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# iHome: iPad application for stroke rehab at home

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## iPad Technology for Home Rehabilitation after Stroke (iHOME): A proof-of-concept randomized trial

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**Background** Tablets are a novel line of computers controlled by a multitouch screen. Fine motor movements are captured on the tablet computer through electrical fields and can be qualitatively and quantitatively assessed. Evidence is limited on tablet use for stroke rehabilitation.

**Methods** iHOME is an investigator-initiated randomized controlled pilot trial with a single-blinded outcome assessment. The intervention consists of iPad use (investigational group) vs. usual care (control group) among patients receiving conventional outpatient rehabilitation. Eligibility includes aged 18–85 years who experienced a mild ischemic or hemorrhagic

stroke (as diagnosed on neuroimaging and determined by the Chedoke–McMaster score  $\geq 3$ ). The STROKE REHAB® software for the iPad was specifically designed for patients with fine motor weakness and/or neglect. Of the total 30 patients, 20 will be in iHOME Acute (enrolled within three-months of stroke onset) and 10 patients in iHOME Chronic (enrolled more than six-months from onset).

**Outcome measures** The primary feasibility outcome is the proportion of the scheduled iPad time used (more than 70% ( $\geq 140$  mins) of the total 'dose' of intervention intended will be considered successful). Efficacy in fine motor movements will be assessed using the nine-hole peg test; time to magnify and pop the balloons in the iPad software application, and improvement in Wolf Motor Function Test.

**Conclusions** iHOME is a randomized controlled trial assessing the feasibility, safety, and efficacy of tablet technology for home use in stroke rehabilitation. The results of this study will serve as the basis for a larger multicenter trial.

**Key words:** outcomes, rehabilitation, stroke, tablet technology

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**Principal investigators:** Dr Saposnik and Dr Chow are the co-PIs of iHOME Acute. Dr Saposnik, Dr Gladstone, and Dr Schweizer are the co-PIs of iHOME Chronic. Dr Bayley is the site PI at Toronto Rehabilitation.

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### Background

Rehabilitation services are an increasingly large and important aspect of health care, especially post-stroke. The well-documented shortage of rehabilitation providers and resources has challenged the provision of adequate and appropriate rehabilitation services to stroke survivors (1–3). This includes a sub-optimal degree of intensity and duration of rehabilitation services, scarcity of care professionals and resources, and the need for more coordination of services and research (2). Risk of stroke increases with age; with the aging of the population, an increase in the prevalence of stroke is expected. Consequently, more and more patients will face the challenge of managing functional impairments (2). While conventional rehabilitation (i.e., physiotherapy and occupational therapy) helps improve motor function after stroke, the magnitude of its benefit has limitations (1,2,4). Conventional rehabilitation is time-consuming, labor- and resource-intensive, dependent on patient adherence, and limited in its availability depending on geography, and in some patients, it has modest and delayed effects (the benefit is not initially appreciated by stroke survivors) (1,3).

Tablet technology and gaming systems are novel and potentially useful strategies that apply relevant concepts in rehabilitation (i.e., repetition, intensity, and task-oriented training of the paretic extremity). Two meta-analyses evaluating virtual reality using gaming technology showed an improvement in motor function by nearly five times (OR 4.89; 95% confidence

interval [CI] 1.31–18.3) as compared with controls after stroke (5,6).

The use of virtual reality gaming has shown practice-dependent enhancement of the affected arm through the facilitation of cortical reorganization (brain plasticity) (7). Learning by imitation has been suggested to induce an imitation-dependent organization around the motor cortex through ‘mirror’ neural networks (8). In addition, recent studies have shown an increasing volume of the ventral striatum (mesolimbic pathways of brain reward system) by playing video games (9). Similarly, the implementation of tablet technology (e.g., the iPad™) applies the aforementioned principles, including the provision of multisensorial (visual, auditory and tactile) feedback, affordability, and ease of implementation. There is limited evidence on the use of this technology in stroke.

We herein propose a randomized clinical trial to assess the use of tablet technology (e.g., iPad) after an acute ischemic or hemorrhagic stroke for rehabilitation of patients discharged home.

## Rationale

The standard one-hour of outpatient rehabilitation is insufficient for providing the repetitive, intense training required for rehabilitation of fine motor recovery. In addition, limited interventions are available for home use after discharge from a rehabilitation center. Hence, there is now a need to determine the feasibility of innovative strategies for home use to cover the gap after discharge from rehabilitation institutions. iHOME is a novel, low-cost, potentially high-impact intervention aimed to close this gap.

## Methods

The goal of iHOME is to examine, relative to the standard of care, the feasibility and efficacy of an interactive software application, run on a tablet PC (the iPad), to enhance attention and fine motor function of the upper extremity and remedy visual neglect in stroke patients.

We hypothesize that tablet technology using the iPad is feasible and potentially efficacious to promote fine motor recovery of the upper extremity after stroke.

iHOME is a randomized, investigator-driven controlled pilot trial with a single-blinded outcome assessment. The intervention consists of iPad use (investigational group) vs. usual care (control group) among patients receiving conventional outpatient rehabilitation (Fig. 1). Both groups will receive the same amount of conventional rehabilitation. The iHOME trial is also subdivided into iHOME Acute and iHOME Chronic. Out of a total of 30 patients, 20 patients who have had a stroke within the last three-months will be enrolled in iHOME Acute, and 10 who have had a stroke more than six-months previously will be enrolled in iHOME Chronic. In each group, individuals will be assigned to the intervention arms (i.e., the investigational and control group) randomly. The randomization schedule will be computer-generated using random permuted-block randomization with blocks of varying sizes using an allocation ratio of 1:1.

iHOME has been registered on Clinicaltrials.gov (NCT01836159).

## Tablet technology

The iPad ([www.apple.com/ipad](http://www.apple.com/ipad)) is a novel model of tablet computer that is controlled by a multitouch display. When a user taps, swipes, pinches, or flicks the display screen using the fingers, the movements are sensed through electrical fields and are instantly transformed into lifelike actions. The iPad also uses a Wi-Fi data connection to browse the Internet, load and stream media, and install software. Our team has developed a software game application in which different-colored balloons appear on the display panel (Fig. 2). The objective of the game is for users to virtually magnify each balloon that appears to a diameter of 1.5 inches (3.8 cm) and then pop the balloon, using only their fingers. Depending on the time taken by the user to complete this task, the game progressively becomes faster, requiring the user to complete the task at a faster pace. As with other virtual reality platforms (e.g., Nintendo Wii™, Kinect™), the accessibility of the iPad also makes it potentially useful for rehabilitation at home.

## Inclusion criteria

To be eligible for the study, patients will have to fulfill the following inclusion criteria:

1. Provision of written informed consent prior to entry into the study
2. Age of 18 to 85 years
3. Evidence of ischemic or hemorrhagic stroke confirmed by CT or MRI head scan
4. Onset of symptoms less than three-months before the time of randomization (for iHOME Acute) or more than six-months before the time of randomization (for iHOME Chronic)
5. Measurable motor deficit of the upper extremity  $\geq 3$  (for iHOME Acute) or  $\geq 4$  (for iHOME Chronic) according to the Chedoke–McMaster scale (prospective participants should be able to touch their chin and contralateral knee to be eligible)
6. Functional independence prior to present stroke (0–1 on modified Rankin Scale)
7. Alertness and medical stability (according to the treating physician) and ability to follow simple verbal commands

## Exclusion criteria

Patients will be excluded from the study if any of the following criteria apply:

1. Stroke onset more than three-months ago (for iHOME Acute) or less than six-months ago (for iHOME Chronic)
2. Global aphasia or inability to follow verbal commands
3. Severe illness with life expectancy less than three-months
4. Uncontrolled hypertension, unstable angina, or recent myocardial infarction
5. History of seizures
6. Participation in another clinical trial involving rehabilitation or investigational drug
7. Any medical condition that might confound the interpretation of results or put the patient at risk (e.g., finger amputation)

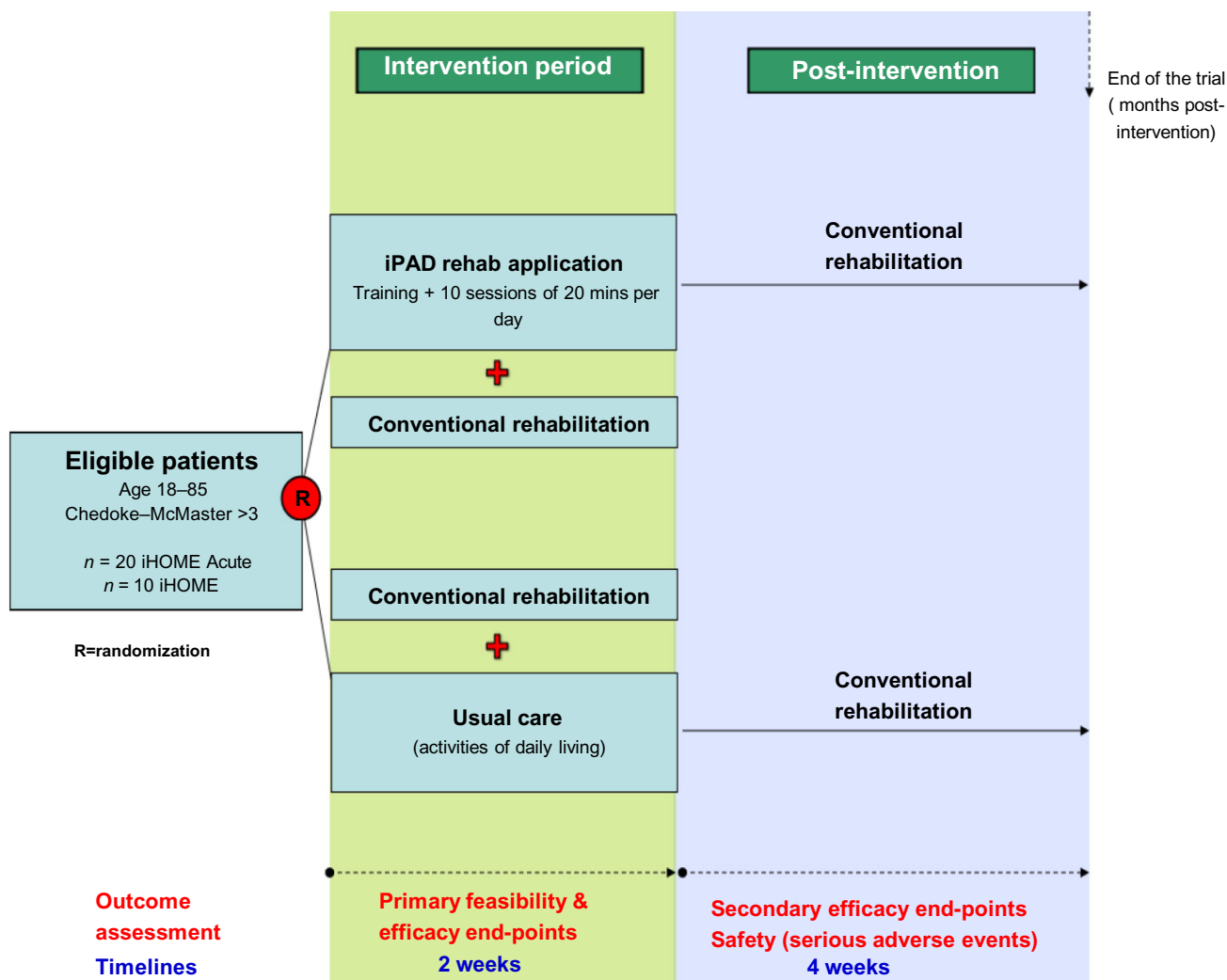


Fig. 1 iHOME design.

## Description of study arms

### iPad arm

Patients randomized to the iPad arm will be instructed to self-administer 20 mins of game sessions per day for 10 days over a two-week (14-day) period; this approach allows a grace period of four-days. Patients may play the game application for 10 mins twice per day, 20 mins once per day, or in any other configuration that is preferred. Patients will be instructed to play the iPad game with the more affected arm/hand. Start and stop times of the iPad intervention will be downloaded from the iPad, which will allow calculation of the total 'dose' received. Patients may receive outpatient rehabilitation as required as part of usual care.

The STROKE REHAB® game for the iPad was specifically designed for patients with fine motor weakness and/or neglect (see Fig. 2). The STROKE REHAB software will be treated as a Class I medical device, and this trial will be managed in accordance with the applicable sections of the Canadian Medical Devices Regulations SOR/98-282. An investigational testing authorization is not required. STROKE REHAB is not commercially available.

The STROKE REHAB game consists of six stages:

1. Popping a stationary balloon
2. Popping a moving balloon
3. Popping a pair of stationary balloons
4. Popping a pair of moving balloons
5. Stretching a balloon to pop
6. Balloon/text distraction test

### Control arm

Patients randomized to the control arm will be instructed not to play with an iPad during the two-week intervention period (in case they have one). Patients may receive outpatient rehabilitation, as required per usual care.

### Implementation of interventions

Patients will be approached for consent to participate in the iHOME study. Consent will be obtained following Good Clinical Practice guidelines. Patients will be randomly assigned to one of the two groups: the iPad intervention group or the control group. Patients randomized to receive the iPad intervention will be provided with a specially configured iPad to take with them, with the intervention application installed on it but no other applications (i.e., a locked device). Patients randomized to the iPad will receive

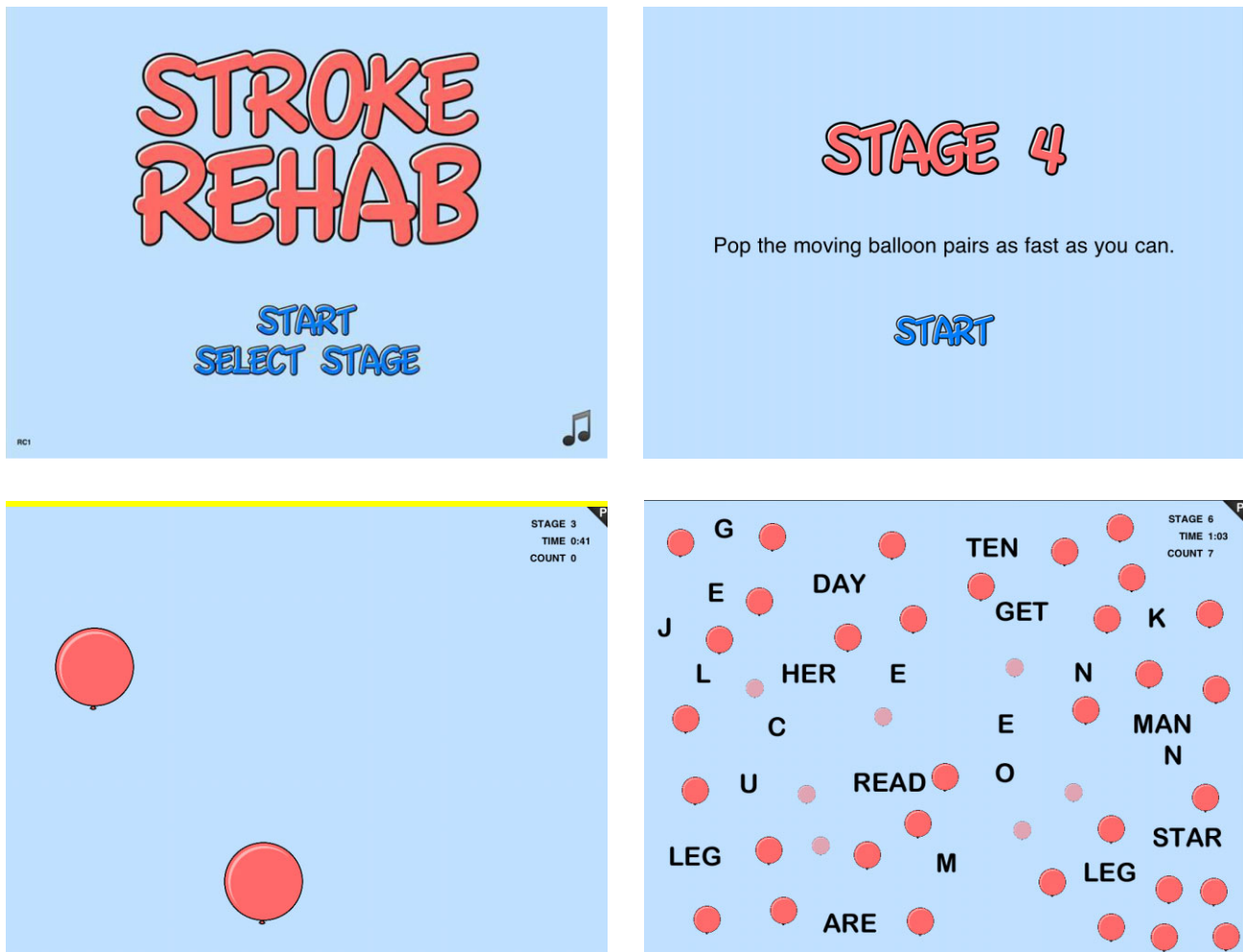


Fig. 2 Snapshots of STROKE REHAB® application interface.

verbal instructions facilitated by the training mode of the STROKE REHAB software. Patients in the control group will not receive an iPad and will be asked not to use an iPad if one is available at home.

**Data collection**

Data on patient characteristics will be collected at baseline; characteristics assessed will include sociodemographic factors, handedness, comorbid conditions, whether or not patients are daily iPad users, and stroke features at baseline (type, severity on the Canadian Neurological Scale or the National Institutes of Health Stroke Scale, side and site of stroke, and disability at baseline according to the modified Rankin Scale and the Barthel Index for activities of daily living) (Table 1). The assessors are already trained and accredited in the use of the scales. Baseline motor function will be assessed using the nine-hole peg test, a modified version of the Wolf Motor Function Test (10), and the Box and Block Test (11,12); quality of life will be determined by the Stroke Impact Scale (13) and visual neglect using the Star Cancellation Test or Line Bisection test. In addition, a single training session will be delivered to introduce the iPad technology to all patients in both treatment arms; the training session will be con-

ducted using the iPad’s ‘training mode’. Subsequently, baseline data on an actual/live iPad game score will be collected for all patients.

**Outcome measures**

The primary outcome is feasibility, defined as the total ‘dose’ of intervention received as a proportion of the amount of time scheduled for iPad use (20 mins per day × 10 days = 200 mins). If patients receive at least 70% (≥140 mins) of the total ‘dose’ of intervention intended, the outcome will be considered successful. This will be measured by the amount of time the patient uses the application (these data will be stored in the application).

Efficacy is a secondary outcome measure of this pilot study. Efficacy in fine motor function will be measured by improvement in the time to complete the nine-hole peg test, time taken to magnify and pop the balloons in the iPad software application as determined by the iPad game score, number of fine motor tasks completed on the Wolf Motor Function Test (10), and improvement on the Box and Block Test (12) in the postintervention visit. Efficacy in visual neglect will be measured by improvement in the Star Cancellation Test or Line Bisection bisection test (14).

**Table 1** Study procedures and assessments

Study Procedure	Baseline/ randomization	Postintervention visit (15–17 days afterward)
Inclusion/exclusion	✓	✗
Informed consent	✓	✗
Training session	✓	✗
Randomization	✓	✗
Medical history and patient characteristics prior to stroke	✓	✗
Assessment of qualifying stroke	✓	✗
Canadian Neurological Scale or National Institutes of Health Stroke Scale (severity)	✓	✗
Modified Rankin Scale	✓	✓
Barthel Index	✓	✓
Star Cancellation or Line Bisection Test (visual neglect)	✓	✓
Primary outcome measure (feasibility)		
Total time of iPad use (mins)	✗	✓
Main efficacy outcomes		
Nine-hole peg test score	✓	✓
Modified Wolf Motor Function Test score	✓	✓
Secondary efficacy outcomes		
Box and Block Test score	✓	✓
Stroke Impact Scale	✓	✓
iPad game scores	✓	✓
iPad questionnaire	✗	✓

**Table 2** Postintervention iPad questionnaire

1. Did you enjoy playing with the iPad (STROKE REHAB application)?										
1	2	3	4	5	6	7	8	9	10	
Not at all										Very much
2. Did you like using your fingers?										
1	2	3	4	5	6	7	8	9	10	
Not at all										Very much
3. Did you like the music when popping balloons?										
1	2	3	4	5	6	7	8	9	10	
Not at all										Very much
4. I thought playing the STROKE REHAB application was quite enjoyable.										
1	2	3	4	5	6	7	8	9	10	
Not at all										Very much
5. I would be willing to continue using the STROKE REHAB application because it improves my arm and hand control for my daily activities.										
1	2	3	4	5	6	7	8	9	10	
Not at all										Very much

Measures of efficacy will include the Box and Block Test, visual neglect as measured by the Star Cancellation Test or Line Bisection Test, and the modified Rankin Scale, Barthel Index, and Stroke Impact Scale, scores on all of which will be collected within three working days after the final study intervention session (10–14). In addition, posttreatment data on the iPad game score will be collected for all patients. Finally, all patients will be asked to reply to a questionnaire on their perception of the iPad intervention (Table 2).

### Blinding

The study coordinator and patients participating in this study will not be blinded to the intervention. To limit knowledge of the iPad software, and to ensure that other caregivers and support staff are, as far as possible, not aware of subject allocation (which may introduce bias), all baseline, postinterventional, and follow-up data will be collected by a blinded assessor.

### Study samples

For iHOME Acute, 20 patients will be enrolled. Patients will be randomly allocated in a 1:1 ratio to two treatment arms: 10 will be allocated to usual care (control group), and 10 will be allocated to the iPad intervention arm (investigational group). Patients will be recruited from the Toronto Rehabilitation Institute and St. Michael's Hospital.

For iHOME Chronic, 10 patients will be enrolled. Patients will be randomly allocated in a 1:1 ratio to two treatment arms: 5 will be allocated to usual care (control group), and 5 will be allocated to the iPad intervention arm (investigational group). Patients will be recruited from Sunnybrook Health Sciences Centre and St. Michael's Hospital.

### Analytical plan

As this is a pilot study, feasibility is the primary outcome. The primary analysis is based on the total amount of intervention

received with respect to the total amount of time scheduled for intervention. We consider a patient having received 70% of the total amount of intervention scheduled (i.e.,  $\geq 140$  mins) to be a successful outcome. We will compute the proportion of patients having a successful outcome along with the 95% confidence interval. We will also compute the average intervention time with 95% confidence interval.

Efficacy (the secondary outcome) will be compared between the groups by means of analysis of covariance, where the follow-up score is the outcome and the baseline score is the covariate (in addition to the group indicator). Although no statistically significant difference is expected to be found in this trial, the standard deviation will be used in planning the next efficacy trial. Proportions of adverse events in each group will be computed and also compared with Fisher's exact test. Differences are not anticipated, so if one were to be found, it would be important to characterize it. Appropriate descriptive statistics for the efficacy outcomes will be computed (means and standard deviations for pseudocontinuous variables and proportions for discrete variables).

### Privacy, safety, and ethics

The protocol is simple, with no safety or ethical concerns. Individual-level consent will be obtained prior to enrollment. We will comply with the Personal Health Information Protection Act and the Personal Information Protection and Electronic Documents Act. iHOME was approved by the Research Ethics Boards at St. Michael's Hospital, Sunnybrook Health Sciences Centre, and Toronto Rehabilitation Institute. The study will involve no drug intervention, blood work, or invasive procedures. Patients may potentially benefit from improvement in fine motor function facilitated by iPad usage.

### Discussion

Neurorehabilitation has been proven the most effective therapy after stroke. In a systematic review and meta-analysis of motor recovery after stroke, high-intensity physiotherapy and constraint-induced movement therapy were found to be among the most effective interventions (4). Other novel technologies (e.g., robotics, virtual reality) are promising (5,15). Little information is available on the use of tablet technology in stroke rehabilitation. Some studies suggest that interactive visuohaptic technology could be beneficial for attention training for patients with severe traumatic brain injury in the early stages of recovery (16). Another study including 100 occupational therapy patients revealed that over 90% could communicate and set up clinical goals by using an iPad application to aid decision-making (17).

Conventional rehabilitation has been described as tedious and resource-intensive, offering low immediate reward for stroke survivors (1,3,5,18). Moreover, it requires transportation to a rehabilitation facility after patients are discharged home. Few interventions are currently available for home use. iHOME is a pilot randomized clinical trial aiming to determine the feasibility and potential efficacy of tablet use for stroke patients after discharge home.

Recovery of motor skills depends on neurological recovery, adaptation, and learning of new strategies and motor programs. Repetitive, intensive, and task-specific functional training is the current paradigm applied in neurorehabilitation after stroke to facilitate motor relearning and consequent improvement of function (19,20). Such improvement may be due to cortical reorganization and brain plasticity (21,22), made possible by engagement of the mirror neuron system (23), long-term potentiation effects, and the 'brain reward system' (motivation) (24).

If proven to be effective, the use of tablet technology will have a broad range of potential outcomes and benefits. At the patient level, there is an opportunity for a new, exciting mode of stroke rehabilitation that may be undertaken in various clinical and nonclinical settings. For example, this innovative, low-cost approach may help intensify treatment by expanding the time opportunity to promote fine motor improvement for stroke patients residing at home, who would otherwise have limited exposure to such activities. Moreover, iHOME includes a broad range of outcome measures to ensure that information will become available regarding fine motor improvement, visual perception, cognition, quality of life, and patients' preferences and satisfaction. The results of this study will be transferable to practice across Ontario as well as nationally and internationally.

### References

- 1 Jutai JW, Teasell RW. The necessity and limitations of evidence-based practice in stroke rehabilitation. *Top Stroke Rehabil* 2003; **10**:71–8.
- 2 Teasell RW, Foley NC, Salter KL, Jutai JW. A blueprint for transforming stroke rehabilitation care in Canada: the case for change. *Arch Phys Med Rehabil* 2008; **89**:575–8.
- 3 Teasell R, Meyer MJ, McClure A et al. Stroke rehabilitation: an international perspective. *Top Stroke Rehabil* 2009; **16**:44–56.
- 4 Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol* 2009; **8**:741–54.
- 5 Saposnik G, Levin M. Virtual reality in stroke rehabilitation: a meta-analysis and implications for clinicians. *Stroke* 2011; **42**:1380–6.
- 6 Henderson A, Korner-Bitensky N, Levin M. Virtual reality in stroke rehabilitation: a systematic review of its effectiveness for upper limb motor recovery. *Top Stroke Rehabil* 2007; **14**:52–61.
- 7 Jang SH, You SH, Hallett M et al. Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind preliminary study. *Arch Phys Med Rehabil* 2005; **86**:2218–23.
- 8 Buccino G, Solodkin A, Small SL. Functions of the mirror neuron system: implications for neurorehabilitation. *Cogn Behav Neurol* 2006; **19**:55–63.
- 9 Kuhn S, Romanowski A, Schilling C et al. The neural basis of video gaming. *Transl Psychiatry* 2011; **1**:e53.
- 10 Wolf SL, Catlin PA, Ellis M, Archer AL, Morgan B, Piacentino A. Assessing wolf motor function test as outcome measure for research in patients after stroke. *Stroke* 2001; **32**:1635–9.
- 11 Desrosiers J, Bravo G, Hebert R, Dutil E, Mercier L. Validation of the box and block test as a measure of dexterity of elderly people: Reliability, validity, and norms studies. *Arch Phys Med Rehabil* 1994; **75**:751–5.
- 12 Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the box and block test of manual dexterity. *AM J Occup Ther* 1985; **39**:386–91.
- 13 Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. *Stroke* 1999; **30**:2131–40.

- 14 Friedman PJ. Spatial neglect in acute stroke: The line bisection test. *Scand J Rehabil Med* 1990; **22**:101–6.
- 15 Laver KE, George S, Thomas S, Deutsch JE, Crotty M. Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev* 2011; (9):CD008349.
- 16 Dvorkin AY, Ramaiya M, Larson EB *et al.* A ‘virtually minimal’ visuo-haptic training of attention in severe traumatic brain injury. *J Neuroengineering Rehabil* 2013; **10**:92.
- 17 Tomori K, Uezu S, Kinjo S, Ogahara K, Nagatani R, Higashi T. Utilization of the iPad application: aid for decision-making in occupation choice. *Occup Ther Int* 2012; **19**:88–97.
- 18 Lucca LF. Virtual reality and motor rehabilitation of the upper limb after stroke: a generation of progress? *J Rehabil Med* 2009; **41**:1003–100.
- 19 Barreca S, Wolf SL, Fasoli S, Bohannon R. Treatment interventions for the paretic upper limb of stroke survivors: a critical review. *Neurorehabil Neural Repair* 2003; **17**:220–6.
- 20 Kwakkel G. Impact of intensity of practice after stroke: issues for consideration. *Disabil Rehabil* 2006; **28**:823–30.
- 21 Nudo RJ, Milliken GW. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *J Neurophysiol* 1996; **75**:2144–9.
- 22 Luft AR, McCombe-Waller S, Whittall J *et al.* Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. *JAMA* 2004; **292**:1853–61.
- 23 Mukamel R, Ekstrom AD, Kaplan J, Iacoboni M, Fried I. Single-neuron responses in humans during execution and observation of actions. *Curr Biol* 2010; **20**:750–6.
- 24 Ikemoto S. Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. *Neurosci Biobehav Rev* 2010; **35**:129–50.