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A non-task-oriented approach based on high-dose playful movement exploration for rehabilitation of the upper limb early after stroke: A proposal

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Abstract.
BACKGROUND: Stroke is one of the leading causes of disability in the world, with the upper limb being affected up to 80% of the time. Current rehabilitative therapies for the upper limb, primarily centered on task-oriented training, are ineffective at boosting recovery from motor impairment beyond what is expected from spontaneous biological recovery and instead promote compensatory strategies in order to perform specific activities of daily living.
PURPOSE: To give a critical overview of animal and clinical literature that support the idea that a non-task-oriented approach may be more fruitful for recovery from motor impairment, and to propose a novel therapeutic paradigm designed to bolster spontaneous biological recovery early after stroke.
CONCLUSIONS: A focus on movement quality, rather than task completion, practiced at high intensity and dosage in an enriching environment may be the training approach that best exploits the sensitive period early after stroke in order to amplify the generalized gains seen with spontaneous biological recovery.

Keywords: Upper extremity rehabilitation, stroke rehabilitation

1. Introduction

Stroke is one of the leading causes of disability in the world (Benjamin et al., 2017; Feigin et al., 2017), with the upper limb being affected up to 80% of the time (Parker et al., 1986; Heller et al., 1987; Rathore et al., 2002). Recent therapeutic advances in the hyperacute poststroke period have dramatically improved clinical outcomes (Albers et al., 2000; Berkhemer et al., 2015; Benjamin et al., 2017). After surviving the stroke, however, patients face a more discouraging landscape: rehabilitative therapies are ineffective at boosting recovery from motor impairment beyond what is expected from spontaneous biological recovery and instead emphasize training compensatory strategies in order to perform specific activities of daily living (ADLs) (Pollock et al., 2014; French et al., 2016). *Task-oriented training,* based on motor learning principles, is the gold standard for poststroke rehabilitation, both for current therapeutic approaches and clinical investigation (Winstein et al., 2014). We argue, however, that a

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non-task-oriented approach may be more fruitful for recovery from motor impairment, and based on this contention, propose a novel therapeutic paradigm designed to bolster the spontaneous biological recovery early after stroke.

First, we will review the proportional recovery rule and shed light on how this mathematical relationship signifies spontaneous biological recovery. We will also argue for the possible existence of a sensitive period in humans in which behavioral gains can be maximized by engaging intrinsic neural repair processes. Next, we will discuss the evidence that suggests that in order to recover from impairment, the focus of training should be on movement quality rather than task accomplishment. We will then review the role of environmental enrichment and playful exploration in potentiating practicing high quality movements. Lastly, we will describe a novel video gaming paradigm, currently employed in an ongoing phase II clinical trial, which encourages playful motor exploration of arm movements early after stroke.

2. Spontaneous biological recovery and the rule of proportional recovery

Spontaneous biological recovery is used to refer to the phenomenon by which almost all patients recover from impairment to some degree, mostly within the first three months after stroke (Cramer, 2008; Krakauer et al., 2012). The word "spontaneous" irritates some because it implies that the observed recovery is attributable solely to an endogenous repair process rather than to current rehabilitative interventions. In support of this, however, is the fact that recovery from motor impairment in the upper limb can be captured by a remarkably simple and predictable proportional recovery rule, which states that most patients will recover a fixed proportion of their maximal potential recovery at three months after stroke (Prabhakaran, 2008; Winters et al., 2015; Buch et al., 2016). The very existence and regularity of this proportional recovery rule implies that current therapies do not have an additional effect on recovery above that expected from spontaneous biological recovery. This has recently been confirmed empirically, as higher doses of conventional therapy do not alter this mathematical relationship (Byblow et al., 2015). In other words, the proportional recovery rule captures spontaneous biological recovery processes that are not impinged upon by existing rehabilitation paradigms. This can be asserted because there is great heterogeneity in clinical care, and assuming that these various kinds of therapy would have differential effects on impairment, then the observed correlation would be diluted out. Notably, however, about 50% of patients with severe hemiparesis do not exhibit proportional recovery ("non-recoverers") (Winters et al., 2015; Zarahn et al., 2011). The ability to recover is dependent on the degree of damage to the corticospinal tract (Byblow et al., 2015).

Animal studies have demonstrated that training early after stroke can boost the gains expected from spontaneous biological recovery, suggesting that the conditions enabling spontaneous biological recovery also appear to have the ability to enhance responsiveness to training (Nudo & Milliken 1996; Murata et al., 2008). Zeiler and colleagues showed that mice that have been given a focal cortical infarction in the caudal forelimb area (CFA), analog to the primary motor cortex, regained their preinfarct performance level on a prehension task when poststroke training was initiated within forty-eight hours but only showed small gains if training was delayed by a week (Fig. 1A) (Ng et al., 2015). This result, along with other studies in rodents (Biernaskie et al., 2004; Murphy & Corbett 2009), strongly suggests the existence of a time-limited window of increased responsiveness to training, presumably induced by a unique poststroke plasticity milieu. A counterintuitive implication of such an ischemia-induced sensitive period is that it should be possible to reopen it with a second stroke and thereby trigger recovery from a first stroke. This hypothesis has been directly tested by inducing a second focal stroke in the ipsilesional medial premotor area of mice that had only partially recovered prehension after a first CFA stroke because training had been delayed (Zeiler et al., 2016). The remarkable finding was that even though the second stroke worsened the initial deficit, training initiated within forty-eight hours of the second stroke allowed prehension to fully return to normal levels (Fig. 1B). This benefit in recovery was not observed if the second stroke was placed in the ipsilesional occipital cortex, ruling out a nonspecific effect. Obviously, inducing second strokes is not an option for patients, but it does suggest that unique molecular, cellular, and physiological changes greatly enhance responsiveness to training for a short period of time after stroke. As of late 2017, there is as yet no evidence, either physiological or behavioral, for an equivalent poststroke sensitive period in humans. A couple of ongoing studies, however, are exploring this crucial issue (McDonnell et al., 2015; Dromerick et al., 2015).

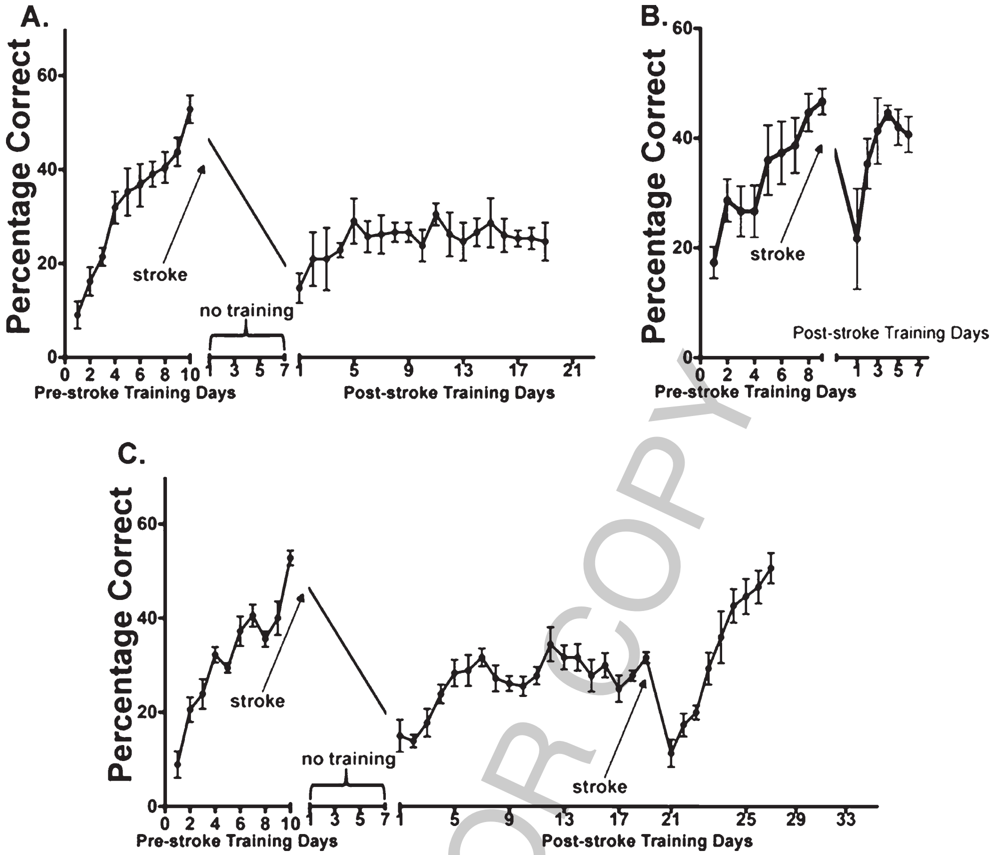

Fig. 1. Resetting the sensitive period window for recovery with a second stroke. Mice were trained to perform a skilled prehension task to an asymptotic level of performance after which they underwent photocoagulation-induced stroke in the caudal forelimb area (CFA). (A) When poststroke training was delayed by seven days, mice hit a low performance level despite two weeks of training. (B) Starting training the following day after stroke, mice returned to normal levels of performance. (C) A second photocoagulation-induced stroke was then induced in the ipsilesional medial premotor cortex (agranular medial cortex). Subsequently, the mice were retrained the following day after the second stroke and returned to pre-stroke levels of performance. Adapted from Zeiler et al. (2016).

3. Stroke rehabilitation: Movement quality versus task accomplishment

The International Classification of Functioning, Disability, and Health (ICF) provides a conceptual framework for disability with different hierarchical levels: impairment, activity limitation, and participation restriction (World Health Organization 2002); each level underlying the next one. Motor impairment after stroke comprises deficits in strength and motor control, the latter being defined as the ability to make coordinated, accurate, goal-directed movements (Krakauer, 2005). These deficits are at the core of stroke-related disability, nonetheless, at the current time no form of upper limb rehabilitation has meaningful impact at the level of impairment. Indeed, perhaps in an unspoken admission of this fact, the entire system of modern post-stroke rehabilitative care focuses instead on relearning ADLs at a fixed level of impairment. The main concept is that of compensation, which is the use of task-oriented training to employ the capacities that a patient has left. Current rehabilitation of stroke, therefore, consists of training on specific ADLs to reduce disability and promote independence, while emphasizing compensatory strategies.

Repetitive task-oriented training is considered by many to be the new gold standard for neurorehabilitation, superior to both standard therapy and to the neurophysiological approach advocated by Brunnstrom and others (Winstein et al., 2014). That said, it is hard to accurately define the actual content of "standard therapy".

In the 1980's, there was a shift from a neurophysiological toward a motor learning–based perspective in neurorehabilitation. The neurophysiological approach is based on facilitation; the encouragement of normal-looking movement patterns through assistive guidance that reproduces normal sensory feedback. There was a growing dissatisfaction, however, with this approach because of a lack of "functional carryover" to ADL tasks (Gordon, 1987). In essence there was a shift from improving movements per se to task performance and completion. The conceptual shift toward task-oriented training had a practical consequence: patient care moved to a focus on practicing everyday tasks and learning coping strategies. The efficacy of this new rehabilitative approach was deemed to be best captured by global ADL scales. For example, in the United States, the Functional Independence Measure (FIM) is the standard tool to measure responsiveness during inpatient stays. It was designed in 1984 with the aim of capturing global disability by combining motor and cognitive activities and social functioning, by measuring degrees of independence in ADLs (Keith et al., 1987; Ottenbacher et al., 1996). Unfortunately, however, the measurement became the treatment target. This is known as Goodhart's law, originally used in the context of economics, which states, "As soon as the government attempts to regulate any particular set of financial assets, these become unreliable as indicators of economic trends", more generally when a measure becomes the target, it ceases to be a good measure (Strathern, 1997).

Currently, the central tenet of stroke neurorehabilitation is motor training; motor training, however, is a much more ambiguous notion than is generally appreciated. For a healthy individual, motor training usually means extended practice at a goal-directed task, which leads to motor learning with subsequent task-specific improvements. Motor training after stroke can promote either recovery or compensation. In both cases, as in healthy individuals, the goal of the training is task-specific. In contrast to task-specific learning, spontaneous biological recovery can lead to a return of all behaviors to varying degrees (Cramer, 2008; French et al., 2016; Kitago & Krakauer 2013).

Recapitulating thus far, early after a stroke two phenomena seem to be happening in parallel: conventional therapy targets ADLs by training compensatory strategies, while spontaneous biological recovery reverses impairment. Is there a way to optimize rehabilitative efforts by amplifying spontaneous biological recovery mechanisms to target impairment? Murata and colleagues addressed this question in macaques that were given lesions in the digit representation in primary motor cortex (Murata et al., 2008). Subsequent testing with a Klüver board with five cylindrical wells of different diameter revealed that precision grip could recover to prelesion performance levels in one to two months if the monkeys were given intensive training beginning one day after the lesion. In contrast, when the primates were not given any training, spontaneous biological recovery led to the ability to flex and extend all the joints of the thumb and index finger, allowing the use of compensatory grip strategies, but not precision grip. Close examination of the time courses of recovery for both the trained and untrained monkeys, strongly suggest that spontaneous repair processes have separable effects on recovery but interact with intense training. For example, around day 30, both groups of monkeys made a small proportion of precision grips, but within days the proportion increased in the trained group, whereas, it reduced to zero in the untrained group. This finding strongly suggests that the ability to individuate the digits for precision grip emerged spontaneously, albeit tenuously, in both groups at around a month, but training was needed to consolidate this behavior. It appears that without practice, precision grip was not explored or improved upon, being outcompeted by a compensatory strategy.

Clinical studies have shown that spontaneous biological recovery occurs in the first 3 months after stroke in humans (Skilbeck et al., 1983; Parker et al., 1986; Duncan et al., 1992; Nakayama et al., 1994) and that there is a short-lived window (one week) of increased responsiveness to training in experimental rodent strokes (Biernaskie et al., 2004; Murphy & Corbett 2009; Ng et al., 2015; Zeiler et al., 2016). How can this information be combined to develop new rehabilitation approaches that go beyond task-oriented compensatory training? First, one must begin with the assumption that there is mechanistic overlap between spontaneous biological recovery in humans and the sensitive period shown in mice. If this assumption is correct, then it is to be hoped that a window of increased responsiveness to training exists in humans but that it may last longer, perhaps for at least a month or more. A second assumption is that it should be possible to devise a form of motor training that can be given at sufficiently high dose within the sensitive period so that it leads to general gains and not just task-specific ones—that is, it overcomes motor learning's curse of task specificity (Bavelier et al., 2012).

As argued above, current levels of rehabilitation do not appear to have an impact on impairment beyond what can be expected from spontaneous biological recovery. Unfortunately, most studies and randomized controlled trials (RCTs) in neurorehabilitation have been conducted in patients with chronic stroke (Hatem et al., 2016). Very few equivalently sized studies have been conducted in the first weeks to three months after stroke, which is the period when most conventional neurorehabilitation is given (Stinear et al., 2013). Thus, RCTs have not been conducted to prove efficacy for the current standard of inpatient and outpatient care during the first three months after stroke or to test new interventions in this same time period (Stinear et al., 2013). Moreover, very few studies in humans have explicitly sought to test whether intense training early after stroke can either augment or add to spontaneous biological recovery in a manner analogous to the nonhuman primate studies described above. Few of the recent trials that investigated interventions within the first three months had an impairment measure as either a primary or secondary outcome.

There are many reasons why there have been so few studies to date that have tried to significantly increase the dose and frequency of either current therapeutic approaches or to test new ones at high intensity. These include logistics, economics, practice biases (an emphasis on participation and activity levels over impairment), and the persisting scientific concern, based largely on rodent studies in the 1990s, that very early intense therapy may extend infarct volume and worsen outcome (Kozlowski et al., 1996; Humm et al., 1999; Bland et al., 2000). These concerns have, in our view, been exaggerated and are probably only relevant in the case of large cortical strokes. In addition, the most notable studies to date that have studied early intervention, either did not target impairment of the upper limb (Dromerick et al., 2009) or focused on balance and gait (the AVERT Trial Collaboration Group, 2015). For a more in-depth critique of these studies see (Krakauer & Carmichael, 2017).

The Explaining PLastICITy (EXPLICIT) trial is directly relevant to the question of how task-based training may or may not interact with spontaneous biological recovery (van Kordelaar et al., 2013; Kwakkel et al., 2016). In the arm of the trial pertinent to the current discussion, fifty-eight patients, deemed to have a favorable prognosis because they had >10° of finger extension, were randomly allocated to three weeks of modified Constraint-Induced Movement Therapy (mCIMT) or usual care only, both of which were started within 14 days of the stroke. Patients in the CIMT group received sixty minutes a day, while the usual care group received thirty minutes a day. Clinically relevant differences in Action Research Arm Test (ARAT) in favor of mCIMT were found at five, eight, and twelve weeks but not after twenty-six weeks. In contrast, there were no statistically significant differences between the mCIMT and usual care groups for the Fugl-Meyer Assessment of the Upper Extremity (FMA-UE). Thus, while increased task-oriented training led to improvement on a scale that measures activity, this was not accompanied by concomitant reductions in impairment. The authors concluded that there was no evidence of an influence on spontaneous biological recovery of underlying impairments based on clinical scales, suggesting that functional improvements of the mCIMT group were based on compensatory strategies. This is indeed true with respect of the FMA-UE, but it is important to note that in the monkey studies that we have reviewed, it is control of prehension that was assayed. It is possible therefore that the ARAT changes are not just compensatory. In support of this conclusion, a recent study failed to achieve a similar large ARAT change in the chronic stage (Lang et al., 2016). Thus we may need not just better treatments for impairment, but better compensation-proof measures of it. The FMA-UE simply may not suffice. Finally, we should briefly mention the recently completed Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) trial, which enrolled patients on average at forty-five days post-stroke (Winstein et al., 2016). The goal of this phase III trial was to both investigate the effect of dose of occupational therapy and compare two types of occupational therapy controlling for dose. There was no difference across the different interventions for any of the outcome measures. Importantly for this discussion, impairment changes were not examined. Several conclusions can be drawn from this survey of early rehabilitative intervention (within three months of stroke) in both nonhuman primates and humans. In the nonhuman primates, intense training at the level of the motor control deficit/impairment can augment what is expected from spontaneous biological recovery. In contrast, there is still no good evidence that this is true in humans early after stroke. This lack of evidence, however, should not be taken as an indication that a favorable interaction between training and spontaneous biological recovery cannot occur in humans. Rather, the problem is that impairment is rarely targeted in patients early after stroke, so the necessary studies have not been done. As outlined above, the largest trials did not measure impairment changes. Those trials that did look at impairment, such as EXPLICIT, did not have an impairment-targeted treatment (van Kordelaar et al., 2013; Kwakkel et al., 2016). Thus, either impairment is not measured at all or therapies do not target it.

Overall, the current findings in humans suggest that whereas spontaneous biological recovery has an effect on motor activity measures via its effect on impairment, the reverse has not been demonstrated for task-oriented training even early after stroke, as it primarily teaches compensation and has no appreciable effect on the FMA-UE. In contrast, the kind of training given in the primate studies focuses heavily on movement execution rather than goal completion and is given at much higher doses.

4. Enrichment and playful exploration

A way to think about the difference between the effects of training and spontaneous biological recovery is that the former is usually task specific and the latter is general. This leads to a paradox: how does one train general recovery or target impairment when training must always be with a particular task? This question strongly suggests that a new kind of rehabilitation needs to be developed for patients early after stroke that will interact with spontaneous biological recovery to maximize generalization of gains. A clue to how to do this was provided by Dale Corbett and colleagues, in an influential experiment in rats that investigated the rehabilitative effects of a more varied and enriched environment (Biernaskie et al., 2004). Rats were given a middle cerebral artery occlusive stroke and were exposed to an enriched environment (ER). The ER consisted of large cages that could house five to seven rats and contained toys, ramps, tubes and ropes, and a prehension apparatus, which was not overtly trained on. There were significant gains in prehension when tested on a different task when ER was initiated within five or fourteen days but not thirty days after stroke. In an interesting follow-up study, the same group showed that repeating the ER two more times, at a level even more intense than the initial session for two weeks at a time, beginning about three months poststroke provided no additional benefit even though there still was room for improvement. This failure of tune-ups again demonstrated that there is a window of responsiveness to ER that then closes, with no further responsiveness to even intensified versions of the original therapy.

The precise mechanisms of enrichment are yet to be elucidated, but likely work through providing task variety, and motivational effects that increase the gain on skill learning and retention through the provision of reward, perhaps mediated through the modulatory effects of neurotransmitters such as dopamine (Johansson & Ohlsson 1996; Biernaskie & Corbett 2001; Hosp et al., 2011). It has been shown in non-human primates and humans that reward can lead to an instantaneous shift in the speed-accuracy trade-off for a task (Xu-Wilson et al., 2009; Manohar et al., 2015; Wong et al., 2015), this phenomenon could potentially interact with larger practice-induced gains in skill (Hikosaka et al., 2013).

In order for spontaneous biological recovery and increased responsiveness to training, both consequences of a short-lived postischemic milieu, to optimally combine in the rehabilitation setting, it is necessary to come up with training regimens for the upper limb that are very different from current ones and are perhaps analogous to enrichment in rodents.

What kind of arm movements should patients be encouraged to explore? A clue comes from a very interesting study of six healthy subjects who were given a wearable motion-tracking system to record their arm movements as they went about their daily life (Fig. 2) (Howard et al., 2009). Despite the large range of possible movements, the investigators found that during most normal everyday tasks, the arms are confined to a small volume of space around the body and movements are predominantly in the vertical, not the horizontal plane, across a variety of tasks. Just as enriched environments for rodents provide full-field stimulation of social, physical, and perceptual needs, Virtual Reality (VR) and video gaming could provide an equivalently enriched environment for humans to practice arm movements in the statistical cloud of everyday life.

5. Bringing it all together: The SMARTS 2 trial

Seeking to devise a novel therapeutic approach that targets impairment, an ongoing phase II, randomized, single-blinded, pilot multicenter trial, Study to enhance Motor Acute Recovery with intensive Training after Stroke (SMARTS 2) (NCT02292251), enrolls patients with moderate to severe arm paresis. They are encouraged to make playful non-task-based exploratory arm movements while playing a sui generis video game (Fig. 3). The primary objective of

Fig. 2. 3-D probabilistic clouds of hand and elbow positions in healthy adults. Front (left) and side views (right) show the outer boundaries of regions that represent 90% of all locations visited by a typical subject's wrists and elbows. Courtesy of Daniel Wolpert, modified from Howard et al. (2016).

this trial is to investigate the effect of early and intensive non-task oriented therapy on the recovery from motor impairment in the upper limb after stroke.

The trial relies on a model of training-induced recovery that we created based on a synthesis of existing human and animal data. The hypothesis we have developed is that training and enhanced plasticity conditions can only operate on preexisting cortical substrate (latent architecture) that is already wired for control of the relevant effector. So for example, premotor regions can project to the spinal cord and control the upper limb, but these pathways need to be facilitated or upregulated by training plus spontaneous biological recovery. This model does not depend on the notion of map expansion or invasion of one representation into another as we think that these phenomena are not causally related to recovery. This model can be summarized by the equation:

$$\text{Recovery}_{[\text{magnitude}]} = \text{Behavior}_{[\text{dose}]} \times \text{Representation}_{[\text{residual amount}]} \times \text{Plasticity}_{[\text{level}]}$$

Here, $\text{Behavior}_{[\text{dose}]}$ refers to behavioral training that can engage spontaneous biological recovery and is relevant to a specific impaired effector. $\text{Representation}_{[\text{residual}]}$ presumes cortical regions with prestroke effector representations of varying strengths that can be augmented via repair mechanisms and behavioral training. $\text{Plasticity}_{[\text{level}]}$ refers to the conditions of heightened plasticity that are present around the infarcted brain tissue and fall off with distance and normalize over time.

The video game used in the trial was designed in-house and is provides highly immersive virtual oceanic environment (Russell, 2015). The basic component of the videogame is a full physical simulation of three different cetaceans (Bottlenose Dolphin, Commerson's Dolphin, and Orca), Fish, and Sharks. Each cetacean is composed of a muscular-skeletal biological simulation, and an advanced physics engine. A user is able to control the intention of the cetaceans by moving their arm in 3D with an exoskeletal robot that provides anti-gravity weight support but no assistance along the line of movement. In essence the patient is "jacked into" the animal. The goal is to provide a visceral experience in which the patient is so motivated to be the dolphin and so immersed in the oceanic environment that they are unaware that they are making arm movements relevant to everyday life at high frequency. Thus the patient makes a large number of exploratory arm movements, somewhat analogous to the playful non goal-directed arm movements that infants make–akin motor babbling (Saegusa et al., 2008). This game was designed to be used in combination with an exoskeletal robot arm (Fig. 3).

The target schedule is 2 one-hour-long sessions a day, 5 days a week, for 3 weeks. If other commitments, such as doctor's appointments and

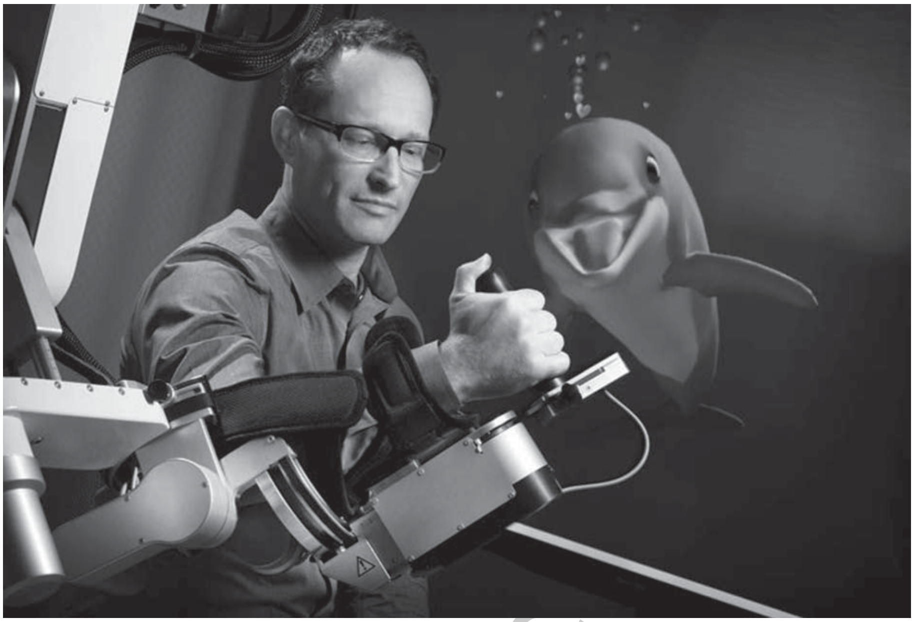

Fig. 3. Exoskeletal robotic arm used to control a dolphin simulation. Setup currently used in the SMARTS 2 trial (NCT02292251). The goal in this trial is to allow movement exploration in an immersive and engaging video game in order to boost motor recovery of the upper limb. Adapted from Krakauer and Carmichael (2017).

physical and speech therapy visits, prevent this target schedule from being feasible for the patient, the 30 hours of therapy will be redistributed, but will not exceed four hours a day and will be completed within 10 weeks of stroke onset.

To be eligible for the trial the patients cannot be more than five weeks out from stroke onset. The core hypothesis is that general recovery from impairment above what is expected from spontaneous mechanisms will occur because patients will perform about two to three miles of continuous arm movements per day that cover the space of arm configurations that are used across a range of everyday tasks (Ingram et al., 2008) and will do so within a poststroke-sensitive period. Skilled exploratory movements at this dose and intensity have never been tried before so early after stroke. It is an empirical question whether results as dramatic as have been seen in animal models will translate to patients. Regardless, it is to be hoped that the reasoning and work presented here, which culminated in the testing of a new rehabilitation approach, exemplify the potential of translating ideas and findings from neuroscience to human health and well being.

Assessments are conducted at baseline, day 3 post-training (±2 days), day 90 post-training (±10 days), and day 180 post-training (±10 days). The primary outcome of this study is the change in upper limb impairment, defined by the FMA-UE, from baseline to the first post-training session. Secondary outcome measures include upper limb kinematics, arm function as measured by the ARAT, and measures of independence and quality of life (modified Rankin Scale, Barthel Index, and the Stroke Impact Scale). The results of this trial will be reported sometime in 2018, and will hopefully pave the way for a larger phase III clinical trial.

6. Conclusion

The hypothesis presented here is that a focus on movement quality, rather than task completion, practiced at high intensity and dosage in an enriching environment may be the training approach that best exploits the sensitive period early after stroke in order to amplify the generalized gains seen with spontaneous biological recovery. This hypothesis is based on observations extending back over a century showing that movement rather than task-based training can enhance spontaneous recovery for prehension in both rodents and nonhuman primates (Krakauer & Carmichael, 2017). An ongoing phase II multicenter pilot trial, SMARTS 2 (NCT02292251), which tested this hypothesis is drawing to a close and results will be forthcoming.

Conflict of interest

None to report.

References

Albers, G. W., Bates, V. E., Clark, W. M., Bell, R., Verro, P., & Hamilton, S. A. (2000). Intravenous tissue-type plasminogen activator for treatment of acute stroke: The Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *Journal of the American Medical Association*, *283*(9), 1145-1150.

The AVERT Trial Collaboration Group (2015). Efficacy and safety of very early mobilisation within 24h of stroke onset (AVERT): A randomised controlled trial. *Lancet*, *386*, 46-55

Bavelier, D., Green, C. S., Pouget, A., & Schrater, P. (2012). Brain plasticity through the life span: Learning to learn and action video games. *Annual Review of Neuroscience*, *35*, 391-416.

Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., de Ferranti, S. D., Floyd, J., Fornage, M., Gillespie, C., Isasi, C. R., Jiménez, M. C., Jordan, L. C., Judd, S. E., Lackland, D., Lichtman, J. H., Lisabeth, L., Liu, S., Longenecker, C. T., Mackey, R. H., Matsushita, K., Mozaffarian, D., Mussolino, M. E., Nasir, K., Neumar, R. W., Palaniappan, L., Pandey, D. K., Thiagarajan, R. R., Reeves, M. J., Ritchey, M., Rodriguez, C. J., Roth, G. A., Rosamond, W. D., Sasson, C., Towfighi, A., Tsao, C. W., Turner, M. B., Virani, S. S., Voeks, J. H., Willey, J. Z., Wilkins, J. T., Wu, J. H. Y., Alger, H. M., Wong, S. S. & Muntner, P. (2017). Heart disease and stroke statistics—2017 update: A report from the American Heart Association. *Circulation*, *135*(10), e146-e603.

Berkhemer, O. A., Fransen, P. S., Beumer, D., Van Den Berg, L. A., Lingsma, H. F., Yoo, A. J., Schonewille, W. J., Vos, J. A., Nederkoorn, P. J., Wermer, M. J. & van Walderveen, M. A. (2015). A randomized trial of intraarterial treatment for acute ischemic stroke. *New England Journal of Medicine*, *372*(1), 11-20.

Biernaskie, J., & Corbett, D. (2001). Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *Journal of Neuroscience*, *21*, 5272-5280.

Biernaskie, J., Chernenko, G., & Corbett, D. (2004). Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *Journal of Neuroscience*, *24*(5), 1245-1254.

Bland, S. T., Schallert, T., Strong, R., Aronowski, J., & Grotta, J. C., (2000). Early exclusive use of the affected forelimb after moderate transient focal ischemia in rats: Functional and anatomic outcome. *Stroke*, *31*, 1144-1152.

Buch, E. R., Rizk, S., Nicolo, P., Cohen, L. G., Schnider, A., & Guggisberg, A. G. (2016). Predicting motor improvement after stroke with clinical assessment and diffusion tensor imaging. *Neurology*, *86*(20), 1924-1925.

Byblow, W. D., Stinear, C. M., Barber, P. A., Petoe, M. A., & Ackerley, S. J. (2015). Proportional recovery after stroke depends on corticomotor integrity. *Annals of Neurology*, *78*(6), 848-859.

Cramer, S. C. (2008). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Annals of Neurology*, *63*(3), 272-287.

Dromerick, A. W., Lang, C. E., Birkenmeier, R. L., Wagner, J. M., Miller, J. P., Videen, T. O., Powers, W. J., Wolf, S. L., & Edwards, D. F. (2009). Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): A single-center RCT. *Neurology*, *73*(3), 195-201.

Dromerick, A. W., Edwardson, M. A., Edwards, D. F., Giannetti, M. L., Barth, J., Brady, K. P., Chan, E., Tan, M. T., Tamboli, I., Chia, R., Orquiza, M., Padilla, R. M., Cheema, A. K., Mapstone, M. E., Fiandaca, M. S., Federoff, H. J., & Newport, E. L., (2015). Critical periods after stroke study: Translating animal stroke recovery experiments into a clinical trial. *Frontiers in Human Neuroscience*, *9*, 231.

Duncan, P. W., Goldstein, L. B., Matchar, D., Divine, G. W., & Feussner, J. (1992). Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. *Stroke*, *23*(8), 1084-1089.

Feigin, V. L., Norrving, B., & Mensah, G. A. (2017). Global burden of stroke. *Circulation Research*, *120*(3), 439-448.

French, B., Thomas, L. H., Coupe, J., McMahon, N. E., Connell, L., Harrison, J., Sutton, C. J., Tishkovskaya, S., & Watkins, C. L. (2016). Repetitive task training for improving functional ability after stroke. *Cochrane Database of Systematic Reviews*, (11), CD006073.

Gordon, J. (1987). Assumptions underlying physical therapy intervention: Theoretical and historical perspectives. In: *Movement science: Foundations for Physical Therapy in Rehabilitation*, edited by J. Carr and R. Sheppard. Aspen Publishers, Rockville, MD.

Hatem, S. M., Saussez, G., della Faille, M., Prist, V., Zhang, X., Dispa, D., & Bleyenheuft, Y. (2016). Rehabilitation of motor function after stroke: A multiple systematic review focused on techniques to stimulate upper extremity recovery. *Frontiers in Human Neuroscience*, *10*, 442.

Heller, A, Wade, D. T., Wood, V. A., Sunderland, A., Hewer, R. L., & Ward, E. (1987). Arm function after stroke: Measurement and recovery over the first three months. *Journal of Neurology, Neurosurgery & Psychiatry*, *50*(6), 714-719.

Hikosaka, O., Yamamoto, S., Yasuda, M., & Kim, H. F. (2013). Why skill matters. *Trends in Cognitive Sciences*, *17*(9), 434-441.

Hosp, J. A., Pekanovic, A., Rioult-Pedotti, M. S., & Luft, A. R. (2011). Dopaminergic projections from midbrain to primary motor cortex mediate motor skill learning. *Journal of Neuroscience*, *31*(7), 2481-2487.

Howard, I. S., Ingram, J. N., Körding, K. P., & Wolpert, D. M. (2009). Statistics of natural movements are reflected in motor errors *Journal of Neurophysiology*, *102*(3), 1902-1910.

Humm, J. L., Kozlowski, D. A., Bland, S. T., James, D. C., & Schallert, T. (1999). Use-dependent exaggeration of brain injury: Is glutamate involved? *Experimental Neurology*, *157*,349-358.

Johansson, B. B., & Ohlsson, A. L. (1996). Environment, social interaction, and physical activity as determinants of functional outcome after cerebral infarction in the rat. *Experimental Neurology*, *139*(2), 322-327.

Keith, R. A., Granger, C. V., Hamilton, B. B., & Sherwin, F. S. (1987). The functional independence measure. *Advances in Clinical Rehabilitation*, *1*, 6-18.

Kitago, T., & Krakauer, J. W. (2013). Motor learning principles for neurorehabilitation. *Handbook of Clinical Neurology*, *110*, 93-103.

Kozlowski, D. A., James, D. C., & Schallert, T. (1996). Use-dependent exaggeration of neuronal injury after unilateral sensorimotor cortex lesions. *Journal of Neuroscience*, *16*,4776-4786.

Krakauer, J. W. (2005). Arm function after stroke: From physiology to recovery. In: *Seminars in Neurology*, *25*(04), 384-395.

Krakauer, J. W., Carmichael, S. T., Corbett, D., & Wittenberg, G. F. (2012). Getting neurorehabilitation right what can be learned from animal models? *Neurorehabilitation and Neural Repair*, *26*(8), 923-931.

Krakauer, J. W., & Carmichael, S. T. (2017). *Broken Movement: The Neurobiology of Motor Recovery after Stroke*. MIT Press, Cambridge, Massachusetts, USA. p. 288. Print. ISBN: 9780262343978.

Kwakkel, G., Winters, C., Van Wegen, E. E. H., Nijland, R. H. M., Van Kuijk, A. A. A., Visser-Meily, A., De Groot, J., De Vlugt, E., Arendzen, J. H., & Geurts, A. C. H. (2016). Effects of unilateral upper limb training in two distinct prognostic groups early after stroke: The EXPLICIT-stroke randomized clinical trial. *Neurorehabilitation and Neural Repair*, *30*(9), 804-816.

Lang, C.E., Strube, M.J., Bland, M.D., Waddell, K.J., Cherry-Allen, K.M., Nudo, R.J., Dromerick, A.W., & Birkenmeier, R.L. (2016). Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial. *Annals of Neurology*, *80*(3), 342-354.

Manohar, S. G., Chong, T. T. J., Apps, M. A. J., Batla, A., Stamelou, M., Jarman, P. R., Bhatia, K. P., & Husain, M. (2015). Reward pays the cost of noise reduction in motor and cognitive control. *Current Biology*, *25*(13), 1707-1716.

McDonnell, M. N., Koblar, S., Ward, N. S., Rothwell, J. C., Hordacre, B., & Ridding, M. C. (2015). An investigation of cortical neuroplasticity following stroke in adults: Is there evidence for a critical window for rehabilitation? *BMC Neurology*, *15*(1), 109.

Murata, Y., Higo, N., Oishi, T., Yamashita, A., Matsuda, K., Hayashi, M., & Yamane, S. (2008). Effects of motor training on the recovery of manual dexterity after primary motor cortex lesion in macaque monkeys. *Journal of Neurophysiology*, *99*(2), 773-786.

Murphy, T. H., & Corbett, D. (2009). Plasticity during stroke recovery: From synapse to behaviour. *Nature Reviews Neuroscience*, *10*(12), 861-872.

Nakayama, H., Jørgensen, H. S., Raaschou, H. O., & Olsen, T. S. (1994) Recovery of upper extremity function in stroke patients: The Copenhagen stroke study. *Archives of Physical Medicine and Rehabilitation*, *75*(4), 394-398.

Ng, K. L., Gibson, E. M., Hubbard, R., Yang, J., Caffo, B., O'Brien, R. J., Krakauer, J. W., & Zeiler, S. R. (2015). Fluoxetine maintains a state of heightened responsiveness to motor training early after stroke in a mouse model. *Stroke*, *46*(10), 2951-2960.

Nudo, R. J., & Milliken, G. W. (1996). Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *Journal of Neurophysiology*, *75*(5), 2144-2149.

Ottenbacher, K. J., Hsu, Y., Granger, C. V., & Fiedler, R. C. (1996). The reliability of the functional independence measure: A quantitative review. *Archives of Physical Medicine and Rehabilitation*, *77*(12), 1226-1232.

Parker, V. M., Wade, D. T., & Hewer, R. L. (1986). Loss of arm function after stroke: Measurement, frequency, and recovery. *International Rehabilitation Medicine*, *8*(2), 69-73.

Pollock, A., Farmer, S. E., Brady, M. C., Langhorne, P., Mead, G. E., Mehrholz, J., & van Wijck, F. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database of Systematic Reviews*, (11), CD010820.

Prabhakaran, S., Zarahn, E., Riley, C., Speizer, A., Chong, J. Y., Lazar, R. M., Marshall, R. S., & Krakauer, J. W. (2008). Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehabilitation and Neural Repair*, *22*(1), 64-71.

Rathore, S. S., Hinn, A. R., Cooper, L. S., Tyroler, H. A., & Rosamond, W. D. (2002). Characterization of incident stroke signs and symptoms. *Stroke*, *33*(11), 2718-2721.

Russell, K. (2015) Helping Hand—Robots, Video Games, and a Radical New Approach to Treating Stroke Patients, *The New Yorker—Annals of Medicine*.

Saegusa, R., Metta, G., Sandini, G., & Sakka, S. (2009). Active motor babbling for sensorimotor learning. In: *Robotics and Biomimetics*. ROBIO 2008, IEEE International Conference, pp. 794-799.

Skilbeck, C. E., Wade, D. T., Hewer, R. L., & Wood, V. A. (1983). Recovery after stroke. *Journal of Neurology Neurosurgery and Psychiatry*, *46*(1), 5-8.

Strathern, M. (1997). Improving ratings': Audit in the British University system. *European Review*, *5*(3), 305-321.

Stinear, C., Ackerley, S., & Byblow, W. (2013). Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not. *Stroke*, *44*(7), 2039-2045.

van Kordelaar, J., van Wegen, E. E. H., Nijland, R. H. M., Daffertshofer, A., & Kwakkel, G. (2013). Understanding adaptive motor control of the paretic upper limb early poststroke: The EXPLICIT-stroke program. *Neurorehabilitation and Neural Repair*, *27*(9), 854-863.

Winstein, C. J., Wolf, S. L., & Schweighofer, N. (2014). Task-oriented training to promote upper extremity recovery. *Stroke Recovery and Rehabilitation*, *2*, 320-343.

Winstein, C. J., Wolf, S. L., Dromerick, A. W., Lane, C. J., Nelsen, M. A., Lewthwaite, R., Cen, S. Y., & Azen, S. P. (2016). Effect of a task-oriented rehabilitation program on upper extremity recovery following motor stroke: The ICARE randomized clinical trial. *Journal of the American Medical Association*, *315*(6), 571-581.

Winters, C., Wegen, E. E. H. v., Daffertshofer, A., & Kwakkel, G. (2015). Generalizability of the proportional recovery model for the upper extremity after an ischemic stroke. *Neurorehabilitation and Neural Repair*, *29*(7), 614-622.

Wong, A. L., Lindquist, M. A., Haith, A. M., & Krakauer, J. W. (2015). Explicit knowledge enhances motor vigor and performance: Motivation versus practice in sequence tasks. *Journal of Neurophysiology*, *114*(1), 219-232.

World Health Organization (2002). Towards a common language for functioning, disability and health: ICF. Geneva, Switzerland.

Xu-Wilson, M., Zee, D. S., & Shadmehr, R. (2009). The intrinsic value of visual information affects saccade velocities. *Experimental Brain Research*, *196*(4), 475-481.

Zarahn, E., Alon, L., Ryan, S. L., Lazar, R. M., Vry, M.-S., Weiller, C., Marshall, R. S., & Krakauer, J. W. (2011). Prediction of motor recovery using initial impairment and fMRI 48h poststroke. *Cerebral Cortex*, *21*(12), 2712-2721.

Zeiler, S. R., Hubbard, R., Gibson, E. M., Zheng, T., Ng, K., O'Brien, R., & Krakauer, J. W. (2016). Paradoxical motor recovery from a first stroke after induction of a second stroke reopening a postischemic sensitive period. *Neurorehabilitation and Neural Repair*, *30*(8), 794-800.