelves were placed at the same height in the visual field as the PE targets to avoid differences in distance perception. To further improve depth perception, the products had the same shape and size dimensions with respect to the participant’s actual hand as in the real world.

The environment was calibrated such that the VE objects appeared to be at the same distance as the PE targets, i.e., just beyond arm’s length. The virtual target grid and the hand, arm and trunk positions of the subjects were calibrated in the same CAREN-Optotak global axis system. As in the PE, the centre of the virtual grid was placed just beyond arm’s length and target collision detection was extended in the Z axis, in relation to the subject’s arm length for the ipsilateral and contralateral targets. Finger tip movement was indicated by the blue dot on the screen (Fig.5-1D). The supermarket scene was rear-projected onto a 1.5mx2m screen and viewed using stereoscopic glasses. Arm and trunk positions were tracked as for the PE. Feedback was identical to PE (no haptic feedback) with two additional features at the end of each trial: the target increased in size when the pointing movement met speed and accuracy constraints and a game score indicated the number of successful reaches. These features were intended to engender greater motivation and interaction with the environment.
5.4.4 Assessments

Clinical and kinematic assessments were done before (PRE), immediately after (POST) and at retention testing (RET), three-months after the intervention to evaluate changes at two levels of the International Classification of Functioning: Structure/Function and Activity. The primary outcome was change in arm motor impairment measured clinically and kinematically and secondary outcomes were changes in activity levels. Motivation was assessed POST-intervention only. All assessments were reliable and valid.

5.4.4.1 Clinical Assessments

Motor impairment was measured with the FMA and Reaching Performance Scale for Stroke (RPSS). The arm section of FMA \(0-66\)pts assesses movement made in- and out-of-synergy patterns, coordination, speed and reflexes. Participants were classified into two motor severity groups: mild (FMA\(\geq\)50pts; PE:n=5, VE:n=7) and moderate-to-severe (FMA\(\leq\)49pts; PE:n=11, VE:n=9). The RPSS evaluates reach-to-grasp performance to objects placed within (RPSS\_close) and beyond (RPSS\_far) arm length. Six movement components: trunk, shoulder and elbow movement, endpoint smoothness, prehension quality; are scored on 4pt scales (18pts/task). Arm motor activity was evaluated with the Wolf Motor Function Test – Functional Assessment Scale (WMFT-FAS) as the mean value of 15 tasks scored on 6pt scales. This scale was chosen over the timed portion of the WMFT since it takes movement quality into account such that tasks performed with abnormal movement patterns are scored lower. Arm use was assessed through structured interview with the Motor Activity Log Amount Scale (MAL\_AS) mean scores.

The MAL\_AS measures how much the more-impaired arm was used in 30 tasks over the previous week. Each item was scored on a 6pt scale where 0=“never used” and 5=“the same amount of use as before the stroke”. The amount scale has also been used for criterion validity measurements of upper limb use in everyday activities. Motivation levels were assessed using the 13-item self-report Intrinsic Motivation Task Evaluation Questionnaire (IM-TEQ) divided into 5 categories– interest/enjoyment, perceived competence,
value/usefulness, pressure/tension and effort/importance. Items were scored on 7pt scales where 1=“not at all true”, 4=“somewhat true” and 7=“very true”.

5.4.4.2 Kinematic Data Acquisition and Analysis

Arm and trunk kinematics were recorded from 25 pointing trials each towards the lower middle (LM) target and upper ipsilateral (UI) target (T1 or T3 depending on the more-affected side; Fig 5-1A). Target positions required different combinations of joint excursions to reach into different parts of the workspace. Elbow extension was combined with a greater range of shoulder horizontal adduction for LM and with a greater range of shoulder flexion for UI, although reaches to both targets required all three movements. Outcomes were measured at two levels: motor performance (endpoint velocity, precision) and movement pattern (joint angular excursions, trunk displacement). Movements were recorded with Optotrak 3020 (Northern Digital Corp., 100Hz, 6s, Waterloo, Canada). Six infrared-emitting diodes (IREDs) were placed on the fingertip (endpoint), wrist styloid, lateral epicondyle, ipsilateral and contralateral acromions and mid-sternum.

For motor performance outcomes, endpoint tangential velocity was computed from the velocity vector amplitude obtained from the finger marker. Movement beginning and end were defined as times at which velocity exceeded and remained above or fell and remained below 10% of peak velocity. Precision was computed as the root mean square error of the absolute distance between the final endpoint position and target centre.

For movement pattern outcomes, three joint angles were computed at the end of the movement – elbow extension, shoulder horizontal adduction and flexion based on vectors formed by IRED pairs. For elbow movement, vectors were defined between wrist and elbow and elbow and ipsilateral shoulder IREDs (full extension=180°). Shoulder horizontal adduction was measured as the angle between vectors formed by ipsilateral shoulder-elbow IREDs and a line traced by the contralateral-ipsilateral shoulder IREDs projected horizontally (fully abduction=0°). For shoulder flexion, vectors were defined between elbow and ipsilateral shoulder IREDs and the vertical through the ipsilateral shoulder IRED (arm...
alongside body=0°). Trunk movement was measured as forward sagittal displacement (mm) of the sternal IRED.

5.4.5 Statistical Analysis

Descriptive statistics highlighted main demographic characteristics and motivation levels. Distributions were inspected to verify normality assumptions and to identify potential outliers and influential observations. Homogeneity of variance assumptions were assessed with Levene's tests. Demographic and initial characteristics were compared using independent t-tests. Mixed-model analyses of variance (ANOVAs) with repeated measures and pre-planned least significant difference post-hoc tests compared kinematics and clinical outcomes (SPSS v17, SAS v9.2). Models included 1 within-subject (time: PRE, POST, RET) and 2 between-subject factors (environment: PE, VE; severity: mild, moderate to severe). Responses on each category of the motivation questionnaire were compared between groups using Chi-Squared ($\chi^2$) tests. Significance levels were set at $\alpha=0.05$ and effect sizes (ES) estimated using standard response means.35

5.5 Results

Thirty-two subjects completed all PRE and POST assessments and 25 subjects (PE=13, VE=12) completed RET (see CONSORT statement). Participants in both environments were similar in age, gender, side affected, duration post-stroke, type of stroke, clinical scores (Table 1) and initial kinematic outcomes. All participants reported being comfortable throughout the training and did not experience any side-effects. There were overall effects of time (Fig.5-2), training environment (Fig.5-3) and severity group (Fig.5-4).

Table 5-1, CONSORT_Statement_near_here

5.5.1 Effect of Time

Overall, participants increased endpoint velocity ($F_{(2,49)}=3.39, p<0.05$) and shoulder horizontal adduction (ShHor) range ($F_{(2,49)}=5.18, p<0.01$) at both POST (Post-hoc tests: Vel: 311mm/s, $t_{49}=2.24, p<0.05$; ShHor: 6°, $t_{49}=2.92, p<0.01$) and RET phases (Vel: 334mm/s,
For the LM target, endpoint velocity increased ($F_{(2,49)}=3.05$, $p<0.05$) at POST only (411 mm/s, $t_{49}=2.51$, $p<0.05$, Fig. 5-2C).

For clinical outcomes, participants increased elbow extension during a reach-to-grasp task (RPSSelbow close target: $F_{(2,51)}=4.22$, $p<0.02$; far target: $F_{(2,51)}=3.23$, $p<0.05$) and WMFT scores ($F_{(2,51)}=3.63$, $p<0.05$). For the reaching scale, the greatest increase (13%) occurred at RET for the close target (Post-hoc: $t_{51}=3.90$, $p<0.01$, Fig. 5-2D) whereas the whole group improved by 10% on the RPSS scale from POST to RET for the far target (Fig. 5-2E). The mean increase in WMFT at POST was 0.22 pts (Post-hoc: $t_{51}=2.31$, $p<0.05$; Fig. 5-2F), which was retained (RET: 0.23, $t_{51}=2.30$, $p<0.05$).

Figure 5-2, 5-3_near_here

5.5.2 Effect of Training Environment and Environment by Time

While there was no overall effect of environment, environment by time interactions were found for two kinematic variables. Shoulder horizontal adduction range (ShHor: $F_{(2,49)}=3.52$, $p<0.05$) for the LM target increased more in VE ($9^\circ$) compared to PE ($2^\circ$) at POST ($t_{15}=4.019$, $p<0.01$, ES=1.00; Fig. 5-3A). Shoulder flexion range (ShFl: $F_{(2,49)}=3.89$, $p<0.05$) for the UI target increased in VE at both POST ($6^\circ$, $t_{49}=2.04$, $p<0.05$; ES=0.71) and RET ($13^\circ$, $t_{49}=4.03$, $p<0.01$; ES=0.79; Fig. 5-3D).

5.5.3 Effect of Impairment Severity

Among kinematic variables, elbow extension ($F_{(2,49)}=4.86$, $p<0.05$) and trunk displacement ($F_{(2,47)}=3.19$, $p<0.05$) changed only for movements to the UI target. Elbow extension range changed differently in each group at RET. In the moderate-to-severe group, extension increased by $11^\circ$ ($t_{49}=2.21$, $p<0.05$, ES=0.74, Fig. 5-4A) in PE, but this was accompanied by a concomitant increase in trunk displacement (30 mm, $t_{47}=2.52$, $p<0.05$, ES=0.47; Fig. 5-4C). For the mild group, extension range increased only in VE ($24^\circ$, $t_{49}=3.53$, $p<0.01$, ES=1.13; Fig. 5-4B).
For clinical measures, performance on the reach-to-grasp task (RPSSclose total, $F_{(2,51)}$ =3.25, p<0.05; Fig. 4E) and amount of arm use (MAL-AS $F_{(2,53)}$=4.14, p<0.05) improved in the moderate-to-severe group. Those training in VE improved MAL-AS scores at POST by 0.5pts ($t_{53}$=1.97, p<0.05, ES=0.63; Fig.5-4G) and RPSSclose total scores at RET by 2.2pts ($t_{51}$=2.38, p<0.05, ES=0.47, Fig.5-4E). Those training in PE improved RPSSclose total scores at POST by 1.7pts ($t_{51}$=2.04, p<0.05, ES=0.64, Fig. 5-4E) and MAL-AS scores at RET by 0.4pts ($t_{53}$=2.05, p<0.05, ES=1.01; Fig.5-4G).

In the mild group, while no changes were noted in VE, those training in PE decreased MAL-AS scores at RET by 0.9pts ($t_{53}$=-2.97, p<0.05, ES=-0.81, Fig.5-4H).

5.5.4 Motivation Questionnaire Results

IM-TEQ scores indicated that participants enjoyed training in the two environments equally and considered the experiences useful and important. Participants felt more competent practicing movements in PE compared to VE ($\chi^2$=6.77, p < 0.01; PE:100% scored ≥5; VE:53% scored ≥5). However, participants in VE reported feeling less stress in response to the question “I was anxious while working on this task” compared to the PE ($\chi^2$=5.24, p<0.05; PE:40% scored ≤3, VE:75% scored ≤3). In addition, of these 75%, 50% scored one, indicating no stress.

5.6 Discussion

Effects of practice in VE compared to PE on arm motor impairment and activity levels were addressed. Training environments were matched by practice intensity and frequency and type of feedback delivered. They only differed in that the VE provided a more colorful interface, additional visual feedback about target acquisition and a game score. Following practice, both groups improved arm motor impairment measures (increased endpoint velocity: both targets, shoulder horizontal adduction: LM target only) and clinical impairment scores (RPSSelbow subscales) and activity levels (WMFT-FAS).
Improvements in both groups over time can be attributed to practice intensity. Repetition intensity (72 trials/session) was greater than twice that used (32) in typical stroke rehabilitation sessions. Studies have shown better motor outcomes with more intensive practice regardless of the treatment medium (e.g., robotics versus conventional therapy). Potential mechanisms of better outcomes with intensive training include higher levels of neurotrophic factors like brain-derived neurotrophic factor (BDNF) known to contribute to motor learning after stroke.

The number of trials (n=72) was considered “intensive” based on previous results, which indicated that learning asymptoted after a larger number of trials (average 36) compared to controls performing the same task (average 15). Generally, motor learning studies can include as many as 200-800 repetitions. A recent study showed that subjects with stroke could perform an average of 332 repetitions of tasks involving graded movements of reaching and grasping, manipulating and releasing objects in a one-hour session without fatigue. However, as in our previous study, while subjects showed behavioral changes, concomitant neuronal plasticity changes were not assessed. However, our results allow us to conclude that at least 72 repetitions per session may be necessary for the nervous system to find motor solutions based on redundancy leading to improvements in movement patterns at the behavioral level.

Since the effect of practice intensity has been well-documented, we intentionally controlled for this factor as well for the type and frequency of feedback. Our goal was to identify whether the additional attributes of VE (motivation, interactivity) offered any advantage to motor learning in stroke. Motivation and interactivity of the VE were enhanced by the added visual effects and game score that enabled subjects to track success. Despite the fact that both groups had the same practice intensity and feedback, the VE group had better target-specific changes in ranges of shoulder horizontal adduction for LM and shoulder flexion for UI targets. Greater ranges of shoulder horizontal adduction and flexion result in successful pointing to LM and UI targets respectively because of their placement in the arm workspace. Similar results were reported by Mirelman et al., for the lower limb in a single-blind RCT. Compared to ankle training using a robotic device, dose-matched practice on a robotic device
coupled with a VE resulted in greater improvements in gait velocity and walking distance (on the six minute walk test) and number of steps in the community (measured using accelerometers). Changes were retained at follow-up. Combined with our findings, this provides encouraging evidence of the advantage of using VEs in upper and lower limb rehabilitation post-stroke.

Recent systematic reviews have stressed the importance of providing salient feedback about arm movement quality for improved motor learning\textsuperscript{42,43} and studies have shown that appropriate feedback about movement performance provided by a therapist\textsuperscript{4} or virtual teacher\textsuperscript{5} facilitates learning and motivates subjects to improve further. We provided feedback about both motor performance (KR–velocity, precision) and movement patterns (KP–trunk displacement). Both groups used KR similarly as indicated by the overall increase in velocity (Fig. 5-3A,C). However, KP may have been used differently in each environment. When delivered in VE, KP resulted in more adaptive outcomes in the mild subgroup as increased elbow extension without compensatory trunk movement. Conversely, when delivered in PE, an improvement in elbow extension was accompanied by increased trunk displacement in the moderate-to-severe group, considered maladaptive or compensatory.\textsuperscript{44}

The finding that the VE group improved motor performance without using excessive trunk displacement suggests that VE may be a more effective medium for providing feedback, especially trunk movement KP. In VE, it is possible that subjects may have been more aware that successful task performance depended upon the movement pattern used and this may have engaged subjects to use more cognitive effort\textsuperscript{45} and better motor planning to increase the essential ranges of arm motion required for successful pointing. Indeed, previous research involving use of VEs in subjects with chronic stroke\textsuperscript{46} has reported better performance in the trail-making test, an assessment of task switching and visual attention. The lower stress levels felt by subjects in this environment may have added to their enjoyment and ability to concentrate on the movement patterns used. In contrast, the higher levels of perceived competence of the PE group may have led this group to believe that they were already proficient at performing the task so that they placed less importance on using more optimal movement patterns.
After practice in both environments, all participants accomplished tasks better with the impaired arm (WMFT) and used their arm more in everyday activities (MAL-AS). The improvement in the MAL-AS reached a meaningful clinical significance level (change of 0.5\textsuperscript{32}) however, only in the moderate-to-severe subgroup training in the VE. This suggests that task practice in VE was meaningful and improved performance of everyday life activities.

The moderate-to-severe group changed in both kinematic and clinical outcomes compared to the mild group which only increased the range of elbow extension. The lack of change in clinical outcome measures in the mild group may partly be attributable to ceiling effects. Clinical outcome measures may also not particularly focus on identifying movement patterns changes in movement patterns. In a previous study, upper limb movement pattern changes in upper limb movement patterns of 33-300\% were not reflected in Fugl-Meyer scores in a group of subjects with mild post-stroke hemiparesis (FMA≥50)\textsuperscript{22}. Thus, existing clinical measures may not be sensitive enough to detect deficits identified using kinematic analysis, especially in subjects with mild hemiparesis. However, this will have to be examined separately for each outcome measure.

5.7 Limitations

Although we found significant between-group differences, these were small for most outcomes. One reason could be that the VE used in this study, though ecologically valid, was especially designed to differ from the PE only in terms of the feedback delivery medium. This was intentionally done to isolate and compare only the effects of the feedback delivery medium on changes in arm motor impairment and activity levels. The differences found between environments in some aspects of motivation, cannot be attributed specifically to different parts of the VE (i.e., opening scene animation vs interactive pointing scene). Although we found changes on the RPSS total score and elbow subscale, the absence of an established minimal detectable change or the minimum clinically importance difference value limits a broader interpretation of these results. Aside from a few items on the MAL, we did not assess participation or quality of life. Inclusion of these measures in future studies will provide more information about the effects of VE training on these domains.
5.8 Implications for neurorehabilitation

VEs that are custom designed according to the needs of the individual have the potential to increase patient engagement by making therapy more fun and interesting. At the same time, custom designed applications allow clinicians to adapt the levels of difficulty and activities according to patient preferences and rehabilitation goals. The small but statistically significant improvements with moderate to large effect sizes on some motor outcomes in the VE compared to the PE group, when training was matched in intensity, suggests an additional value of using a VE as a training environment to enhance arm-motor recovery, especially in chronic stage post-stroke. This supports the use of VE as a means to increase the amount of rehabilitation specific exercise time – specifically for targeted upper limb tasks such as that used in this study.

5.9 Conclusion

Dose-matched practice in VE resulted in arm motor recovery at the behavioral level\textsuperscript{47} compared to PE in chronic post-stroke subjects, that might be considered more-adaptive. This may be attributable to more efficient use of feedback in VE. Our results corroborate earlier findings that even patients with mild levels of upper limb hemiparesis have motor deficits that are not always identifiable using common clinical measures\textsuperscript{22,44} and that they have the potential for further motor recovery (e.g., elbow extension range) given appropriate task practice and feedback.

5.10 Acknowledgements

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Rhona Guberek and Christian Beaudoin for their assistance with patient recruitment and technical support.

5.11 References


Figures

CONSORT Statement

Assessed for eligibility (n=761)

Excluded (n=727)
  • Not meeting inclusion criteria (n=354)
  • Declined to participate (n=331)
  • Other reasons (n=8)

Randomized (n=34)

18 allocated to PE intervention
  16 received allocated intervention
    Two did not receive allocated intervention (one subject injured himself outside the experiment and the other went back to work)

16 allocated to VE intervention
  16 received allocated intervention

Three lost to follow-up (RET)
  (Two moved away from Montreal and one had shoulder pain)

Four lost to follow-up (RET)
  (One subject started therapy; two refused to come and one had medical complications)

16 included in analysis (POST)
  13 included in analysis (RET)
  Three excluded from analysis (RET)

16 included in analysis (POST)
  12 included in analysis (RET)
  Four excluded from analysis (RET)
A) Subject starting position in relation to the targets. Target 5 was the Lower Middle (LM) and Target 3 was the Upper Ipsilateral (UI) target for right arm movements; B) Physical training environment (PE) with six numbered targets; Initial (C) and final (D) virtual training environment (VE) – three dimensional scene of six consumer products on a supermarket shelf projected on a large screen
Post-hoc test results for the overall effects of time from PRE to POST and PRE to RET for (A) endpoint velocity and (B) shoulder horizontal adduction for Lower Middle Target, (C) endpoint velocity for Upper Ipsilateral Target, (D,E) Reaching Performance Scale for Stroke elbow subscale scores for close (D) and far (E) targets and Wolf Motor Function Test-Functional Assessment Scale mean scores (F). Data are overall mean (SD) values across both groups and training environments. Asterisks indicate significance. *p<0.05, **p<0.01
Figure 5-3. Effects of training environment on outcomes

Mean (SD) values for Shoulder Horizontal Adduction and Shoulder Flexion for Lower Middle target (A, C) and Upper Ipsilateral target (B, D) for the two groups training either in PE or VE at PRE, POST and RET. Asterisks indicate significance. All significance refers only to the VE. *p<0.05, **p<0.01
Figure 5-4. Effects of impairment severity on outcomes.

Mean (SD) values for Elbow extension (A, B) and Trunk displacement (C, D) for pointing movements to Upper Ipsilateral target, Reaching Performance Scale for Stroke - close target total scores (E, F) and Motor Activity Log – Amount Scale (G, H) scores for the moderate-to-severe and mild subgroups training either in PE or VE at PRE, POST and RET. Asterisks indicate significance. Significance for the PE is indicated above the symbol and for VE below the symbol. *p<0.05, **p<0.01
Table 5-1. Demographic and clinical characteristics of study participants at baseline

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Whole Group</th>
<th>Mild Subgroup (FMA ≥50/66)</th>
<th>Moderate-to-severe Subgroup (FMA ≤49/66)</th>
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<td>PE (n=16)</td>
<td>VE (n=16)</td>
<td>PE (n=5)</td>
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<td>Gender, n (%)</td>
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<td>12 (75%)</td>
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<tr>
<td>Female</td>
<td>5 (31.3%)</td>
<td>4 (25%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Paretic side, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>7 (43.8%)</td>
<td>8 (50%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Right</td>
<td>9 (56.3%)</td>
<td>8 (50%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Age (yrs), mean (SD)</td>
<td>60.0 (11.0)</td>
<td>62.0 (9.7)</td>
<td>60.6 (12.4)</td>
</tr>
<tr>
<td>Time since onset (yrs), mean (SD)</td>
<td>3.0 (1.9)</td>
<td>3.7 (2.2)</td>
<td>3.4 (1.8)</td>
</tr>
<tr>
<td>Lesion information (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical (MCA, Frontal)</td>
<td>8</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Subcortical</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical (MCA, Frontal)</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Subcortical</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No information</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Clinical data</td>
<td>Mean (SD)</td>
<td>Whole Group</td>
<td>Mild Subgroup (FMA ≥50/66)</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>PE (n=16)</td>
<td>VE (n=16)</td>
<td>PE (n=5)</td>
</tr>
<tr>
<td>FMA score</td>
<td>42.1 (15.1)</td>
<td>41.1 (17.7)</td>
<td>58.8 (4.4)</td>
</tr>
<tr>
<td>RPSS Close target</td>
<td>10.6 (5.9)</td>
<td>10.6 (6.8)</td>
<td>16 (1)</td>
</tr>
<tr>
<td>RPSS Close target Elbow</td>
<td>1.8 (1.2)</td>
<td>1.7 (1.2)</td>
<td>2.6 (0.5)</td>
</tr>
<tr>
<td>RPSS Far target</td>
<td>10.1 (6.4)</td>
<td>9.5 (7.2)</td>
<td>16 (2.7)</td>
</tr>
<tr>
<td>RPSS Far target Elbow</td>
<td>1.8 (1.2)</td>
<td>1.7 (1.3)</td>
<td>2.6 (0.5)</td>
</tr>
<tr>
<td>WMFT</td>
<td>2.8 (1)</td>
<td>2.7 (1.3)</td>
<td>3.8 (0.6)</td>
</tr>
<tr>
<td>MAL-AS</td>
<td>2.9 (1)</td>
<td>2.7 (1.1)</td>
<td>3.2 (1.1)</td>
</tr>
</tbody>
</table>

Severity cut-offs were based on Fugl-Meyer Assessment (FMA)\textsuperscript{20,22} scores; PE – Physical Environment; VE – Virtual Environment, MCA- Middle Cerebral Artery, RPSS – Reaching Performance Scale in Stroke, WMFT – Wolf Motor Function Test, MAL-AS – Motor Activity Log, Amount Scale.
CHAPTER 6

6.1 Preface

As discussed previously in Sections 2.4.5, 2.5.3 and 2.5.4, cognitive impairments seen after stroke in the domains of attention, verbal and visuospatial memory, mental flexibility, problem solving, visuoconstruction and visuoperception and depression influence motor learning and recovery (measured using clinical outcomes). As noted in Chapter 3, cognitive deficits are also associated with movement performance outcomes. For example, when training in PE, better motor performance outcomes of accuracy for upper limb movements (drawing a triangle within a rectangular frame), movement smoothness and variability in endpoint velocity were related to fewer deficits in memory, problem solving and mental flexibility in people with stroke.

Similarly, better performance outcomes of faster response times and greater success rates while practicing upper limb tasks (games involving repetitions of upper limb movements) in a 2D immersive VE were related to fewer deficits in attention and cognitive flexibility. Thus, studies have addressed the relationship between cognitive deficits post-stroke and motor learning resulting in improvements in motor performance outcomes. However, the association between cognitive impairments post-stroke and learning and recovery of movement pattern outcomes is unknown, especially in VEs, as mentioned in Section 2.9.5. In addition, guidelines about the minimum cognitive abilities required for different types of feedback delivery for motor learning need to be established for better individualized treatment prescription.

The question of whether and to what extent cognitive impairments in the chronic stage post-stroke are associated with the use of feedback to learn and recover upper limb motor performance and movement pattern variables was addressed in the manuscript included in chapter 6. Changes in variables on which KR (movement speed) and KP (trunk displacement) feedback was provided were considered for the multiple regression analyses. In addition, changes in the movement pattern outcomes of elbow extension, shoulder horizontal adduction and shoulder flexion, found in the RCT (Chapter 5) were also considered. Scores on neuropsychological tests assessing the domains of attention, verbal and visuospatial memory, visuoperception and visuoconstruction, mental flexibility and problem solving (Cirstea et al.,
2006) were used as predictors in the multiple regression analyses to answer the question in addition to depression scores.
The role of cognitive status on the ability to use feedback for arm motor recovery in chronic stroke - a secondary analysis

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Key words: rehabilitation, kinematics, upper-limb, depression, virtual reality

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6.2 Abstract

Background: Feedback provision during training is an essential component of motor learning that improves upper limb motor recovery in patients with stroke. Along with sensorimotor impairments, individuals post-stroke have cognitive deficits (depression, memory, attention, visuoperception, mental flexibility and problem-solving) which can influence motor learning. However, few studies have identified whether cognitive impairments limit the ability to use feedback for motor recovery.

Objective: To evaluate whether and to what extent cognitive deficits are associated with the ability to use feedback for upper limb motor learning and recovery in post-stroke patients.

Methods: Participants (n=24) practiced pointing movements to 6 targets in a random sequence 72 times/session for 4wks (12trials/target; 3sessions/wk) either in a physical (PE) or virtual environment (VE). Feedback about movement speed (knowledge of results) and trunk displacement (knowledge of performance) was provided on each trial. Movement kinematics (endpoint speed, trunk displacement, elbow extension (Elb), shoulder horizontal adduction (ShHor) and flexion (ShFl) movements) were measured before (PRE), immediately after (POST) and 3-months after (RET) practice. Depression and cognitive functioning were also assessed only at PRE. Repeated measures ANOVAs analyzed changes in kinematic outcomes. Correlation analysis assessed the relationships between kinematic outcomes within each training environment and cognitive scores. Multiple regression analyses estimated the strength of the associated between changes in kinematics at POST and RET from PRE (dependant variables) and cognitive test scores (predictors).

Results: Participants training in the VE tended to make faster movements and had greater improvements in kinematic measures (increased Elb, ShHor and ShFl ranges and less trunk displacement) compared to the PE group. VE group improvements correlated with memory, problem solving and perceptual abilities. Changes in the PE group were related to memory, attention and problem solving ability. Individuals who had fewer deficits in memory, cognitive flexibility, visuoperception ability and lower depression levels made greater improvements in
kinematics immediately after training (POST). Kinematic improvements were retained (RET) better in those who had higher memory scores, visuoperception ability and lower depression levels.

Conclusion: Deficits in memory, attention, problem solving ability and visual perception ability were associated with the ability to use feedback for motor learning in addition to depression. Presence of mood and cognitive deficits influences the ability to use feedback for motor recovery and learning. Information about cognitive deficits can help clinicians to select appropriate interventions to maximize arm motor recovery post-stroke.
6.3 Introduction

Stroke contributes significantly to the incidence of motor, sensory and cognitive impairments. Functional recovery from stroke extends well into the chronic stages and involves (re)learning of new movements (Cirstea & Levin, 2007; Subramanian, Lourenco, Chilingaryan, Sveistrup, & Levin, 2013). Continued functional improvement can be attributed to adaptive plasticity in the remaining cortical and subcortical brain tissue (Nudo, 2003; Warraich & Kleim, 2010). Adaptive plasticity mechanisms are thought to be engaged by rehabilitation interventions that focus on motor learning principles.

Motor learning involves a relatively permanent change in the capacity to make movements associated with practice or experience (Schmidt & Lee, 2011). Factors related to experience-dependent adaptive plasticity that have been identified as pertinent to optimize post-stroke motor recovery and learning include practice intensity, variable- and task-specific practice, motivation, the practice environment and feedback (Kleim & Jones, 2008; Levin, Sveistrup, & Subramanian, 2010).

Upper limb recovery after stroke is generally measured using clinical outcome measures. However, with the use of clinical outcome measures, the focus is often on task achievement and not on how the task was completed. This potentially confounds the interpretation of results as it is unclear whether recovery or compensation has occurred in terms of how the task was performed. Motor recovery has been defined as the ability to perform a movement in the same manner as before stroke while compensation refers to the ability to perform the movement in a manner different from before stroke (i.e., use of additional degrees of freedom, use of different end effectors; Levin et al., 2009a). Efforts at upper limb rehabilitation must focus primarily on motor recovery to channel or drive neuroplasticity towards re-organization that results in better long-term motor outcomes (Krakauer et al., 2012; Alaverdashvili et al., 2008).

Information on how a movement is performed can be obtained primarily with the use of kinematic analysis. Movements can be broadly described at two levels using kinematic analysis: motor performance (describing the results of the movements; measures of error, smoothness, movement time and velocity) and movement patterns (describing how the movement was
performed using measures of trunk displacement and joint ranges of motion, interjoint-co-
ordination).

Long-lasting functional recovery and changes in adaptive plasticity (i.e. increased growth of
basilar dendrites) with intense training was observed in rats housed in environments that
provided enriched physical and social stimulation/interaction compared to those in standard
housing (Biernaskie & Corbett, 2001). Virtual reality (VR) environments can provide enriched
environments for treatment delivery for individuals post-stroke (Bach-y-Rita et al., 2002;
Murphy & Corbett, 2009; Levin, 2011).

VR is a multisensory experience in which a person is immersed and can interact with custom
designed computer generated two- (2D) and three-dimensional (3D) virtual environments (VEs;
Schultheis, Himelstein, & Rizzo, 2002), affording high levels of control over individual practice
parameters. VEs can be designed to include novel interactive games involving variable and
intensive task specific practice to motivate subjects. This can serve to limit fatigue and loss of
enthusiasm as well as to improve co-operation, factors that have been known to influence
participation in rehabilitation interventions and recovery (Lang et al., 2009). VEs thus serve as
platforms to incorporate factors essential for experience-dependant plasticity for motor learning
and recovery of the upper limb.

Feedback can be incorporated in VEs in the form of knowledge of results (KR) and of
performance (KP; Subramanian, Knaut, Beaudoin, McFadyen, Feldman, & Levin, 2007). Task
practice in VEs with feedback is known to increases activation in the ipsilesional hemisphere
(Jang et al., 2005; Merians, Tunik, & Adamovich, 2009) and promotes better motor learning
outcomes in subjects with chronic stroke.

Motor learning and recovery of endpoint performance variables in people with chronic stroke are
influenced by cognitive impairments. In the chronic stage of stroke, these impairments are often
present in the domains of attention, memory, problem solving, cognitive flexibility and
visuoperceptual and visuoconstructional skills (Saxena, Ng, Koh, Yong, & Fong, 2007;
Tatemichi et al., 1994). Sustained and divided attention functions were found to be impaired in
31% and 44% respectively in a sample of 48 individuals with stroke (Hyndman and Ashburn,
2003). Prevalence of short-term and visual memory deficits was found to be 8.5%, while deficits
in executive functioning (cognitive flexibility, motor planning and problem solving) was 13.5% (sample size = 111; Nys, Van Zandvoort, De Kort, Jansen, Van der Worp, Kappelle, & De Haan, 2005). In the same study, visuospatial functioning deficits were prevalent in about 9% of people with stroke, especially in visual perception and constructional abilities. In addition to cognitive impairments, subjects with chronic post-stroke hemiparesis also have depression. At 6 months post-stroke the prevalence of depression was found to be 34% (total sample of 104 subjects) and decreased to about 21% (sample size = 106) at 2 years post-stroke (Whyte & Mulsant, 2002).

For example, in people with stroke training in a PE, better motor performance outcomes for upper limb movements (drawing a triangle within a rectangular frame) or reaching tasks were related to fewer deficits in memory, problem solving and cognitive flexibility (Cirstea, Ptito, & Levin, 2006; Dancause, Ptito, & Levin, 2002; Platz, Denzler, Kaden, & Mauritz, 1994). Similarly, in a 2D interactive therapeutic VE, better success rates and response times for upper limb tasks in activities involving repetitions of upper limb movements were related to fewer deficits in cognitive flexibility and attention respectively (Kizony, Katz, & Weiss, 2004).

However, the relationship between cognitive impairments post-stroke and learning and recovery of movement pattern outcomes, especially in VEs is unknown. In particular, guidelines about the cognitive abilities needed by individuals to benefit from the type of feedback delivered in VEs for motor learning need to be established for better individualized treatment prescription (Fluet & Deutsch, 2013). We addressed the objective of whether and to what extent cognitive impairments in people with chronic stroke are associated with the use of feedback to learn and recover upper limb motor performance and movement pattern variables.

6.4 Methods

The study was designed as a randomized controlled trial. Participants were included if they i) were aged between 40 and 80 yrs; ii) sustained a single ischemic or hemorrhagic stroke 6 to 60 mos previously, iii) scored 3 – 6/7 on the Chedoke-McMaster Stroke Assessment arm subscale (Gowland et al., 1993), and iv) had no other neurologic or orthopedic problems affecting the upper limb and trunk. Individuals were excluded if they had i) brainstem/cerebellar lesions; ii) comprehension difficulties and iii) marked apraxia or visual field deficits. Participants signed
informed consent forms approved by the institutional review boards of the Center for Interdisciplinary Research in Rehabilitation of Greater Montreal and the Montreal Neurological Institute (MNI). These participants were amongst those who had previously participated in our earlier study (Subramanian et al., 2013).

Participants were stratified at baseline by severity (Fugl-Meyer Stroke Assessment Upper Limb (FMA) score ±5 pts; Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975) and age (±5 yrs) and block randomized to VE or PE training groups. Randomization, clinical and neuropsychological evaluations, training, and data analysis were done by different individuals who were not involved and blinded to other study aspects. Clinical and kinematic assessments along with training were carried out at the Sensorimotor Control and Rehabilitation lab at the Jewish Rehabilitation Hospital and neurocognitive evaluations were done at the MNI.

Subjects in both groups (PE and VE) practiced repetitive pointing movements towards six targets placed just beyond their arm’s length. A computer-generated auditory signal indicated each target in the random sequence of 72 trials. Earlier work (Cirstea, Ptito, & Levin, 2003) demonstrated that improvement in movement variables (e.g., movement speed) asymptoted only after an average of 30-35 repetitions depending upon arm-motor impairment level. This number was doubled to ensure practice of adequate intensity. Trials were divided into 3 blocks of 24 each, with 5-minute intervals between blocks. The acquisition phase duration was 12 days spaced over 4 wks (3 times/wk).

The starting position was the same as our earlier study (Subramanian et al. 2013). For both environments, subjects sat with their back supported and their hips and knees flexed to 90°, shoulder abducted (20°) and internally rotated, elbow slightly flexed, forearm pronated and wrist in neutral. Prior to movement, the index finger was placed ipsilaterally on a 41.5cm high platform, 10cm lateral to the hip. This position was chosen to encourage full range shoulder and elbow movement during pointing. Subjects were instructed to point as fast and as accurately as possible.
6.4.1 Physical Environment

In the PE, six square (6x6 cm) numbered targets were mounted on a wooden frame and arranged in a 2-row by 3-column grid numbered 1 to 6 (Fig. 6-1A). The grid’s midpoint was aligned with the sternal notch and placed at a height of 90° shoulder flexion. Targets were located in the middle (T2-upper, T5-lower), ipsilateral (T3-upper, T6-lower) and contralateral (T1-upper, T4-lower) arm workspaces separated by a center-to-center distance of 26 cm. During task practice, arm and trunk position were tracked using three electromagnetic sensors (Fastrak, Cochester, VT) placed on the index fingertip, anterior acromion (ipsilateral shoulder) and mid-sternum. Positional data were used to generate feedback about movement precision, speed and trunk displacement by the Computer Assisted Rehabilitation Environment (CAREN) software (Motek BV, Amsterdam).

6.4.2 Virtual Environment

A 3D VE (CAREN system) simulated a supermarket scene with six consumer products – soda cans, water, juice, ice cream, peas - arranged on two shelves (Fig. 6-1B). The VE scene had the same dimensions and visual array as the PE. The VE was rear-projected onto a large 2m long x 1.5m high screen and viewed using polarized glasses to create a stereoscopic effect. Arm and trunk position were tracked using the same system as PE. The hand endpoint position (obtained from the index marker) was represented in the scene by a blue dot. Feedback was identical to that used for the PE. The VE had two additional features compared to the PE: the target appearance changed when movement met speed and accuracy criteria (see below) and a game score indicated the number of successful reaches. This feature was intended to engender greater motivation and interaction with the environment.

6.4.3 Feedback

Feedback was provided to facilitate motor learning in the form of terminal auditory plus visual KR about movement speed and precision and concurrent auditory KP about use of compensatory trunk movement. Positive KR in the form of a ‘ping’ sound was heard if the movement met
speed and accuracy criteria and excessive trunk displacement was not used. If subjects were not able to point to the correct target within the allotted time, a buzzer sounded (negative KR). In addition, if trunk movement exceeded 5cm, a “whoosh” sound was heard (KP) regardless of whether the movement met speed and accuracy constraints. The initial speed constraint was set during the practice trials according to the subject’s baseline impairment level. The task difficulty was increased according to Fitt’s law (Fitt, 1954) by manipulating the speed constraint from low to high difficulty: When the subject succeeded in hitting the target at least 75% of the time, the speed constraint was increased: for example, movement time was decreased in 2 s steps between 6s to 2s.

6.4.4 Assessments

Neuropsychological and kinematic assessments were carried out. Neuropsychological functioning was only assessed before the intervention (PRE), while kinematics were assessed at PRE, immediately after (POST), and at retention testing (RET), 3 months after the intervention, to evaluate changes in motor performance and movement pattern variables.

6.4.4.1 Neuropsychological Assessment

All participants underwent a comprehensive neuropsychological examination by a trained psychologist. Cognitive domains assessed included: 1) attention (Stroop Test, Stroop, 1935); 2) learning and memory (Weschler Memory Scale Stories, WMSS. Wechsler, 1955; Rey Auditory Verbal Learning Test, RAVLT, Rey, 1964; and Rey Osterrith Complex Figure, ROCF, Osterrith, 1944); 3) mental flexibility (Wisconsin Card Sorting Test, WCST, Berg, 1948); 4) planning/problem-solving abilities (Tower of London, TOL, Shallice, 1982); 5) visuoconstruction and visuoperception (ROCF copy) and 6) depression (Beck Depression Inventory, BDI- II; Beck, Steer, Ball, & Ranieri, 1996). For each test, a Z score was calculated by selecting a representative variable from each test: 1) Stroop (color word interference score; Stroop interference); 2) WMSS: 90-minute delayed recall, WMS – DR; RAVLT: 5 trials, 30-minute delayed recall of 15-word list, RAVLT- DR, ROCF 40-minute delayed recall – ROCF -
6.4.4.2 Kinematic Assessments

Arm and trunk kinematics were recorded in a Test Task performed at PRE, POST and RET. The Test Task consisted of 25 pointing trials each towards the lower middle (LM) target and upper ipsilateral (UI) target (T1 or T3 depending on the more-affected side; Fig 6-1A). These target positions were chosen because they required different combinations of joint excursions to reach into different parts of the workspace. Elbow extension was combined with shoulder horizontal adduction for LM and with shoulder flexion for UI. Kinematic outcomes were measured at two levels: motor performance (endpoint velocity) and movement pattern (joint angular excursions and trunk displacement). Movements were recorded with Optotrak 3020 (Northern Digital Corp., 100Hz, 6s, Waterloo, Canada).

Six infrared-emitting diodes (IREDs) were placed on the fingertip (endpoint), wrist styloid, lateral epicondyle, ipsilateral and contralateral acromions and mid-sternum. For motor performance outcomes, endpoint tangential velocity was computed from the amplitude of the velocity vector obtained from the finger marker. Movement beginning and end were defined as times at which velocity exceeded and remained above or fell and remained below 10% of the peak velocity.

For movement pattern outcomes, three joint angles were computed at the end of the movement – elbow extension (ElbExt), shoulder horizontal adduction (ShHor) and flexion (ShFlex) based on vectors formed by IRED pairs. For elbow movement, vectors were defined between wrist and elbow and elbow and ipsilateral shoulder IREDs (full extension = 180°). Shoulder horizontal adduction was measured as the angle between vectors formed by ipsilateral shoulder-elbow IREDs and a line traced by the contralateral-ipsilateral shoulder IREDs projected horizontally (fully abduction = 0°). For shoulder flexion, vectors were defined between elbow and ipsilateral shoulder IREDs and the vertical through the ipsilateral shoulder IRED (arm alongside body = 0°). Trunk movement was measured as forward sagittal displacement (mm) of the sternal IRED.
6.4.5 Data Analysis

Change scores were used to assess whether improvements had occurred after task practice. Change scores were calculated as the difference at POST and RET from PRE scores. Scores were normalized as (change score/PRE scores) * 100. Data were checked for normality, linearity and homogeneity. Repeated measures ANOVAs with pre-planned least square difference post-hoc tests compared the kinematic change scores with group (PE, VE) as the fixed factor and time as the repeated measure.

Relationships between neurocognitive test-scores and kinematic changes within each environment were assessed using appropriate correlation analysis (Pearson or Spearman, depending upon the distribution). Correlations were defined as strong (≥0.7), moderate (0.4-0.69), or mild (≤ 0.39; Streiner & Norman, 2008).

For the whole group, multiple linear regression analyses were used to estimate the strength of the association between the change in kinematic measures (dependent variables) and neurocognitive test-scores (predictors). The strength of correlation between predictors was estimated using Pearson correlations. Strong correlation between any 2 predictors indicates measurement of the same construct, which does not allow the amount of variance predicted to be attributed uniquely to one variable. Thus, variables with correlations less than 0.70 were accepted in the model.

The variables on which feedback was provided (endpoint speed and trunk displacement) were considered as the primary dependent variables. In addition, changes in the ranges of ElbExt, ShHor and ShFlex were considered. To estimate which predictor or combination thereof (verbal and visuospatial memory, problem solving, cognitive flexibility, attention, visuoperception and depression scores) explained the greatest amount of variance in the dependent variable, best-fit models were obtained (Cohen and Cohen, 1983). Data were analyzed using SPSS (v20) with significance levels set at p<0.05.

6.5 Results

A total of 24 participants (PE, 12; VE, 12) completed all clinical and neuropsychological assessments. As previously mentioned, these 24 participants were a subgroup of 32 subjects
who had participated in our earlier study (Subramanian et al. 2013). Demographic characteristics and results of the clinical and neurocognitive assessments are listed in Table 6-1. Participants were similar in terms of age, duration post-stroke and type of stroke between groups. Both groups were comparable at baseline except for depression scores, which were higher in the PE compared to the VE group (Mann-Whitney U test, \( U = 27.5, p<0.01 \)). All participants reported being comfortable throughout the training and did not experience any side effects.

\[ \text{Insert Table 6-1 near here} \]

6.5.1 Kinematic Evaluations

There was an overall effect of group for all movement quality variables - ElbExt (\( F_{(1,22)} = 6.28, p<0.05 \)), ShHor (\( F_{(1,22)} = 6.97, p<0.05 \)), ShFl (\( F_{(1,22)} = 5.35, p<0.05 \)) and TrDis (\( F_{(1,22)} = 6.06, p<0.05 \)). A group x time interaction effect was noted for endpoint speed (\( F_{(1,22)} = 5.07, p<0.05 \)).

Post-hoc testing (pre-planned comparisons) was conducted using 1-way ANOVAs (Fig. 6-2). Those training in VE made greater gains in range of active motion of ElbExt (UI-RET, \( p<0.05 \); Fig. 6-2B), ShHor (LM-POST and RET; \( p<0.05 \), Fig. 6-2C), ShFl (LM-POST and RET, \( p<0.05 \), Fig. 6-2E; UI-RET- \( p<0.05 \), Fig. 6-2F), and used less TrDis (LM-POST, \( p<0.05 \); UI-POST \( p<0.05 \), Fig. 6-2G). There was also a tendency to move the upper limb faster to the LM target at POST (\( p = 0.057 \)) in the VE group (Fig. 6-2I).

\[ \text{Insert Figure 6-2 near here} \]

6.5.2 Correlation Analysis by Environment

In the PE group, changes in pointing movements to both the LM and UI targets were related to neurocognitive impairments (Table 6-2A). For the LM target, greater endpoint speed was highly correlated with fewer deficits in verbal and visuospatial memory. Changes in ShFlex range were highly correlated with verbal memory at both POST and RET and moderately to problem-solving at RET. Changes in Elb range for the LM target were highly correlated with verbal and
visuospatial memory at POST. In addition, there was a moderate correlation with problem-solving. For the UI target, changes in ElbExt range were correlated to attention at POST. In addition, these changes were highly negatively correlated with depression at POST and moderately at RET.

In the VE group, greater endpoint speed was moderately correlated with problem-solving at POST (Table 6-2B). Decreases in trunk displacement for reaches to the UI target were moderately correlated with fewer deficits in verbal memory at POST and highly correlated with cognitive flexibility at RET. Increases in the range of ShHor and ShFlex for pointing movements were moderately correlated with depression levels. Greater ElbExt range was highly correlated with better visuoperceptual abilities at POST and at RET. Thus in both environments, kinematic changes were related to memory, problem solving ability and depression levels.

The moderate correlation with depression observed for the increase in ShHor and ShFl ranges was influenced by the fact that there was only one subject in this group who was mildly depressed according to the BDI-II cut-off scores (Beck et al., 1996). Given these results and others regarding differences in levels of depression between groups, a correlation analysis was run combining data of all 24 participants. Results of this analysis revealed that depression was moderately associated with TrDis at POST ($r=0.405$, $p<0.05$) and with ElbExt at both POST ($r=-0.659$, $p<0.01$) and RET ($r=-0.470$, $p<0.05$) for the UI target.

6.5.3 Multiple Regression Analyses

There were low to moderate correlations between predictors. Significant correlations were found between the three measures of memory (Table 6-3) as well as between verbal memory (WMS-DR) and problem solving (TOL moves) and between visuoperception (ROCF-DR) and cognitive flexibility (WCST categories). These results meant that all neurocognitive scores could be considered as predictors for the multiple regression analyses. As the numbers of participants in each group were small, data from both groups were combined for the multiple regression analysis. The data met assumptions of linearity, normality and homogeneity of variances. The
best-fit models consisted of different combinations of predictors depending upon the target and time of assessment (Table 6-4).

Insert_Table 6-3_near_here

6.5.3.1 Improvements in Pointing Movements to the LM target

For the LM target, best fit models of predictors were found for endpoint speed, ShHor, ShFl and ElbExt. Immediately after practice (POST), greater endpoint speed was associated with fewer deficits in visuospatial memory (ROCF DR) and lower levels of depression ($r^2 = 0.33$). At RET, visuospatial memory (ROCF DR) alone explained 24% of the variance. Increased ShHor range at POST was associated with better mental flexibility and attention ($r^2 = 0.25$). The best-fit model for the increase in ShFl range for the LM target consisted of better scores on verbal memory (RAVLT DR) alone ($r^2 = 0.20$). The change in elbow extension range at POST was associated with better visuoperception ability and attention ($r^2 = 0.38$). At RET, increased elbow extension range was associated with better verbal memory (RAVLT DR; $r^2 = 0.27$).

Insert_Table 6-4_near_here

6.5.3.2 Improvements in Pointing Movements to the UI target

Best fit models of predictors were found for TrDis, ShFl and ElbExt ranges of motion for the UI target. An increase in trunk displacement at POST was associated with higher levels of depression ($r^2 = 0.16$). The best-fit model at RET included mental flexibility, attention and visuoperception, which explained 50% of the variance. An increase in ShFl range at POST was associated with better mental flexibility and visuospatial memory (ROCF DR; $r^2 = 0.37$). At RET, the best fit model for the increase in ShFl range consisted of visuoconstruction and visuoperception ability alone (ROCF copy), which explained 20% of the variance. The best fit model for the change in the elbow extension range to the UI target consisted of only depression immediately after practice ($r^2 = 0.43$) and at RET ($r^2 = 0.22$).
6.6 Discussion

Effects of feedback provision on learning of motor performance and movement pattern variables were assessed. We also evaluated the relationship between cognitive deficits and the ability to use feedback for motor learning. We found that, similar to previous results (Subramanian et al., 2013), subjects training in VE improved their ranges of elbow extension, shoulder horizontal adduction, shoulder flexion and decreased the amount of trunk displacement. Subjects who practiced reaching in the VE also tended to make faster pointing movements. Those who practiced in the PE had no appreciable change or increased the amount of trunk displacement after training.

Our intervention consisted of repetition of multi-joint arm movements (elbow extension combined with shoulder horizontal adduction and/or shoulder flexion depending upon the location of the target in the workspace). These movements are particularly disrupted after stroke (Levin, Michaelsen, Cirstea, & Roby-Brami, 2002; Cirstea & Levin, 2007) and relevant for the successfully accomplishment of many daily life tasks. The number of practice repetitions was considered fairly intensive based upon previous studies (Cirstea et al., 2003) and were more than double the number of functional repetitions commonly employed in inpatient and outpatient rehabilitation (Lang et al., 2009). Despite both groups having the same practice intensity and feedback, the VE group made greater improvements than the PE group and had a pattern of motor recovery characterized by less compensatory trunk movement. These results are consistent with our previous study (Subramanian et al. 2103) and suggest that the VE may be a more effective medium for providing feedback for motor learning, especially KP.

The motor improvements observed with better use of KP feedback may be due to the availability of information on how to improve selective elements of the movement pattern and the advantage of limiting the amount of trunk displacement during the reaching movement. Thus, feedback on the motor patterns used during the reaching task may have allowed the nervous system to find more effective ways to combine different degrees of freedom and to find better motor solutions to the movement task based on the system’s kinematic redundancy (Bernstein, 1967; Feldman & Levin, 1995).
Rossi, Mitnitski and Feldman (2002) showed that in healthy subjects making beyond-the-reach reaching tasks involving unrestricted trunk motion, the influence of the trunk motion on the hand trajectory is neutralized by shoulder movement in order to maintain a straight reaching path. When the trunk was unexpectedly blocked, the reaching path is identical to that when the trunk was free to move. The superposition of the reaching path was achieved by an instantaneous increase in elbow extension and/or shoulder adduction movements and a smooth shoulder-elbow inter-joint co-ordination was maintained. This is an example of the redundancy in the healthy nervous system which ensures successful task performance involving a wide range of different movement pattern combinations and patterns of inter-joint co-ordination.

The variations in the joint angle combinations that contribute to achieving a stable performance variable, such as a consistent reaching path has been referred to as goal equivalent variance (GEV) in the Uncontrolled Manifold (UCM) approach (Latash, Scholz, & Schoner, 2002). Variations in joint angle combinations that contribute to variability in the reach path are referred to as non-goal equivalent variance (NGEV).

For reaching tasks involving targets placed at arm’s length, Riesman and Scholz (2003) found that the proportion of GEV was higher compared to NGEV in both controls and subjects with post-stroke hemiparesis, when trunk movement was restrained. Similarly, active trunk restraint using an electromagnet led to an improvement in elbow and shoulder ranges of motion and elbow-shoulder interjoint co-ordination values in individuals with post-stroke hemiparesis (Michaelsen et al., 2001). Similar results were obtained when trunk movement was limited using KP feedback on movement patterns to individuals with post-stroke hemiparesis (Cirstea & Levin, 2007). Thus, it is likely that the provision of feedback in our study may have led to an increase in GEV as evidenced by the increase in the range of elbow and shoulder movements while reducing trunk movement, but this possibility needs to be specifically addressed in future research.

Included in the process of learning new movement patterns is the opportunity for learners to perform error detection and self-correction - components of problem-solving ability and mental flexibility. These abilities in conjunction with memory help in appropriately modifying and adapting behavior to task constraints. The changes in joint ranges after training were related to
verbal memory and problem solving abilities in both environments (Table 6-2A and 6-2B), but to mental flexibility and visuoconstruction and visuoperception ability only in the VE (Table 6-2B). This correlation to visuoperception ability may have enabled the subjects to better perceive the location of the targets leading to the production of more effective movement patterns, similar to those seen in healthy individuals for similar pointing tasks (Cirstea and Levin, 2000; Knaut, Subramanian, McFadyen, Feldman, & Levin, 2009). Our results support those obtained by Cirstea et al. (2006) who only assessed the effect of KR and KP feedback about precision and trunk movement respectively on motor performance measures (movement segmentation, endpoint precision and velocity variability). In that study, they found that fewer deficits in verbal memory, problem-solving ability and cognitive flexibility were related to better motor performance outcomes in the KP group compared to the group receiving KR feedback.

The importance of memory and mental flexibility is further supported by the results of the multiple regression analyses (Table 6-4). Immediately after practice, the majority of the variance was explained either by one of these two variables alone or by a combination of one of these two with other variables such as depression and attention. Better learning at RET was associated with lower levels of depression, fewer deficits in attention and visuoperception and visuoconstruction ability in addition to verbal memory, problem solving ability and mental flexibility (Table 6-2A, 6-4).

Thus, fewer deficits in memory, attention, and mental flexibility along with lower levels of depression were associated with better use of feedback and learning how to combine different degrees of freedom for more effective motor performance both immediately after practice and at retention. These findings can be explained on the basis of refinement or modification of schemas that accompany the learning of a generalized set of movement combinations (Schmidt, 1975; Bernstein, 1967) or learning a new set of control variables underlying a synergy (Latash, 2010), coordinative structure (Kugler and Turvey, 1987) or referent body configuration (Feldman, 2011). These questions can be explored with a larger sample of individuals post-stroke with and without depression and deficits in memory, attention and mental flexibility to further understand the role of different cognitive functions on motor learning.
The results of the correlation and multiple regression analyses also revealed that depression was associated with and may have influenced motor learning. Higher levels of depression were associated with poor motor learning outcomes as evidenced by higher trunk displacement levels; (Table 6-2B, 6-4) and the negative β values for changes in movement speed and elbow extension. The relationship between depression and motor learning may be attributed to brain derived neurotrophic factor (BDNF), a group of molecules that promote growth and survival of neurons and are associated with motor learning. Better motor learning and motor recovery has been associated with higher levels of BDNF in the brain in animal models of stroke (MacLellan, Keough, Granter-Button, Chernenko, Butt, & Corbett, 2011; Biernaskie & Corbett, 2001) while lower levels of BDNF have been associated with the development of post-stroke depression in individuals post-stroke (Yang, Zhang, Sun, Xu, Yuan, Zhang, & Li, 2011; Zhou, et al., 2011). Individuals with post-stroke depression may have been unable to use feedback for motor learning due to low levels of BDNF. This will however have to be examined separately.

6.7 Limitations

The interpretation of our results is limited by the small sample size. There was difference in the baseline levels of depression between groups. This was an incidental finding as we had not randomized subjects on the basis of depression. Future studies should take this factor into account. The z scores for the neurocognitive outcomes were not adjusted for age and educational levels. Due to the small sample, we combined data obtained from both training environments for the multiple regression analyses. Future studies, should address the relationship between cognitive factors and use of feedback, especially in VEs in a larger group of individuals.

6.8 Implications for Neurorehabilitation

The presence of cognitive deficits can influence the ability of the individuals with stroke to respond to rehabilitation interventions that include feedback about movements and movement patterns. It is suggested that individuals post-stroke be screened for the presence of cognitive deficits, especially in the chronic phase. While it may not be feasible clinically to conduct a detailed neuropsychological assessment, evidence based screening measures such as the Montreal Cognitive Assessment (MoCA; Godefroy et al., 2011) or Cognistat (Nokleby et al.,
2008) could be used in addition to measures of depression. This information may also help in tailoring therapy according to the needs of the individual.

6.9 Conclusions

Levels of cognitive functioning were associated with the ability to use critical information about the results of the pointing performance to modify movement kinematics and improve movement pattern learning outcomes. This modification may lead to improved task performance. Information on the presence of cognitive deficits can help in the selection of the most appropriate interventions for maximizing recovery of arm motor performance and movement patterns in patients with stroke.

6.10 Acknowledgements

Supported by Heart and Stroke Foundation of Canada (HSFC), Canadian Institute of Health Research (CIHR) and in part by the Physiotherapy Foundation of Canada. MFL holds a Canada Research Chair in Motor Recovery and Rehabilitation. SKS was supported by a Focus on Stroke Doctoral Research award (CIHR, HSFC, Canadian Stroke Network).

Special thanks to Heidi Sveistrup. We also acknowledge the individuals who participated in the study and thank Ruth Dannenbaum and Rhona Guberek for subject recruitment and evaluation, Maria Fraraccio and Dr. Joelle Crane for carrying out the neuropsychological evaluations and Christian Beaudoin and Eric Johnstone for technical support.

6.11 References


Figures

Figure 6-1. Physical and virtual training environments.

A. Physical training environment with 6 numbered targets. B. Virtual training environment—3D scene of 6 consumer products on a supermarket shelf projected on a large screen.
Figure 6-2: Effects of training environment on kinematic outcomes

Mean (SD) of normalized percent change values for elbow extension, shoulder horizontal adduction shoulder flexion, trunk displacement and endpoint speed for lower-middle target (A, C, E, G, I) and upper-ipsilateral target (B, D, F, H, J) for the 2 groups training either in PE or VE at POST and RET. Asterisks indicate significance: all significance refers only to the VE; *$P < 0.05$, **$P < 0.01$. Abbreviations: SD, standard deviation; PE, physical environment; VE, virtual environment; POST, change from pre immediately after testing; RET, change from pre at retention testing.
Table 6-1. Demographic characteristics and neurocognitive scores of study participants at baseline

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>PE (n=12)</th>
<th>VE (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (66.7%)</td>
<td>10 (83.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (33.3%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Paretic side, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>8 (66.7%)</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>Right</td>
<td>4 (33.3%)</td>
<td>8 (66.7%)</td>
</tr>
<tr>
<td>Age (yrs), mean (SD)</td>
<td>60.0 (11.0)</td>
<td>62.0 (9.7)</td>
</tr>
<tr>
<td>Time since onset (yrs), mean (SD)</td>
<td>3.0 (1.9)</td>
<td>3.7 (2.2)</td>
</tr>
<tr>
<td>Lesion information (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical (MCA, Frontal)</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Subcortical</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical (MCA, Frontal)</td>
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<td>1</td>
</tr>
<tr>
<td>Subcortical</td>
<td>1</td>
<td>2</td>
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</table>

<table>
<thead>
<tr>
<th>Clinical and neurocognitive outcomes; Mean (SD)</th>
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<tr>
<td>Fugl-Meyer score (/66)</td>
<td>47.1 (13.9)</td>
<td>41.5 (17.0)</td>
</tr>
<tr>
<td>WMS DR (/23)</td>
<td>7.2 (4.6)</td>
<td>8.3 (3.4)</td>
</tr>
<tr>
<td>RAVLT DR (/15)</td>
<td>8.1 (3.7)</td>
<td>8.3 (4.2)</td>
</tr>
<tr>
<td>ROCF DR (/36)</td>
<td>9.2 (5.5)</td>
<td>10.3 (4.8)</td>
</tr>
<tr>
<td>WCST categories (/6)</td>
<td>3.8 (2.6)</td>
<td>4.9 (1.8)</td>
</tr>
<tr>
<td>TOL moves (number)</td>
<td>33.3 (20.4)</td>
<td>31.3 (20.0)</td>
</tr>
<tr>
<td>Stroop Int (sec)</td>
<td>48.7 (88.6)</td>
<td>23.7 (14.7)</td>
</tr>
<tr>
<td>ROCF copy (/36)</td>
<td>19.0 (5.6)</td>
<td>19.3 (3.5)</td>
</tr>
<tr>
<td>Depression (/63)</td>
<td>14.6 (10.3)*</td>
<td>5.0 (4.4)</td>
</tr>
</tbody>
</table>

(PE – Physical Environment, VE – Virtual Environment, SD – Standard deviation, MCA – Middle Cerebral Artery, SE – Standard error, DR – Delayed Recall, WMS – Weschler’s Memory Scale, RAVLT – Ray Auditory Verbal Learning Test, ROCF – Rey-Osterrith Complex Figure, WCST – Wisconsin Card Sorting Test, TOL – Tower of London, * - indicates significant difference from VE group, p<0.05)
Table 6-2. Correlations between predictors based on Pearson or Spearman tests

<table>
<thead>
<tr>
<th>Variable</th>
<th>Target</th>
<th>Time of evaluation</th>
<th>Neurocognitive scores</th>
<th>Attention</th>
<th>Visuo-perception</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Verbal memory</td>
<td>Problem solving</td>
<td>Cognitive flexibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WMS DR</td>
<td>RAVLT DR</td>
<td>ROCF DR</td>
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<td></td>
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<td></td>
<td>TOL Moves</td>
<td>WCST categories</td>
<td>Stroop_Int</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ROCF copy</td>
<td>Depression</td>
</tr>
<tr>
<td>A. Environment: PE (n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint Speed</td>
<td>LM</td>
<td>Post</td>
<td>-0.743&lt;sub&gt;b&lt;/sub&gt;**</td>
<td>-0.655&lt;sub&gt;b&lt;/sub&gt;**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RET</td>
<td>-0.651&lt;sub&gt;b&lt;/sub&gt;*</td>
<td>-0.683&lt;sub&gt;b&lt;/sub&gt;*</td>
<td></td>
</tr>
<tr>
<td>Shoulder Flexion</td>
<td>LM</td>
<td>Post</td>
<td>0.676&lt;sub&gt;a&lt;/sub&gt;*</td>
<td></td>
<td>-0.578&lt;sub&gt;a&lt;/sub&gt;*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RET</td>
<td>0.721&lt;sub&gt;a&lt;/sub&gt;**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow Extension</td>
<td>LM</td>
<td>RET</td>
<td>0.729&lt;sub&gt;a&lt;/sub&gt;**</td>
<td>0.776&lt;sub&gt;a&lt;/sub&gt;**</td>
<td>0.726&lt;sub&gt;a&lt;/sub&gt;**</td>
</tr>
<tr>
<td></td>
<td>UI</td>
<td>Post</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>RET</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B. Environment: VE (n=12)</td>
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<td></td>
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</tr>
<tr>
<td>Endpoint Speed</td>
<td>LM</td>
<td>Post</td>
<td>-0.685&lt;sub&gt;a&lt;/sub&gt;*</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>UI</td>
<td>Post</td>
<td>-0.676&lt;sub&gt;a&lt;/sub&gt;*</td>
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<tr>
<td>Trunk Displacement</td>
<td>UI</td>
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<td>-0.688&lt;sub&gt;b&lt;/sub&gt;*</td>
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<tr>
<td></td>
<td></td>
<td>RET</td>
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<td></td>
<td>0.703&lt;sub&gt;b&lt;/sub&gt;*</td>
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<tr>
<td>Shoulder Horizontal Adduction</td>
<td>UI</td>
<td>RET</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shoulder Flexion</td>
<td>UI</td>
<td>RET</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Elbow Extension</td>
<td>UI</td>
<td>Post</td>
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<td>-0.754&lt;sub&gt;a&lt;/sub&gt;**</td>
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<td>RET</td>
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<td></td>
<td>-0.698&lt;sub&gt;a&lt;/sub&gt;*</td>
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</table>
(DR – Delayed Recall, WMS – Weschler’s Memory Scale, RAVLT – Ray Auditory Verbal Learning Test, ROCF – Rey-Osterrith Complex Figure, WCST – Wisconsin Card Sorting Test, TOL – Tower of London; a – Pearson correlation, b – Spearman correlation, *p<0.05, **p<0.01)
Table 6-3. Correlations between predictors

<table>
<thead>
<tr>
<th></th>
<th>RAVLT-DR</th>
<th>ROCF-DR</th>
<th>WCST - Categories</th>
<th>TOL Moves</th>
<th>Stroop Interference</th>
<th>ROCF copy</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMS DR</td>
<td>0.553**</td>
<td>0.440*</td>
<td>0.282</td>
<td>-0.530**</td>
<td>-0.064</td>
<td>-0.036</td>
<td>-0.212</td>
</tr>
<tr>
<td>RAVLT DR</td>
<td></td>
<td></td>
<td>0.471*</td>
<td></td>
<td>-0.330</td>
<td>-0.211</td>
<td>-0.261</td>
</tr>
<tr>
<td>ROCF DR</td>
<td></td>
<td></td>
<td>0.526**</td>
<td></td>
<td>-0.133</td>
<td>0.066</td>
<td>-0.139</td>
</tr>
<tr>
<td>WCST - Categories</td>
<td></td>
<td></td>
<td></td>
<td>0.016</td>
<td>-0.321</td>
<td>0.329</td>
<td>-0.194</td>
</tr>
<tr>
<td>TOL Moves</td>
<td></td>
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<td></td>
<td></td>
<td>0.102</td>
<td>0.258</td>
<td>0.237</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.321</td>
<td>-0.094</td>
</tr>
<tr>
<td>ROCF copy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.075</td>
</tr>
</tbody>
</table>

(DR – Delayed Recall, WMS – Weschler’s Memory Scale, RAVLT – Ray Auditory Verbal Learning Test, ROCF – Rey-Osterrith Complex Figure, WCST – Wisconsin Card Sorting Test, TOL – Tower of London; *p <0.05, **p <0.01)
### Table 6-4. Multiple Regression Analyses

#### A. Results for the LM target immediately after practice

<table>
<thead>
<tr>
<th>Dependant variable</th>
<th>Best fit model</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endpoint speed</strong></td>
<td><strong>Visuospatial memory + Depression</strong>&lt;br&gt;ANOVA: $F_{(2,21)} = 5.145$, $p = 0.015$&lt;br&gt;$\beta$ (ROCF DR) = -0.46&lt;br&gt;$\beta$ (Depression) = -0.41</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Shoulder Flexion</strong></td>
<td><strong>Verbal memory</strong>&lt;br&gt;ANOVA: $F_{(1,22)} = 5.36$, $p = 0.030$,&lt;br&gt;$\beta$ (RAVLT DR) = 0.44</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Shoulder Horizontal Adduction</strong></td>
<td><strong>Cognitive flexibility + Attention</strong>&lt;br&gt;ANOVA: $F_{(2,21)} = 3.50$, $p = 0.048$,&lt;br&gt;$\beta$ (WCST categories) = 0.523&lt;br&gt;$\beta$ (Stroop Int) = 0.237</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Elbow Extension</strong></td>
<td><strong>Visouperception ability + Attention</strong>&lt;br&gt;ANOVA: $F_{(2,21)} = 5.36$, $p = 0.030$,&lt;br&gt;$\beta$ (ROCF copy) = -0.571&lt;br&gt;$\beta$ (Stroop Int) = 0.471</td>
<td>0.38</td>
</tr>
</tbody>
</table>

#### B. Results for the LM target at retention

<table>
<thead>
<tr>
<th>Dependant variable</th>
<th>Best fit model</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endpoint speed</strong></td>
<td><strong>Visuospatial memory</strong>&lt;br&gt;ANOVA: $F_{(1,22)} = 7.022$, $p = 0.015$&lt;br&gt;$\beta$ (ROCF DR) = -0.49</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Elbow Extension</strong></td>
<td><strong>Verbal memory</strong>&lt;br&gt;ANOVA: $F_{(1,22)} = 8.22$, $p = 0.009$,&lt;br&gt;$\beta$ (RAVLT DR) = 0.52</td>
<td>0.27</td>
</tr>
</tbody>
</table>

#### C. Results for the UI target immediately after practice

<table>
<thead>
<tr>
<th>Dependant variable</th>
<th>Best fit model</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trunk Displacement</strong></td>
<td><strong>Depression</strong>&lt;br&gt;ANOVA: $F_{(1,22)} = 4.323$, $p=0.049$,&lt;br&gt;$\beta$ (Depression) = 0.41</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Shoulder Flexion</strong></td>
<td><strong>Cognitive flexibility + Verbal memory</strong>&lt;br&gt;ANOVA: $F_{(2,21)} = 6.17$, $p = 0.008$,&lt;br&gt;$\beta$ (WCST categories) = 0.64&lt;br&gt;$\beta$ (ROCF DR) = -0.61</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Elbow Extension</strong></td>
<td><strong>Depression</strong>&lt;br&gt;ANOVA: $F_{(1,22)} = 16.85$, $p&lt; 0.000$&lt;br&gt;$\beta$ (Depression) = -0.66</td>
<td>0.43</td>
</tr>
</tbody>
</table>
D. Results for the UI target at retention

<table>
<thead>
<tr>
<th>Dependant variable</th>
<th>Best fit model</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trunk Displacement</td>
<td><strong>Attention + Cognitive flexibility + Visuoperception ability</strong></td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>ANOVA: $F_{(3,20)} = 6.75$, $p = 0.003$</td>
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</tr>
<tr>
<td></td>
<td>$\beta$ (Stroop Int) = -0.62</td>
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</tr>
<tr>
<td></td>
<td>$\beta$ (WCST categories) = -0.65</td>
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</tr>
<tr>
<td></td>
<td>$\beta$ (ROCF copy) = 0.77</td>
<td></td>
</tr>
<tr>
<td>Shoulder Flexion</td>
<td><strong>Visuoperception ability</strong></td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>ANOVA: $F_{(1,22)} = 5.56$, $p = 0.028$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\beta$ (ROCF copy) = -0.45</td>
<td></td>
</tr>
<tr>
<td>Elbow Extension</td>
<td><strong>Depression</strong></td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>ANOVA: $F_{(1,22)} = 6.24$, $p = 0.020$,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\beta$ (Depression) = -0.47</td>
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</table>
CHAPTER 7 SUMMARY AND CONCLUSIONS

7.1 Summary of results

The global aim of this thesis was to examine the role of extrinsic feedback on motor learning of the upper limb in stroke. The specific objectives were to estimate: 1) the effectiveness of the use of extrinsic feedback on implicit learning of upper limb movement; 2) the validity of movement pattern kinematics in individuals with post-stroke hemiparesis to determine the best measures to be used as outcomes in studies of feedback provision 3) the effect of feedback provided through the medium of VEs for upper limb motor recovery and 4) the influence of cognitive impairments on using feedback to learn and recover motor performance and movement pattern variables (i.e. upper limb kinematics).

These objectives were addressed in four manuscripts included in the thesis. The systematic review (Chapter 3) helped to provide evidence that provision of extrinsic feedback is beneficial for implicit motor learning of upper limb movement. The second study (Chapter 4) addressed the validity of movement pattern kinematic variables for a pointing and reach-to-grasp task for the purpose of using valid and reliable outcomes to investigate the effect of feedback provision through the medium of VR and to estimate whether cognitive impairments are associated with learning kinematic variables. In the RCT (Chapter 5), feedback provided through the medium of VR was more beneficial compared to feedback provided in the PE and led to a pattern of motor recovery indicative of the use of less compensation. Scores obtained on clinical outcomes of impairment and laboratory and real life situation-based performance of ADL tasks also improved, indicating transfer of training from the VE to the real world. The final study (Chapter 6) showed that cognitive impairments, especially in the domains of attention, verbal and visuospatial memory, cognitive flexibility and depression were associated with the ability to use feedback to learn and improve on motor performance and movement pattern outcomes.

The significance and relevance of these findings to scientific knowledge in stroke rehabilitation are discussed below. This is done primarily within the framework of the discussion and conclusions of the systematic review (Chapter 3) on feedback provision and
how the results of the other manuscripts included in this thesis support these observations and/or provide answers to questions emerging from the review. The limitations of the thesis and suggestions for future research are discussed in the concluding section.

7.1.1 Effectiveness of feedback provision for motor learning

In Chapter 3, results from a comprehensive systematic review of the literature (specific to studies involving upper limb tasks post-stroke) provided evidence that provision of explicit feedback is beneficial for implicit motor learning of upper limb tasks in individuals after a stroke. The results of the review suggest that after a stroke, individuals with upper limb hemiparesis are able to use explicit feedback and preserve motor learning abilities with both the more-affected (Sackett’s evidence level-1A) and less-affected (Sackett’s evidence level-2B) arms despite having underlying motor deficits (Subramanian et al., 2010a). Feedback provision may result in modulation of neuroplasticity which accompanies motor learning. Provision of feedback resulted in an increased activation of the ipsilesional SM1 (Jang et al., 2005; Adamovich et al., 2009), ventral (Sitaram et al., 2012) and dorsal PMC (Meehan et al., 2011). The increased activations seen in the ipsilesional SM1 and ventral and dorsal PMC are examples of restitution and/or recruitment, which as mentioned earlier in chapter 2 (section 2.6.2.1) are mechanisms that contribute to recovery at the neuronal level.

7.1.2 Type of feedback provided

In the systematic review (Chapter 3), the effects of providing KR compared to KP feedback were compared in three studies (Cirstea and Levin, 2007; Cirstea et al., 2006; Maulucci and Eckhouse, 2001). In the studies by Cirstea and colleagues, provision of KR feedback resulted in an improvement in motor performance variables immediately after practice and effects on movement pattern variables were evident at retention. On the other hand, provision of KP feedback resulted in immediate improvements in both motor performance and movement pattern variables, which were retained at follow up. Provision of KP feedback was more beneficial than provision of KR, probably due to the focus on movement pattern variables and decreasing compensations.
The results of Chapters 5 and 6 were similar to those found by Cirstea and Levin (2007), where better improvements in movement pattern variables were seen with provision of KP feedback. The beneficial effects seen with KP may be due to the kind of information contained in the feedback provided. The KP feedback provided information on how to improve selective elements of the movement pattern (Cirstea and Levin, 2007) and limited the amount of trunk displacement permitted (Subramanian et al., 2013) during the pointing movement in these studies.

The feedback provided during task practice may have fostered the active involvement of the participants (Shea and Morgan, 1979) in trying to improve their performance on the pointing task. The feedback only informed the participants about the result of their movement (KR) and that they had used a greater than permissible amount of trunk displacement and selective movement pattern elements that need to be improved (KP). Participants may have been more aware that successful task performance depended on the movement patterns used. This awareness could have engaged the cognitive processes of estimating how to move and adapt motor behavior to provide alternate successful motor solutions (Winstein et al., 1999; Lee et al., 1994). Results from Chapter 6 support the importance of cognitive involvement for the use of feedback in motor learning and recovery. A discussion on how cognitive processes contribute to learning is found in Section 7.1.5.

7.1.3 Measurement of improvements in motor performance after provision of feedback

The changes in levels of motor impairment and ADL performance seen after task practice with feedback provision were assessed in the majority of the studies included in the systematic review using clinical outcome measures. In Chapter 2 (section 2.6.3), it was concluded that the use of clinical measures alone provide insufficient information about how the movements were performed to determine if the participants really recovered or merely demonstrated improvements in task performance by the use of compensations. This information is obtained primarily by the use of kinematic analysis, especially by measuring movement pattern variables.
A few studies included in the review (Chapter 3) also used kinematic analysis in addition to clinical outcomes. The majority of these studies used motor performance outcomes (endpoint speed, precision, movement time, etc.) and only one study (Cirstea and Levin, 2007) using movement pattern outcomes. Use of kinematic analysis has been shown to be more sensitive for identifying deficits even in those individuals who are considered well-recovered (Chedoke arm scores of 6 & 7/7; Banina et al., 2010, FMA scores of ≥50/66, Cirstea et al., 2003 and upper limb strength score of ≥4/5 on the Medical Research Council scale, Platz et al., 1999). For example, the use of kinematic analysis revealed deficits such as slower speed of movements and greater errors in tasks such as tapping on a screen using a stylus (requiring wrist flexion/extension) and pointing to an object placed in front in the above mentioned studies.

However, the use of only motor performance variables may also prove to be inadequate, as individuals with stroke may still continue to use compensatory movement patterns. Individuals with stroke can still perform precise movements with the use of additional degrees of freedom such as trunk displacement, even for reaching and pointing movements to objects placed within or at arm’s length (Michaelsen et al., 2006; Levin et al., 2002; Cirstea and Levin, 2000). Thus, measurement of only motor performance variables may provide an incomplete assessment of motor abilities of individuals post stroke and it is suggested to use movement pattern variables in addition to motor performance variables in order to gain all relevant information regarding the underlying motor impairments in movement production.

7.1.3.1 Reliability and validity of kinematic variables

The reliability of motor performance and movement pattern kinematic variables was assessed in two studies involving participants with chronic upper limb hemiparesis post-stroke. Both studies involved reaching forward twice to touch a piece of tape (Wagner et al., 2008) or reaching forward to grasp (RTG) a cup three times (Patterson et al., 2011). Motor performance (end point error, peak velocity, movement time, reach extent, movement straightness) and movement quality variables (ranges of shoulder flexion, shoulder abduction, elbow extension, trunk displacement, elbow–shoulder cross-correlation and
maximum aperture at grasp) had moderate to excellent test-retest reliability (intraclass correlation coefficients ≥0.6).

In terms of validity, studies have only measured the known-groups validity for differences between controls and individuals with stroke for tasks like pointing (Levin et al., 2002) and reach-to-grasp (Murphy et al., 2011; Michaelsen et al., 2004). However, concurrent validity has not yet been estimated. This information is useful as it allows us to determine the performance of the new measure against the established gold/silver standard. The concurrent and discriminant validity of movement pattern kinematic variables was estimated in Chapter 4, with the FMA used as the gold-standard measure (Gladstone et al., 2002) of clinical motor impairment.

Results denoted that the variables of elbow extension, shoulder horizontal adduction, shoulder flexion and trunk displacement are valid measures of motor impairment for pointing and RTG tasks. We found that trunk displacement explained the majority (pointing: 45%; RTG: 50%) of the variance in FMA scores and was the only variable which differentiated between mild (FMA scores of ≥50/66) and moderate-to-severe (FMA scores of ≤49/66; Duncan et al., 1994) levels of motor impairment. The results also indicate that even those subjects with a mild level of upper limb hemiparesis may use from 33% (pointing) to 300% (RTG) more compensation compared to controls performing similar tasks. Thus, improvement in FMA scores may not necessarily indicate that test items are accomplished without using compensatory movement patterns.

While we found that trunk displacement contributed to the majority of the variance in FMA scores, a recent study by Alt Murphy and colleagues (Alt Murphy et al., 2012) found that trunk displacement alone contributes about 11% of the variance and in combination with movement smoothness (motor performance variable) explains about 67% of the variance in ARAT scores, a measure of arm function/ADL performance. The differences in the amounts of variance accounted for by trunk displacement could be explained on the basis of the underlying construct being measured.
FMA is a measure of motor impairment in which the total score consists of component scores obtained from measurement of reflexes, ability to move in and out of synergies as well as coordination. Hence the FMA primarily targets the Body Structure and Functions level of the ICF. ARAT on the other hand, mainly consists of items that measure hand functions (Activity level of ICF) while a few items do evaluate gross movements (Body Structure and Function). It is possible that the amount of trunk displacement may be making differential contributions to accomplish the component items in both measures, with a greater contribution to overcome shoulder and elbow range limitations to achieve higher FMA scores.

The same study by Alt Murphy (2012) also found that trunk displacement alone during a RTG task explained 20% of the variance in FMA scores compared to the 50% that was found in the study included in Chapter 4. One explanation for this difference may be the difference in the initial FMA scores. While the participants in the study included in the manuscript in chapter 4 had a mean FMA score of 48.7 (moderate-to-severe motor impairment), the participants in the study by Murphy et al. had a mean FMA score of 53.6 (mild level of motor impairment). Results from the manuscript included in chapter 4 (Subramanian et al., 2010b) and other studies (Cirstea et al., 2003) indicate that the greater the level of initial impairment (as measured by the FMA), the greater the amount of trunk use (12.5 ± 9.16 cm in our study compared to 8.9 ± 5.6 in the study by Murphy) and as suggested above, the greater amount of variance in FMA scores was explained by greater trunk displacement values.

As stated earlier (Section 7.1.3), in the systematic review included in Chapter 3, the majority of the studies have used FMA as one of the primary assessments to measure motor improvements. Recently published studies have shown that improvements in FMA scores may not necessarily distinguish between compensation and recovery. Therefore, in studies involving feedback provision, the use of outcomes that include items which explicitly measure motor compensations should be encouraged at the impairment and/or the activity level of the ICF. Examples of such measures include the RPSS (Levin et al., 2004) and the MESUPES (Van de Winckel et al., 2006) at the impairment level and the WMFT (Wolf et al., 2001) and CAHAI (Barreca et al., 2005) which provide a lower score if a compensatory pattern is used at the activity level.
7.1.4 Medium of feedback provision

Individuals with stroke can use feedback from various sources, including videotapes, VEs, and robotic systems (Section 3.5.2). The advantage of using these media is that they may provide precise information more consistently than individual therapists (i.e., with regard to detailed information on movement parameters). The use of such technologies is rapidly increasing in stroke rehabilitation. Incorporation of such technologies as adjunctive therapies may augment motor learning and outcomes in stroke survivors and can lead to higher patient satisfaction (Gilmore and Spaulding, 2007). However, based on current evidence, there is still no consensus on the best delivery medium for feedback provision, a conclusion that has been supported by other systematic reviews published on the same topic (Molier et al., 2010).

7.1.4.1 Use of virtual environments as mediums to provide feedback

Precise feedback about movement parameters can be incorporated into technologies such as robotics and VR. VR serves as a platform to incorporate the factors such as intensity of practice, repetition, variable- and task-specific practice, motivation and feedback identified as pertinent to improve recovery and enhance motor learning (Kleim and Jones, 2008; Nithianantharajah and Hannan, 2006; sections 2.8 and 2.9.1). Task practice in a 2D non-immersive VE (Piron et al., 2010; Piron et al., 2005) as well as immersive VEs with a first person view watching oneself as part of a therapeutic practice environment (Jang et al., 2005) with enhanced explicit feedback leads to recovery of motor impairment and increased activity levels (measured using clinical outcomes) in those with chronic upper limb hemiparesis post-stroke. However, whether training in a VE with enhanced feedback results in similar or better arm motor recovery compared with real-world training is not very well established. The studies included in Chapters 5 and 6 were done because of a lack of knowledge about the effectiveness of and added value of using VR as a medium to provide feedback over other interventions using rigorous research designs like Randomized Control Trials (RCTs) with appropriate control groups (Saposnik and Levin, 2011).

We used an RCT design to estimate the effects of feedback provision in a VE on arm motor impairment and activity levels in individuals with chronic post-stroke hemiparesis compared
Participants received terminal auditory KR or concurrent auditory KP feedback after every trial. The VE group received additional visual feedback after every trial, which was designed to be a motivating factor. Results indicated that those individuals who trained in the VE increased their ranges of shoulder horizontal adduction and flexion. Participants with mild hemiparesis who trained in the VE improved the range of elbow extension. Participants with moderate-to-severe hemiparesis who trained in the PE increased the range of elbow extension. However this was accompanied by a concomitant increase in trunk displacement in this group. The results suggest that feedback delivered through the medium of VEs was probably better utilized compared to that delivered in the PE and KP was more useful than KR, given the increase in trunk displacement in the PE group.

In terms of clinical outcomes, all participants improved in their use of elbow extension on a reaching task (Impairment level) and had increased scores on the WMFT (Activity level). Similar results in terms of improvements in both Impairment (FMA) and Activity level (FIM) outcomes were obtained by Piron and colleagues (Piron et al., 2010) in both the control and experimental groups. Their study compared clinical and motor performance outcomes after training in a non-immersive VE with enhanced feedback to conventional therapy based on the Bobath approach. The improvements obtained in clinical scores in both studies could be attributed to exercise intensity.

High intensity, task-specific salient practice was used in both studies (Piron et al., 2010 and the manuscript included in Chapter 5). Potential mechanisms of improved outcomes with intensive training include higher levels of neurotrophic factors like brain derived neurotrophic factor (BDNF, IGF and synapsin1, Section 2.8.1; Ploughman et al., 2005; Will et al., 2004) known to contribute to motor recovery and learning after stroke. In the study by Piron et al (2010), improvements were also noted for motor performance outcomes of endpoint speed and movement duration in the experimental group. In our study (Chapter 5), all participants made faster movements both immediately after training and at retention (Fig. 5-2A). However, no movement pattern outcomes were assessed in the study by Piron and colleagues. Thus, whether improvements in task performance occurred by actual behavioral recovery or by the use of compensatory movement patterns in that study cannot be
deciphered. In addition, it is unknown if training in a VE had any long term benefits compared to conventional training, as no retention testing was undertaken.

The study by Piron and colleagues involved 21 sessions on average for both experimental and control groups. In contrast, our study (Chapter 5) included 12 training sessions. However, all participants in both studies improved on outcomes of impairment and arm use/activity levels. The improvements found in the groups training in VE on clinical outcomes of impairment and activity meant that the participants actually transferred the gains from training in the VEs to the real world. The improvements in the amount of upper limb use in daily life activities in subjects (measured using the Motor Activity Log –Amount scale; Uswatte et al., 2006) training in the VE reached a meaning clinically significant level (van der Lee et al., 2004). Similar results in terms of improvements in MAL scores were also reported by Jang et al. (2005). Taken together, these results provide further evidence for the transfer of improvements noted in VEs with use of feedback to the real world, not just on laboratory measures of upper limb use, but also in real life situations.

As mentioned previously, improvements in clinical outcomes were noted in both the Piron study and in Chapter 5 despite the different number of training sessions. This brings the question of intensity into focus. Intensity can be described in terms of duration and frequency (Section 2.8.1). There is no consensus on the minimum number of sessions that are necessary for achieving motor improvements and recovery. Results of the study by Jang et al. (2005) indicated that training for 20 sessions in VEs with feedback caused greater activation in the ipsilesional SM1 after practice compared to bilateral activations noted before task practice involving VR games. However, whether task practice for 12 sessions leads to concomitant neuronal recovery (mediated by restitution and/or recruitment) is not known. Changes in activation levels in specific brain areas and/or white matter connectivity analyses before and after task practice (Johansen-Berg et al., 2010; Scholz et al., 2009) can probably help in providing an answer to this question.

In terms of numbers of repetitions, the manuscripts included in Chapters 5 and 6 and the study by Cirstea (Cirstea and Levin, 2007) involved task-specific intense practice with a minimum of 72 repetitions per session where the motor performance outcome (endpoint
error) reached an asymptote after an average of 36 trials in participants with chronic post-stroke hemiparesis. This number was doubled to ensure high practice intensity. However, the numbers of repetitions may not have been high enough. A recent proof–of–principle study (Birkenmeier et al., 2010) demonstrated that individuals with chronic post-stroke hemiparesis can practice an average of 332 repetitions/session without fatigue and improve ADL performance scores (measures using ARAT).

While the number of repetitions used (72) in our studies (Chapters 5 and 6) may have been sufficient to cause changes in kinematic outcomes, not many training environment specific changes were noted in both kinematic and clinical outcomes. The between group differences were also small-moderate in magnitude for most outcomes. It is possible that higher magnitude changes may have occurred with a higher number of repetitions per sessions. A probable reason for the lack of differences in FMA scores between the two groups in Chapter 5 may be an inadequate number of repetitions. Increasing the numbers of repetitions may also result in sessions lasting longer, a factor that has been suggested as necessary for significant change in clinical measures (Han et al., 2013).

7.1.5 Influence of cognitive factors on use of feedback

Cognitive and mood impairments seen after stroke in the domains of attention, verbal and visuospatial memory, mental flexibility, problem solving, visuoconstruction and visuoperception and depression influence motor learning and recovery (measured using clinical and motor performance kinematic outcomes, Sections 2.4.5, 2.5.3 and 2.5.4). For example, when training in PE, better motor performance outcomes of accuracy for upper limb movements (drawing a triangle within a rectangular frame), movement smoothness and variability in endpoint velocity were related to fewer deficits in memory, problem solving and cognitive flexibility in people with stroke (Cirstea et al., 2006; Dancause et al., 2002; Platz et al., 1994).

Similarly, better performance outcomes (lower response times and greater success rates) were related to fewer deficits in attention and cognitive flexibility while practicing upper limb tasks in a therapeutic 2D immersive VE (involving a first person viewing of oneself)
while playing games involving repetitions of upper limb movements. Thus, studies have addressed the relationship between cognitive deficits after stroke, and motor learning resulting in improvements in motor performance outcomes. However, the association between cognitive impairments and learning and recovery of movement patterns is unknown, especially in VEs. In addition, guidelines about the minimum cognitive abilities required for different types of feedback delivery for motor learning need to be established for better individualized treatment prescription (Fluet and Deutsch, 2013; Levin et al., 2009).

The question of whether and to what extent cognitive impairments in the chronic stage post-stroke are associated with the use of feedback to learn and recover upper limb motor performance and movement pattern variables was addressed in Chapter 6. The study included data from 24 (who underwent a complete neuropsychological examination) of the 32 participants who had been included in the study included in Chapter 5. Similar to the results of Chapter 5, we found that training in a VE resulted in greater improvements in motor performance outcomes (of elbow extension, trunk displacement, shoulder horizontal adduction and flexion) and a tendency to make faster movements.

Changes in the PE group after training and at retention were related to memory, attention and problem solving ability. Improvements in the VE practice group correlated with memory, problem solving and perceptual abilities. Better performance in VEs after training is known to be correlated to a greater sense of presence (Fung et al., 2006; Crosbie et al., 2004, section 2.9.2). Greater sense of presence has been attributed to a greater allocation of attentional resources (Bystrom et al., 1999). However, no correlation was noted between changes in the VE group and attention in the results in manuscript 6. These results could be attributed to a small sample size. It remains to be seen whether a correlation will be found in studies with larger sample sizes.

The majority of the variance in kinematic outcomes immediately after training and at retention testing (after 3 mos.) was explained by individual factors alone or by a combination of memory, problem solving ability, mental flexibility, attention and depression. Improvements in endpoint speed (a factor on which KR feedback was provided) were related
to fewer deficits in visuospatial memory and lower depression levels. Our results support those of Cirstea et al. (2006), who found that a decrease in velocity variability was related to fewer deficits in memory in individuals with chronic stroke. Similar results were found in individuals with Parkinson’s disease in whom lower memory scores predicted a lower upper limb movement speed in a tracking task (Viitanen et al., 1994). The role of depression in movement speed is similar to that found in individuals who were diagnosed with schizophrenia and depression and were found to have slower movement speeds compared to controls (Sabbe et al., 1997).

In Chapter 6, the majority of the variance in improvements in movement pattern variables of elbow extension, shoulder horizontal adduction and flexion was explained by single factors or by a combination of fewer deficits in attention, verbal and visuospatial memory, mental flexibility and visuo-construction and visuoperception ability. Fewer deficits in attention may have enabled the subjects to focus better on the task. Better visuoperception and visuoconstrucational ability may have enabled the subjects to better perceive the location of the targets leading to the production of more effective movement patterns similar to those seen in controls. Fewer deficits in visuospatial memory may have enabled subjects to remember the target location better leading to improved performance on the test task immediately after training and at retention.

Mental flexibility deficits were assessed using the WCST. This test measures the ability to be flexible when frequent changes in reinforcement are presented. The participants need to be able to determine why their performance on a particular attempt was correct or wrong (i.e. auto evaluate the results) and be able to change their response on the next attempt in case they are wrong. Better learning of movement pattern outcomes was associated with fewer deficits in mental flexibility which meant that subjects were probably able to utilize the results provided by the KP and KR feedback (especially KP feedback, Section 6.6, negative correlation seen between increased trunk displacement at retention for UI target and WCST categories score) and incorporate the feedback in their attempts to improve their performance of the next trial.
Thus, fewer cognitive deficits in the above mentioned domains led to better use of feedback and learning how to combine different degrees of freedom for more effective motor performance both immediately after practice and at retention based on the system’s kinematic redundancy (Feldman and Levin, 1995; Bernstein, 1967) leading to improvements in movement patterns at the behavioral level. These findings can be explained on the basis of refinement or modification of schemas that accompany the learning of a generalized set of movement combinations (Kugler and Turvey, 1987; Schmidt, 1975; Bernstein, 1967) or learning a new set of control variables (Latash, 2010) or referent body configuration (Feldman, 2011). Learning of effective combinations of the different degrees of freedom leading to flexible solutions may contribute to a higher incidence of good variability or goal equivalent variance (GEV, UCM approach, section 6.6). The learning of a set of flexible solutions (consisting probably of a better spatial and temporal combination of different joint movements) leading to successful task performance with movement patterns resembling those (or approaching ranges of motion) used by controls for similar upper limb tasks (Knaut et al., 2009; Cirstea and Levin, 2000) can be postulated to be a form of increase in the GEV, though this will have to be explicitly tested.

Depression is an additional cognitive factor that plays a role in motor learning. Higher levels of depression were associated with poorer motor learning outcomes (positive association with increased trunk displacement, less improvements on elbow extension and movement speed indicated by negative association with these two outcomes). The relation between depression and motor learning could be attributed to BDNF levels (Section 2.5.1.1). Whether individuals with post-stroke depression were unable to use feedback to learn how to combine different degrees of freedom due to the effects of depression or low levels of BDNF is currently not known. One possible method of answering this question is to use anti-depressant drugs such as fluoxetine or citalopram in subjects with post-stroke depression in a study involving motor learning and use of feedback. Drugs such as citalopram and fluoxetine are known to reduce levels of depression and improve motor performance (Section 2.5.4). If better outcomes associated with learning and use of feedback are found, then we could conclude that presence of depression causes impaired use of feedback.
Thus use of feedback-based interventions may not be best suited for individuals with post-stroke depression. In such individuals, alternate techniques to avoid compensatory movement patterns and promote behavioral recovery such as active trunk restraint (for example, with velcro straps) may be more suited. It is suggested that individuals post-stroke be screened for the presence of cognitive deficits, especially in the chronic phase. This information may assist in tailoring therapy according to the needs of the individual.

7.2 Limitations

Lack of information on feedback scheduling amongst studies included in the systematic review in chapter 3 led to an incomplete interpretation on the effects of feedback frequency. On the basis of the only study that addressed this question (using kinematic motor performance measures), feedback provided on a faded schedule (66% of the time) was not found to result in better outcomes compared to feedback provided after every trial. These results were obtained when participants used their less-affected side and it is currently unknown if there are any differences when the more-affected side is used.

In Chapter 4, only trunk displacement, shoulder horizontal adduction, shoulder flexion and elbow extension ranges were considered. Movements of the wrist were not taken into consideration in the multiple regression analyses, especially for the RTG dataset. It remains to be estimated whether incorporation of wrist degrees of freedom will influence the amount of variance explained in participants with mild levels of hemiparesis. In participants with moderate-to-severe levels of hemiparesis, trunk displacement is negatively related to wrist and hand parameters and can compensate for the lack of adequate ranges in these joints. Thus in these participants, it is likely to be the major contributor to FMA variance. However, the amounts of variance explained will most likely depend upon the severity of the whole group.

In Chapter 5, the effects of training in a VE did not include measures of participation and/or quality of life. Inclusion of these measures in future studies will provide more information about the effects of VE training on these domains. The interpretation of change values in the RPSS total and elbow scores are limited by the lack of an established minimal clinically significant difference value.
The role played by the visual display of the game score (additional factor) in the VE also needs to be considered. The score displayed (total number of successful trials) may have encouraged the patients to do better and try harder to increase their scores i.e. have more successful trials. It is well known that feedback on good trials improves learning outcomes (Chiviacowsky and Wulf, 2007). This information was not provided in the PE and was not available during the kinematic recording sessions before and after task practice and at retention testing. This could be one of the factors explaining the differences in motivation scores seen in the domains of pressure/tension between the VE and PE groups. The low pressure tension immediately after practice in the VE group may have enabled them to pay more attention to the quality of their movements used during the pointing task and they demonstrated the use of motor patterns indicative of the use of less compensation (Section 5.5.4).

It would be useful to know whether the absence of the visual display of the game score in the VE or display of the same game score in the PE (using an electronic scoreboard, for example) would result in similar or different outcomes. The display of the game score may have helped in reducing the amount of pressure/tension felt in this group and along with higher levels of perceived competence (Section 5.5.4), led to better outcomes at retention testing. This will also help explain whether the presence of this extra visual feedback was a confounding factor in the interpretation of the results.

In Chapter 6, a statistically significant difference in the levels of depression was found between the two groups of subjects (PE and VE). This was an incidental finding, as participants were not randomized on the basis of depression scores. This may however have served as a confounding factor, with lower levels of depression probably associated with better outcomes obtained in the VE group after training. The interpretation of these results is also limited by the small sample size in the study.

### 7.3 Future directions

Provision of feedback is known to be beneficial for motor learning. Future research should address specific questions in individuals with stroke including whether 1) provision of
feedback at a frequency of <100% results in similar or better arm motor recovery compared to 100% feedback; 2) task practice with 72 trials per session for ≥12 sessions leads to neuronal recovery using neuroimaging methods; 3) use of anti-depressant medication leads to better use of feedback resulting in improved learning of motor performance and movement pattern outcomes while reducing levels of depression; 4) practice of > 72 repetitions per session leads to better outcomes than those of in Chapters 5 and 6; 5) provision of feedback on trunk displacement leads to higher amounts of GEV compared to NGEV; 6) provision of extra visual feedback on the score in the PE leads to similar outcomes as those found in the VE group after training and 7) estimating the amounts of variance explained by trunk displacement in other clinical outcomes of impairment and/or ADL performance.

Future research should also elucidate the role of different types, amounts, and delivery schedules of feedback on motor learning in patients with lesions in specific brain areas. Answers to these questions will help enhance our understanding of the association between use of feedback and motor learning. Incorporation of these basic elements identified as pertinent to optimize motor learning and recovery into task practice with appropriate feedback, adequate attention to movement quality and presence of cognitive deficits may help ensure best recovery of post-stroke arm motor impairment and function.
LIST OF REFERENCES


Pavlovic AM, Pekmezovic T, Obrenovic R, Novakovic I, Tomic G, Mijajlovic M, Sternic N (2011) Increased total homocysteine level is associated with clinical status and


APPENDICES
### Table A-1 Relationship of neuropsychological variables to recovery of ADL and participation

<table>
<thead>
<tr>
<th>Author/Year Subjects, Stage</th>
<th>Intervention/ Exposure</th>
<th>Dependant measure</th>
<th>Predictors (independent variables) and domains assessed</th>
<th>Results</th>
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<tr>
<td>Carter et al., 1988; 21 subjects, acute-to-subacute stroke</td>
<td>ADL and cognitive skills retraining by PTs, OTs and nurses for 3-4 weeks Assessments were carried out before and after training.</td>
<td>• ADL levels using Kenny self care evaluation (Schoening and Iversen, 1968). • This scale assesses performance on 6 categories: bed activities, transfers, locomotion, dressing, personal hygiene, and feeding.</td>
<td>• Cognitive skills evaluation (Carter et al., 1984). • It assesses eight different skills: time judgment, auditory attention, visual scanning, visual-spatial perception, digit span, verbal memory, abstract reasoning and verbal comprehension.</td>
<td>• Both cognitive skills and ADL scores increased after training. • Improvement in ADL correlated positively with improvement on overall cognition ($r = 0.37$). • Overall pre-test cognitive performance correlated moderately with ADL improvement post-test ($r = 0.59$). • Pre-test auditory attention score correlated moderately with bed activities, transfers, locomotion, dressing and personal hygiene ($0.46 \leq r \leq 0.71$). • Pre-test visual-spatial perception scores correlated moderately with bed activities, dressing and</td>
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<tr>
<td>Study</td>
<td>Design &amp; Details</td>
<td>Outcome Measures</td>
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<tr>
<td>Mysiw et al., 1989;</td>
<td>Inpatient rehabilitation (specific details unavailable)</td>
<td>BI (Mahoney and Barthel, 1965) score improvement (difference at discharge from acute care; exact time point not specified)</td>
<td>A combination of orientation, repetition, attention, calculations and judgement explained 57.5% of the variance in BI score improvement.</td>
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<tr>
<td>38 subjects with acute stroke</td>
<td>BI score was assessed at admission and discharge.</td>
<td>Cognistat (NCSE; (Kiernan et al., 1987)</td>
<td>Moderate correlation between SUMSE and Rankin score (r = 0.4)</td>
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<td>The Cognistat assesses levels of orientation, consciousness, attention, language (including repetition, comprehension, naming and fluency), memory, construction abilities, calculations and reasoning.</td>
<td>Moderate correlation between cognitive FIM and SUMSE, BNT and MMSE.</td>
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<td>Factor analysis with all variables on global recovery revealed that SUMSE, Raven’s and BNT loaded on a second factor explaining 22.6% of the variance.</td>
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<tr>
<td>Hajek et al., 1997;</td>
<td>Inpatient rehabilitation for 2-3 months (specific details unavailable)</td>
<td>BI score, FIM (Dodds et al., 1993) and Rankin Functional scale (van Swieten et al., 1988)</td>
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<tr>
<td>66 subjects, acute and sub-acute stroke</td>
<td></td>
<td>Stroke Unit Mental Status Examination SUMSE (Hajek et al., 1989), Raven’s Matrices (Bingham et al., 1966), MMSE (Folstein et al., 1975) and Boston Naming Test (BNT, Kaplan et al., 1978).</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Measures</td>
<td>Results</td>
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<tr>
<td>Fong et al., 2001; 37 subjects; subacute stroke</td>
<td>Inpatient rehabilitation consisting of PT, OT and speech therapy (specific intensity unknown). FIM motor score (FIM-MM), FMA UL, LL and balance scores and Cognistat scores were assessed at admission, 2 and 4 weeks post-admission and at discharge</td>
<td>• FIM motor score (FIM-MM) at discharge. • Length of stay</td>
<td>• MMSE loaded on a third factor and explained about 11.6% of the variance. • Weak-to-moderate correlations between comprehension, repetition, construction, and judgement scores with FIM-MM at all time points. • For the discharge FIM-MM scores- 1. Admission FMA balance score and judgement ability scores of Cognistat explained 51.6% of the variance. 2. FMA LL and repetition scores at 4 weeks explained 74.2% of the variance.</td>
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</table>
| Ozdemir et al., 2001; 43 subjects, acute stroke | Therapeutic exercises (range of motion, passive stretching, muscle strengthening, and mobilization exercises) and neuromuscular facilitation exercises | ● Motor FIM  
● MMSE total score and component score.  
● MMSE components include-orientation, registration, attention and calculation, recall, and language.  
● Improvement in Motor FIM score was correlated with baseline total orientation score of MMSE \( (r=0.28) \) and MMSE total scores \( (r=0.31) \).  
● Improvement in functional scale score was correlated with baseline total orientation score of MMSE \( (r=0.31) \) and MMSE total scores \( (r=0.23) \).  
\textit{Multiple regression analysis revealed}  
1. Baseline total MMSE score was a significant predictor of improvement in motor FIM scores; \( \beta \) (MMSE total) = 0.79, \( r^2 \) not mentioned.  
2. Baseline orientation MMSE score was a... | For length of stay  
FMA LL, naming, calculation and comprehension explained 56.1% of the variance. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Methods</th>
<th>Measures</th>
<th>Results</th>
</tr>
</thead>
</table>
| Patel et al., 2002; 645 subjects, sub-acute stroke | None BI and FAI scores were measured at 3 months, 1, 3 and 4 years post-stroke | • BI score  
• FAI (Wade et al., 1985) score | • MMSE score  
• Subjects were divided into those with and without cognitive impairment based upon MMSE cutoff of 24. | • 38% of the study sample was cognitively impaired at 3 months.  
• Subjects with cognitive impairment had significantly lower BI and FAI scores at 1, 3 and 4 years post-stroke.  
• Those with cognitive impairment at 3 months had greater odds of being severely dependant in ADL and inactive at three (OR; BI score ≤ 9 – 3.76, FAI score ≤15– 4.65) and four years post-stroke (OR;BI score ≤ 9 – 10.4, FAI score ≤ 15 – 7.82). |
| Larson et al., 2003; 158 subjects, acute stroke | Inpatient rehabilitation (specific details unavailable)  
Repeatable Battery for | • Motor FIM and cognitive FIM scores  
• FAI score  
• CHART (Whiteneck et | • RBANS component scores  
• The RBANS assesses 5 domains: attention, | • Cognitive FIM score moderately correlated with immediate memory (r = 0.56) and delayed recall (r = 0.61) |
Assessment of Neuropsychological Symptoms (RBANS; Randolph et al., 1998) was measured at admission and FIM, FAI and Craig Hospital Assessment and Reporting Technique (CHART) scores were measured only at 6 months (follow-up).

| Language, immediate memory, delayed recall and visual-construction skills. | components. |  
|---|---|---|
| Visual construction skills, attention and delayed memory component scores explained 46% of the variance in cognitive FIM scores; $\beta$ (visual-construction) = 0.31, $\beta$ (delayed recall) = 0.53 |  
| Visual construction skills, attention and language component scores explained 22% of the variance in motor FIM scores; $\beta$(visual-construction) = 0.51 |  
| Visual construction skills, attention and immediate memory component scores explained 14% of the variance in FAI scores; $\beta$(visual-construction) = 0.47 |  
| Visual construction skills, attention and delayed memory component scores explained 21% of the variance in CHART scores |  

- Visual construction skills, attention and delayed memory component scores explained 46% of the variance in cognitive FIM scores; $\beta$ (visual-construction) = 0.31, $\beta$ (delayed recall) = 0.53
- Visual construction skills, attention and language component scores explained 22% of the variance in motor FIM scores; $\beta$(visual-construction) = 0.51
- Visual construction skills, attention and immediate memory component scores explained 14% of the variance in FAI scores; $\beta$(visual-construction) = 0.47
- Visual construction skills, attention and delayed memory component scores explained 21% of the variance in CHART scores
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Sample Information</th>
<th>Measures Assessed</th>
<th>FIM Scores</th>
<th>Cognistat Scores</th>
<th>NCSE Scores</th>
<th>Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man et al., 2006</td>
<td>148 subjects, probably acute stroke (not clear whether acute or sub-acute)</td>
<td>Inpatient rehabilitation (specific details unavailable) FIM and Cognistat scores were assessed at admission and discharge.</td>
<td>- FIM mobility, self care and cognition scores at admission and discharge. - Length of stay</td>
<td>- Cognistat scores. - A PCA approach was undertaken and 2 PCs were obtained. - PC1 or NCSE – 1 consisted of repetition, naming, calculation, comprehension and construction scores - PC2 or NCSE – 2 consisted of attention, judgement, memory, orientation and similarity scores.</td>
<td>Weak positive correlation between NCSE – 2 and FIM self care at admission ($r = 0.256$) and discharge ($r = 0.268$). Moderate positive correlation between NCSE – 1 and FIM cognition at admission ($r = 0.55$) and discharge ($r = 0.56$). Moderate positive correlation between NCSE – 2 and FIM cognition at admission ($r = 0.56$) and discharge ($r = 0.57$). Weak negative correlation between length of stay and NCSE- 2 ($r = -0.21$).</td>
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<tr>
<td>Cao et al., 2007; 40 young subjects (age: 18-47 years), chronic stroke</td>
<td>None At 6-12 months post-stroke, Canadian Neurological Scale (CNS, Cote et al., 1986) and BI scores</td>
<td>- CNS score - BI score</td>
<td>Linguistic function which included Token test (Boller and Vignolo, 1966), Word Fluency, and RAVLT delayed recall score), Visuospatial function</td>
<td>Subjects with global cognitive impairment had lower CNS scores and significantly lower BI scores compared to those with no or partial cognitive impairment.</td>
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</table>
were assessed orientation (Raven’s Progressive Matrices Score) and Concept formation (Similarities scale from WAIS)

- Subjects having impaired performance on these tests were divided into two groups: partial cognitive impairment (scores in 3 or 4 tasks below established norms) and global impairment (scores on all 5 tests below norms).

| Saxena et al., 2007; 141 subjects, acute stroke | None. At admission and 6 months post-stroke, Abbreviated Mental Test (AMT; Jitapunkul et al., 1991), Geriatric Depression Scale (GDS; Montorio and Izal, 1996) and BI scores were measured. | BI score | AMT (global cognitive impairment) and GDS scores. | AMT and GDS scores were significantly correlated at admission ($\chi^2=22.32; p <0.001$) and 6 months later ($\chi^2 = 16.26; p <0.001$).

- ADL dependence at 6 months was lower in those with higher AMT scores at admission ($\beta = -0.37$, OR = 0.68) and greater change in AMT scores at 6 months from baseline ($\beta = -0.48$, |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Sample</th>
<th>Measures</th>
<th>Results</th>
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<tbody>
<tr>
<td>Wagle et al., 2011; 194 subjects, acute stroke</td>
<td>Individualized rehabilitation programme tailored to the patients’ specific needs consisting of PT, OT and Speech therapy. NIH stroke scale, modified Rankin scale (mRS), RBANS and BI scores at admission and at follow up, 13 months post-stroke</td>
<td><strong>mRS score at 13 months</strong>&lt;br&gt;<strong>RBANS component scores and individual tests evaluating the different domains</strong></td>
<td><strong>For mRS scores at follow up</strong>&lt;br&gt;- A combined multiple regression of baseline NIHSS, BI, RBANS scores and age of subjects explained 44% of the variance; $\beta$ (RBANS) = -0.25&lt;br&gt;- Combinations of all RBANS component scores explained 26% of the variance; visual construction was the only significant parameter, $\beta$ = -0.31&lt;br&gt;- Component individual tests together explained 42% of the variance, only figure copy ($\beta$ = -0.23) and coding ($\beta$ = -0.48) were significant.</td>
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<tr>
<td>Milinaviciene et al., 2011; 226 subjects, acute stroke</td>
<td>Individualized rehabilitation programme tailored to the patients’ specific needs</td>
<td><strong>FIM score change from admission to discharge</strong>&lt;br&gt;<strong>MMSE score</strong>&lt;br&gt;<strong>Subjects were divided into 4 groups of severity of cognitive impairment</strong></td>
<td><strong>Subjects with moderate and severe cognitive impairment had greater change in total, motor and</strong></td>
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</table>
needs included medication, physical therapy (twice daily), occupational therapy, functional muscular electrostimulation, therapeutic massage and speech correction. Mean duration of rehabilitation was 38.8 ± 8.9 days. FIM and MMSE were measured before and after rehabilitation. depending upon MMSE scores: severe (0-10), moderate (11-20), mild (21-24) and no impairment (≥25). cognitive FIM scores compared to those with mild or no impairment. • Severe cognitive dysfunction at baseline was associated with significantly greater odds (OR = 15.18) of lower FIM scores at discharge; ($\beta$ = 2.72),

| Brown et al., 2012; 27 subjects, acute stroke | Inpatient rehabilitation (specific details unavailable). Cognistat, OT Adult Perceptual Screening Test (OT-ASPT(Cooke et al., 2005) and Developmental test of visual perception – adolescent and adult (DVPT-A(Brown et al., 2008) were assessed at admission. FIM scores were | • FIM scores | • Cognistat score • OT-ASPT score –screens for agnosias, visual spatial and constructional skills, apraxia, aacalculia, reading, writing and arithmetic. • DVPT-A score – consists of 6 subscales, 3 which are motor perception based and 3 which are visuomotor perception based. | A combination of the Cognistat, OT-ASPT and DVPT-A together explained • 71.3% of the adjusted variance in cognitive FIM scores. Visual motor search ($\beta$ = -0.59) component of the DVPT-A uniquely contributed 21% and similarities ($\beta$ = 0.29) component of the Cognistat contributed 5.8% . |
| Brown et al., 2013; 32 stroke patients, acute stroke | Inpatient rehabilitation (specific details unavailable). Cognistat and Developmental test of visual perception—adolescent and adult (DVPT-A were assessed at admission. BI scores were assessed at discharge. | • BI score at discharge | • Cognistat score  
• DVPT-A score | • 39.4% of the adjusted variance in motor FIM scores. Comprehension variable (β = 0.65) of Cognistat explaining 40% of the unadjusted variance.  
• 53.7% of the adjusted variance in FIM total score. Comprehension (β = 0.5) variable of Cognistat uniquely explained 18.2% of the variance.  
For BI score at discharge,  
Cognistat explained 64.4% of the variance. Repetition (β = 0.45) and comprehension (β = 0.48) subscales made unique contributions to the model.  
DVPT-A score explained 27.9% of the variance. Copying component (β = 0.46) made a unique contribution to the model. |
### APPENDIX – 2 Table A-2 Relationship of neuropsychological variables to recovery of motor impairments

<table>
<thead>
<tr>
<th>Author/Year Subjects, Stage</th>
<th>Intervention/ Exposure</th>
<th>Dependant measure</th>
<th>Predictors (independent variables) and domains assessed</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Barreca et al., 1999; 16 subjects, subacute stroke</td>
<td>Inpatient rehabilitation (specific details unavailable)</td>
<td>• Upper extremity function test (UEFT) score (Douglas, 1965) at discharge</td>
<td>• Halstead category test score (Reitan and Wolfson, 1995) assessing executive functioning (specifically complex concept formation and problem solving abilities). • Scores at admission and discharge and admission UEFT score were used as predictors</td>
<td>• A combination of UEFT scores and Category score at admission explained 80% variance in discharge UEFT scores. • Category test scores alone explained about 14% of the variance. • High correlation between category score and Chedoke-McMaster arm (r = -0.81) and hand (r = -0.69) subscale scores at discharge. • Significant correlation (r = -0.48) between category score at discharge and amount of intact cortex on imaging.</td>
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<tr>
<td>Dancause et al., 2002; 10 subjects with chronic stroke, 6</td>
<td>Motor adaptation paradigm involving 50° elbow flexion</td>
<td>• Error correction patterns (accounting for both the number of</td>
<td>• IQ, memory (verbal, non-verbal), attention (focussed, sustained)</td>
<td>• Combination of IQ, verbal, non-verbal memory and executive</td>
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<tr>
<th>controls movements in blocks of 7-10 trials, for a total of 150 trials. Participants were asked to correct movement errors occurring from sudden introduction or removal of load.</th>
<th>trials taken to correct movement errors and the number of errors in a block, if any; after error correction</th>
<th>attention) and executive functions (mental flexibility and problem solving) scores and upper limb FMA scores. • IQ – WAIS revised • Verbal Memory – WMS revised, digit span, short prose passages • Visuospatial (non verbal) memory – ROCF copy • Focussed attention – Cancellation test • Sustained attention – Trail making tests A and B • Mental flexibility – WCST • Problem solving – Tower of London</th>
<th>functioning explained 52.3% of the variance in error correction patterns. • FMA and executive functioning scores together accounted for almost 100% of the variance in error correction behaviors. • Executive functioning scores alone accounted for 33% of the variance.</th>
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<tr>
<td>Cirstea et al., 2006; 37 subjects, chronic stroke</td>
<td>Three groups (KR,KP, control). 75 repetitions of a reaching task per session. Daily 1-hr</td>
<td>• Kinematically measured motor performance measures of movement smoothness and</td>
<td>• Memory (verbal, non verbal), attention (sustained attention) and executive functions (mental flexibility and</td>
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<td>\textit{KP group} • Better retention of movement smoothness related to higher verbal</td>
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</table>
| sessions (total 10) over 2 wks. | variability in endpoint precision and speed.  
- Clinical outcomes – FMA and TEMPA.  
- Verbal Memory – WMS stories, RAVLT  
- Visuospatial (non verbal) memory – ROCF copy  
- Focused attention – Cancellation test  
- Mental flexibility – WCST  
- Decreased endpoint variability related to better mental flexibility and problem solving ability ($r^2 = 0.94$).  
- Greater change in FMA related to fewer deficits in verbal and visuospatial memory and better planning ability ($r^2 = 0.96$)  
- Greater change in TEMPA related to better planning ability ($r^2 = 0.84$). | Control group  
- Better retention of decreased speed variability related to fewer deficits in mental flexibility ($r^2 = 0.83$). | KR group  
- No significant
Boyd et al., 2009; 13 subjects with chronic stroke, 13 controls

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<th>Motor learning paradigm involving serial reaction time task. All subjects had to press a button corresponding to a color that appeared on the computer screen as soon as they saw it. Subjects with stroke used their less-impaired side, controls their dominant side. All subjects practised 6 blocks of 120 trials for 2 days and retention test on 3rd day</th>
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<tr>
<td>• Response time (reaction time + movement time). • The median response time was used to minimize the effect of outliers on the data</td>
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<tr>
<td>• MMSE – as an indicator of dementia • Working memory – digits backwards • Information speed processing – digit symbol coding test</td>
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<tr>
<td>• Information speed processing impaired in stroke group compared to controls. • Information speed processing was related to absolute response time in the stroke group ($r^2=0.6$).</td>
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