A single exercise bout and locomotor learning after stroke: physiological, behavioural, and computational outcomes

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Key points

- Previous work demonstrated an effect of a single high-intensity exercise bout coupled with motor practice on the retention of a newly acquired skilled arm movement, in both neurologically intact and impaired adults.
- In the present study, using behavioural and computational analyses we demonstrated that a single exercise bout, regardless of its intensity and timing, did not increase the retention of a novel locomotor task after stroke.
- Considering both present and previous work, we postulate that the benefits of exercise effect may depend on the type of motor learning (e.g. skill learning, sensorimotor adaptation) and/or task (e.g. arm accuracy-tracking task, walking).

Abstract  Acute high-intensity exercise coupled with motor practice improves the retention of motor learning in neurologically intact adults. However, whether exercise could improve the retention of locomotor learning after stroke is still unknown. Here, we investigated the effect of exercise intensity and timing on the retention of a novel locomotor learning task (i.e. split-belt treadmill walking) after stroke. Thirty-seven people post-stroke participated in two sessions, 24 h apart, and were allocated to active control (CON), treadmill walking (TMW), or total body exercise on a cycle ergometer (TBE). In session 1, all groups exercised for a short bout (~5 min) at low (CON) or high (TMW and TBE) intensity and before (CON and TMW) or after (TBE) the locomotor learning task. In both sessions, the locomotor learning task was to walk on a split-belt treadmill in a 2:1 speed ratio (100% and 50% fast-comfortable walking speed) for 15 min. To test the effect of exercise on 24 h retention, we applied behavioural and computational analyses. Behavioural data showed that neither high-intensity group showed...
greater 24 h retention compared to CON, and computational data showed that 24 h retention was attributable to a slow learning process for sensorimotor adaptation. Our findings demonstrated that acute exercise coupled with a locomotor adaptation task, regardless of its intensity and timing, does not improve retention of the novel locomotor task after stroke. We postulate that exercise effects on motor learning may be context specific (e.g. type of motor learning and/or task) and interact with the presence of genetic variant (BDNF Val66Met).

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Introduction

One of the primary motor activities that is limited after stroke is walking (Alguren et al. 2010; Langhorne et al. 2011). Recovery of walking is feasible (Jørgensen et al. 1995) and is very important to stroke survivors (Bohannon et al. 1988), and therefore considerable effort is spent on relearning to walk during rehabilitation after stroke. Among the various forms of learning (Krakauer & Mazzoni, 2011), sensorimotor adaptation of walking has been extensively investigated using a novel locomotor task, split-belt treadmill walking (Reisman et al. 2005, 2010a; Malone & Bastian, 2010; Helm & Reisman, 2015; Vasudevan et al. 2017). Both neurologically intact and impaired adults are capable of learning this task (Reisman et al. 2005, 2009, 2010b, 2013; Vasudevan & Bastian, 2010), yet those with stroke require more time (i.e. slower learning rate) (Malone & Bastian, 2014; Tyrell et al. 2014). Neuroplasticity is the mechanism by which the brain learns behaviour through strengthening of existing neural connections and the formation of new neural connections (Kleim et al. 1998; Kleim & Jones, 2008). Application of strategies that can enhance this process have therefore gained considerable attention, with the idea that these strategies may enhance learning (Stoykov & Madhavan, 2015; Roig et al. 2016; Stoykov et al. 2017) and subsequently expedite rehabilitation after stroke (Mang et al. 2013).

Among these strategies, a short, high-intensity exercise bout has been found to promote motor skill learning in neurologically intact subjects (Roig et al. 2012, 2016; Skriver et al. 2014; Snow et al. 2016; Thomas et al. 2016a, b, 2017). In this series of studies, motor learning was examined using a unilateral isometric tracking task with the upper extremity and it was found that a single high-intensity exercise bout, administered either before or after the motor practice, enhanced the retention of the motor task 1 and 7 days after the first exposure (Roig et al. 2012). Based on those promising findings, subsequent studies investigated the exercise-related and neurophysiological factors that may contribute to these gains in motor learning (Skriver et al. 2014; Snow et al. 2016; Thomas et al. 2016a, b, 2017). Among the exercise-related parameters, intensity and timing were reported to have a significant effect on motor learning (Roig et al. 2012; Thomas et al. 2016a, b), whereas the exercise type did not seem to have an effect (Thomas et al. 2017). The greatest improvements in motor learning were found when exercise intensity was high (Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016b). In addition, while improvements in motor learning were found when exercise occurred immediately before or after practice of the motor skill, retention was greatest when exercise was administered immediately after (as compared to before) the practice of the motor skill (Roig et al. 2012; Thomas et al. 2016a).

Given the findings in neurologically intact adults, some have suggested that similar application of exercise may have potential clinical implications in neurological populations, who have deficits in motor learning (Mang et al. 2013; Roig et al. 2016). The research in this area is limited, however, with only one study recently investigating the effect of high-intensity exercise on motor learning after stroke (Nepveu et al. 2017). The task (i.e. an upper extremity time-on-target task) and exercise protocol (i.e. 15 min of high-intensity bout using a recumbent bike immediately after motor practice) were similar to the previous work in neurologically intact subjects (Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a). Compared to the subjects in the ‘no exercise’ group, those who exercised at high intensities after the motor practice, had greater retention of the motor task 24 h later (Nepveu et al. 2017). This is the first evidence that a single high-intensity exercise bout can improve retention of an upper extremity motor skill task after stroke. This study did not, however, provide physiological measures to characterize the exercise or the neurophysiological mechanisms (e.g. blood biomarkers) thought to be the linkage between exercise and motor learning.

Previously, all studies showing the positive effects of high intensity exercise on motor learning have utilized an upper extremity task requiring subjects to either use isometric wrist activity or grip force to move a cursor on a screen during a tracking task or to move to specific targets (Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a, b, 2017; Nepveu et al. 2017). This type of motor learning
task requires limited motor control across joints or limbs and may rely heavily on a strategy-based form of learning (Taylor & Ivry, 2012; Haith & Krakauer, 2013). Thus, while these studies have provided an important foundation for our understanding of the role of exercise in facilitating motor learning, they bear little resemblance to the types of whole body tasks, such as locomotion, that are often the focus of neurorehabilitation. In addition, they provide no information regarding the potential effects of exercise on other forms of learning, such as sensorimotor adaptation (i.e. automatic/implicit and iterative process of error reduction) (Bastian, 2008). Studies investigating more functional, whole body tasks that involve other forms of motor learning are therefore necessary if we are to understand the potential usefulness of coupling high-intensity exercise with motor task practice to promote motor learning and recovery after stroke.

Therefore, the overall goal of this study was to investigate the effect of exercise priming on retention of locomotor learning (i.e. how much of the practiced motor patterns have been retained 24 h later) using a split-belt treadmill protocol in chronic stroke survivors. We utilized standard behavioural measures to probe for the potential beneficial effects of exercise on learning and retention. Given that in previous studies, intensity (Roig et al. 2012; Thomas et al. 2016b) and timing (Roig et al. 2012; Thomas et al. 2016a) were reported to be the two most important exercise parameters that influence motor learning, this study had two specific aims. First, we investigated whether an acute high-intensity exercise bout (Charalambous et al. 2018) would influence locomotor learning in those with chronic stroke, and second, whether the timing of the exercise influenced locomotor learning in chronic stroke survivors. We hypothesized that: (a) stroke survivors in both high-intensity exercise groups would show greater gains in locomotor learning than those in the low-intensity exercise group (i.e. active control), and (b) stroke survivors who exercised immediately after the learning task would have greater gains in locomotor learning than those who exercised immediately before. Additionally, we tested the feasibility of applying computational modelling to behavioural data collected from chronic stroke survivors. Though the majority of the computational models have been developed to explain error-based learning during reaching (Smith et al. 2006; Joiner & Smith, 2008; Lee & Schweighofer, 2009; Huang et al. 2011), only a few studies of locomotor adaptation have used model-based approaches, and both included only subjects that were neurologically intact adults (Mawase et al. 2014; Roemmich et al. 2016). Therefore, the computational modelling was used to investigate the component processes of the locomotor learning after stroke and to further understand the underlying mechanisms for long-term retention.

**Methods**

**Ethical approval**

The present study conformed to the standards set by the latest revision of the Declaration of Helsinki. After a thorough explanation of the objectives and procedures of this study, all subjects read and signed a written informed consent approved by the Institutional Review Board at University of Delaware.

**Subjects**

We included subjects if they met the following criteria: (1) age 21–85, (2) unilateral chronic stroke (>6 months post stroke), (3) able to walk for 4 min at self-selected speed without assistance from another person (assistance device allowed), (4) resting heart rate (HR) between 40 and 100 beats min\(^{-1}\), and (5) resting blood pressure between 90/60 and 170/90 mmHg. Subjects were excluded if any of the following criteria were present: (1) evidence of cerebellar stroke on clinical MRI or CT scan, (2) other neurological conditions in addition to stroke, (3) lower limb Botulinum toxin injection <4 months earlier, (4) current participation in physical therapy, (5) inability to walk outside the home prior to the stroke, (6) coronary artery bypass graft or myocardial infarction within past 3 months, (7) musculoskeletal pain that limits walking, (8) inability to communicate with investigators, (9) neglect, and (10) unexplained dizziness in last 6 months.

**Experimental procedures**

Subjects attended one initial evaluation session and two experimental sessions (Fig. 1A). At the initial evaluation session, subjects completed a brief battery of clinical tests, and reported whether they were taking a beta-blocker medication. The fast-comfortable treadmill walking speed of each subject was determined by starting walking speed at 0.2 m s\(^{-1}\), and was gradually increased (0.05 m s\(^{-1}\) every 15 s) until the subjects reported they had reached their fast-comfortable walking speed or when the researcher determined that it was unsafe to further increase the speed. Next, to quantify the baseline step length (a)symmetry and then to subsequently determine the leg with the longer step length that would be placed on the slow belt, all subjects walked for 2 min at half of the previously determined fast-comfortable speed while gait data were collected (see Data analysis). Lastly, subjects were allocated to either a low-intensity exercise control group (CON; walking on treadmill at 25% of their fast-comfortable walking speed) or one of the two high-intensity exercise groups: treadmill walking (TMW), and total body exercise (TBE; seated upper and lower extremity ergometer, SCIFIT, Tulsa, OK, USA) as described previously (Charalambous et al. 2018). Given that both treadmill and ergometer
are widely available in rehabilitation settings, these two exercise types were chosen because treadmill walking has the advantage of the experimenter being able to control the speed (and therefore, to some extent, the intensity) while the ergometer has the advantage of being feasible for a larger number of stroke survivors.

The two experimental sessions were 24 h apart. Exercise priming was administered only on session 1, whereas the split-belt treadmill walking was practiced in both sessions.

**Exercise protocol.** The CON and TMW groups exercised immediately before the novel locomotor task (i.e. split-belt treadmill walking – see below) whereas the TBE group exercised immediately after. Details of the exercise protocol have been described elsewhere (Charalambous et al. 2018). Briefly, the goal for all groups was to exercise (a) continuously for ~5 min, and (b) within the target intensity (low, CON; high, TMW and TBE). Given that beta-blocker medications are commonly used by those post stroke and alter the HR response to exercise (Moore et al. 2016), we quantified intensity using two methods, depending on whether the subject was taking beta-blocker medications or not. The target high-intensity exercise range was defined as 70–85 % of age-predicted HR max.

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**A**

**Initial Evaluation and Experimental Sessions**

<table>
<thead>
<tr>
<th>Initial Evaluation Session</th>
<th>Experimental Session 1*</th>
<th>Experimental Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical tests</td>
<td>Experimental Session 1*</td>
<td>Experimental Session 2</td>
</tr>
<tr>
<td>2. Medication list</td>
<td>LOW Intensity Treadmill Walking</td>
<td>15 minutes Split-belt Walking Adaptation</td>
</tr>
<tr>
<td>3. Anthropometric &amp; Demographic data</td>
<td>CON</td>
<td>15 minutes Split-belt Walking Re-adaptation</td>
</tr>
<tr>
<td>4. Fast comfortable treadmill walking speed</td>
<td>TMW</td>
<td>15 minutes Split-belt Walking Re-adaptation</td>
</tr>
<tr>
<td>5. Baseline step length (a)symmetry</td>
<td>TBE</td>
<td>15 minutes Split-belt Walking Re-adaptation</td>
</tr>
</tbody>
</table>

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**B**

**Step Length Symmetry Index**

**Figure 1.** Experimental design and schematic of step length symmetry index

A, the phases of the experimental procedures. After an initial evaluation session (duration ~1.25 h), participants were allocated to one of the three groups and attended two experimental sessions, 24 h apart. Session 1 (duration ~1.25 h) consisted of baseline walking, exercise (dashed line box), and split-belt treadmill walking (adaptation; thick line box). Baseline walking was always at the beginning of session 1, but the exercise intensity (low: CON; high: TMW and TBE) and timing (before adaptation: CON and TMW; after adaptation: TBE) varied across groups. On session 2 (duration ~1 h), all subjects repeated only the 15 min of split-belt walking (re-adaptation; thick line box). B, calculation of the step length symmetry index. First, the step length (sagittal distance between ipsilateral and contralateral foot at ipsilateral foot contact) was calculated bilaterally. Then, we calculated the symmetry index, which was normalized to baseline symmetry.
(HR\textsubscript{max} = 220 – age) and 13–15 on the 6–20 ‘rate of perceived exertion’ scale (RPE) (Borg, 1982; Goss et al. 2011) for those not taking and taking, respectively, beta-blocker medication (Pescatello, 2014). Exercise intensity was monitored in real time every 15 s using a HR monitor (Polar Electro Inc., Lake Success, NY, USA) and every 30 s using the RPE scale. During all treadmill trials, either during exercise or motor practice, subjects wore a ceiling mounted harness without body weight support, and held onto the front horizontal bar.

**Serum blood biomarkers collection and analysis.** Previous work has suggested that the potential neurophysiological linkage between exercise and motor learning in healthy adults might be the upregulation of certain biomarkers (lactate, brain derived neurotrophic factor-BDNF) (Skriver et al. 2014). Therefore, we collected serum samples from all subjects. For both blood collection and analysis, we used the same experimental procedures as in our previous work (Charalambous et al. 2018; Helm et al. 2017). Briefly, on session 1, we collected blood samples from all subjects to quantify changes in lactate and BDNF concentrations in response to exercise priming. At the first experimental session, a registered nurse collected the blood samples immediately before and after the exercise bout. Each sample sat for half an hour at room temperature to allow clotting and then immediately after was centrifuged (3,000 rpm for 15 min).

For the analysis, samples were divided into several aliquots in microcentrifuge tubes designated for lactate and BDNF and stored at 80°C until assayed. Blood lactate and BDNF were analysed using appropriate kits (Lactate Colorimetric Assay Kit II: Abcam, Cambridge, MA, USA; Human BDNF Quantikine Enzyme Linked Immunosorbent Assay Kit: R&D Systems, Minneapolis, MN, USA) and the protocols supplied by the manufacturers.

**Locomotor learning.** In both experimental sessions, subjects walked on a split-belt treadmill on which belts could move at either the same (tied-belt mode) or different (split-belt mode) speed (Vasudevan et al. 2017). At the beginning of experimental session 1, all subjects walked for 1 min while both belts moved at half the speed of the fast-comfortable treadmill walking speed (i.e. tied-slow mode; 1:1 speed ratio). This condition was used to quantify the baseline walking pattern (i.e. step length) of each subject. All subjects then walked in a split-belt mode (2:1 speed ratio; fast belt: fast-comfortable walking speed, slow belt: half of fast belt) for 15 min. To ensure that step length asymmetry was exaggerated (Tyrell et al. 2015), the leg placed on the slow belt was determined based on step length baseline asymmetry, which was quantified at the initial evaluation session. Twenty-four hours later, in experimental session 2 all subjects walked on the treadmill only in the split-belt mode at the same 2:1 speed ratio for 15 min to test for retention of the previous day’s learning.

Subjects walked on a dual-belt treadmill instrumented with two independent 6 degrees of freedom force platforms (Bertec Corporation, Columbus, OH, USA). Ground reaction forces and marker coordinate data were continuously recorded and acquired using Vicon Nexus (Vicon Motion Systems Ltd, Oxford, UK) as described in our previous work (Helm et al. 2016, 2017). Briefly, force data were recorded by the two force-plates and sampled at 1000 Hz, while the three-dimensional data of 39 retroreflective markers, which were bilaterally placed over the skin of the lower extremities and shoes, recorded with 8 motion capture Vicon cameras (Vicon Motion Systems Ltd) and sampled at 100 Hz.

**Data analysis**

**Gait mechanics.** Gait data were analysed offline using Vicon Nexus and Matlab (Mathworks, Natick, MA, USA). Foot contact and foot off were determined using an automated algorithm (Zeni et al. 2008). All gait events detected by the automated custom-written scripts were visually checked for accuracy.

**Exercise-induced variables.** All exercise variables were calculated as in our previous work (Charalambous et al. 2018). Briefly, to quantify whether subjects exercised at the target high-intensity range and for how long, we calculated the average exercise intensity (% max intensity) and time spent (% total time) at the target high-intensity range using either HR (not on beta-blocker medication) or RPE (on beta-blocker medication). Similarly, to test whether high-intensity exercise increased lactate (mmol l\(^{-1}\)) and BDNF (ng ml\(^{-1}\)), we calculated the magnitude of change between pre- and post-exercise data.

**Locomotor learning parameters.** To quantify locomotor learning, we first calculated the step length symmetry index, which is the difference between the step length of the slow and fast legs normalized by the sum of the two step lengths (Fig. 1B). This index has been shown to be the most robust measure of adaptation and learning during walking on the split-belt treadmill in both healthy subjects and stroke survivors (Reisman et al. 2005, 2007, 2009; Malone et al. 2011). To correct for between-subject differences in baseline (a)symmetry, the average baseline (a)symmetry was subtracted from each raw (a)symmetry value during split-belt walking (Fig. 1B). This normalized step length symmetry index was used to calculate all subsequent locomotor learning measures.

We calculated a total of five locomotor learning measures: three measures of magnitude (Fig. 2A) and two measures of rate (Fig. 2B). We quantified the within-session 1 walking pattern to determine whether all groups
experienced the same perturbation at the beginning of split-belt walking (early asymmetry: average of the first 10 strides in session 1; Fig. 2A) and adapted the same amount (magnitude of adaptation: difference between the average of the first 10 strides of session 1 from the average of the last 30 strides of session 1; Fig. 2A) with similar rates (adaptation rate: number of strides required to fall within the final adapted state on session 1; Fig. 2B). To test whether exercise intensity and timing influenced the longer-term retention (i.e. 24 h) of locomotor learning, we quantified what was retained from session 1 to session 2 (magnitude of retention: the difference between the

Figure 2. Schematic of locomotor learning measures calculation
A, magnitudes of change. Early asymmetry and magnitude of adaptation were calculated in session 1, while magnitude of retention was calculated in session 2. B, adaptation and re-adaptation rates. In session 1 and 2, adaptation and re-adaptations rates were calculated, respectively. In both panels, value of 0 on y-axis indicates perfect baseline symmetry while any non-zero values indicate deviation from the baseline step length symmetry.
average of the first 10 strides of session 1 from the average of the first 10 strides of session 2; Fig. 2A) and how fast the locomotor task was relearned in session 2 (re-adaptation rate: number of strides required to fell within the final adapted state on session 2; Fig. 2B). For the rate calculation, an automated method was used (Malone & Bastian, 2010). First, data were smoothed using a moving average and binning of three strides. Then, the number of strides taken to fall within the final adapted state (e.g. the mean ± SD of the last 30 strides during adaptation and re-adaptation) was calculated. The first point at which five consecutive strides during adaptation and re-adaptation fell within the final adapted state was normalized to the total number of strides taken in each session (% total strides) to get the rate.

Computational modelling

We tested the feasibility of applying a dual-rate computational model to behavioural data collected from chronic stroke survivors. This model of adaptation proposed by Smith and colleagues (2006) has been shown to successfully capture key features of locomotor adaptation in healthy subjects (Mawase et al. 2014; Roemmich et al. 2016). In this study, we were particularly interested in modelling the component processes of locomotor adaptation following stroke and better understanding the underlying mechanisms for long-term retention.

Prior to fitting the split-belt data with a model, we transformed step length asymmetry data into an adaptation index (Mawase et al. 2014; Roemmich et al. 2016).

\[ \text{Adaptation}(n) = \left( \text{perturbation} - \text{step length asymmetry}(n) \right) / \text{perturbation}. \]

Here, \( n \) refers to stride number and ‘perturbation’ refers to the maximum step length asymmetry recorded within the first 10 strides of perturbation onset in day 1.

This adaptation index represents normalized changes in symmetry and scales the data between 0 and 1, such that 0 represents maximal asymmetrical walking and 1 would indicate perfectly symmetrical step lengths. Note that we only fit models to the data during the epochs where the belts were split (i.e. perturbation was on). In addition, any stride that exceeded the group mean perturbation magnitude on the first stride of the split-belt by three SDs was considered an outlier and not used for further analyses. This resulted in <0.05% of all strides being removed, with no strides removed for the majority of subjects and the maximum amount taken out for any single subject totalling 1.5% of that subject’s data.

After converting step length symmetry to an adaptation index, we used a dual–rate state space model to fit these data (Smith et al. 2006). In this model, there are two hidden variables which represent fast and slow learning processes. The fast state, \( x_{\text{fast}} \), learns from error quicker than the slow state, \( x_{\text{slow}} \), but it also ‘forgets’ quicker. The motor output, \( x \), is the sum of the two states. This model takes the following form:

\[ x_{\text{fast}}(n + 1) = A_{\text{fast}} x_{\text{fast}}(n) + B_{\text{fast}} e(n), \]
\[ x_{\text{slow}}(n + 1) = A_{\text{slow}} x_{\text{slow}}(n) + B_{\text{slow}} e(n), \]
\[ x(n) = x_{\text{fast}} + x_{\text{slow}}, \]
\[ 0 \leq A_{\text{fast}} < A_{\text{slow}} \leq 1, 0 \leq B_{\text{slow}} < B_{\text{fast}} \leq 1. \]

In this model, \( A_{\text{fast}} \) and \( A_{\text{slow}} \) are retention parameters, representing the proportion of the state which is retained from one trial to the next. The \( B \) parameters are the learning rates and represent the proportion of the error, \( e(n) \), experienced on stride \( n \) which is corrected for in the next stride.

In order to estimate the relative contributions of fast and slow states to 24 h long-term retention, we applied a previously published model used to characterize long-term retention of force field adaptation (Joiner & Smith, 2008):

\[ \text{Long – term retention(LTR)} = \alpha x_{\text{fast}}(n) + \beta x_{\text{slow}}(n), \]

where \( n \) represents the two states’ final values at the end of training on day 1. Alpha (\( \alpha \)) and beta (\( \beta \)) were constrained to have values between 0 and 1. In the Results, we report \( \alpha \) and \( \beta \) as percentages of LTR (% LTR). That is, the values were scaled to the amount of learning that was retained from day 1 to day 2 and together sum to 1.

Model fitting. For our model fitting we applied standard bootstrapping techniques, constructing group-averaged step symmetry and adaptation index data 1000 times for each of the three groups (i.e. total of 3000 bootstrapped means) by randomly resampling with replacement from the pool of subjects within each group. Using Matlab’s \texttt{fmincon} function, we estimated the retention and learning parameters which minimized the least-squares error between the bootstrapped data and model output \( (x_n) \).

Initial parameters were specified with the following values: \( A_{\text{fast}} = 0.92; A_{\text{slow}} = 0.996; B_{\text{fast}} = 0.03; B_{\text{slow}} = 0.004; \alpha = 0.5; \beta = 0.5 \), and at least five different initial starting points were used to assure the stability of all fits. We fitted the model to each of the bootstrap estimates and used the 2.5 and 97.5 percentile values as the limits for the 95% confidence intervals (in parentheses).

Statistical analysis

We used SPSS v24 (IBM Corp, Armonk, NY, USA) to run statistical analyses of standard behavioural measures, with significance set at \( P < 0.05 \). All modelling-based analyses were performed in Matlab (Mathworks, Inc.).
**Results**

A total of 37 chronic stroke survivors participated in this study (CON, N = 13; TMW, N = 12; TBE, N = 12). Table 1 presents subject data and group means for basic demographic and clinical measurements; among groups, there were no significant differences in any measurement.

**Experimental session 1: exercise-induced changes**

Table 2 presents group means for all exercise-related measures. As in our previous work (Charalambous et al. 2018), all subjects successfully exercised for the target duration (~5 min) without asking for breaks or any adverse events (e.g. nausea, lightheadedness, pain). A significant effect of exercise on the average intensity (H(2) = 24.10, P < 0.001), time spent at the target high-intensity (H(2) = 27.29, P < 0.001), and lactate change (F(2,36) = 36.589, P < 0.001, η^2 = 0.69) was observed, with the CON group never reaching the high-intensity range and with negligible changes in lactate. Compared to TMW, the TBE group exercised at a similar average intensity (U = 61.00; z = −0.639; P = 0.523; r = −0.13) but significantly longer time at the high-intensity (U = 28.50; z = −2.537; P = 0.012; r = −0.52), and had greater changes in lactate (t(22) = −4.301; P = 0.001; d = 1.76). There was no significant main effect of exercise on BDNF change (H(2) = 0.304, P = 0.859).

**Experimental sessions 1 and 2: locomotor adaptation and retention**

**Behavioural data.** In both sessions, all subjects successfully completed all walking trials. During split-belt walking, 31 subjects (84%) had their paretic leg placed on the slow belt and step length asymmetry was initially exaggerated in all subjects (e.g. slow step length was longer than fast leg step length). All groups adapted and re-adapted similarly in session 1 and 2 (Fig. 3A). Given that exercise timing was different between groups, we needed to determine whether within session locomotor learning during experimental session 1 differed across groups. All groups experienced the same perturbation (i.e. early asymmetry: difference between the first 10 strides from the baseline symmetry) when the belts were first split (CON = 0.133 ± 0.152, TMW = 0.134 ± 0.069, TBE = 0.114 ± 0.068, H(2) = 0.619, P = 0.734), adapted (i.e. magnitude of adaptation: difference between the average of the first 10 strides from the average of the last 30 strides) the same amount (F(2,36) = 0.315; P = 0.732; η^2 = 0.02; Fig. 3B) and with similar rate (i.e. adaptation rate; H(2) = 0.227, P = 0.892; Fig. 3C) on session 1. In contrast to our hypotheses, however, an acute bout of
Figure 3. Locomotor learning curves (A) and measures (B–E)

(A) group adaptation and re-adaptation curves (smoothed by 5 strides) and shaded SD regions for step length asymmetry during split-belt treadmill walking during sessions 1 and 2. Value of 0 denotes perfect baseline symmetry while any deviation from 0 denotes step length asymmetry compared to baseline. With initial exposure to 2:1 split-belt ratio, subjects in all three groups were initially perturbed (early asymmetry), but they all returned to their baseline symmetry. On the second exposure (session 2), all groups were initially perturbed less than on session 1 and again returned to around baseline.

(B)–(E), dots denote individual data while the error bars indicate group means and SD (error bar) of (B) magnitude of adaptation, (C) adaptation rate, (D) magnitude of retention, and (E) re-adaptation rate. No main effect of exercise was observed for any of the locomotor learning measures. B and D, larger values denote greater adaptation or retention. C and E, smaller values denote faster adaptation or re-adaptation rate.
Table 1. Subject demographics and clinical measurements

<table>
<thead>
<tr>
<th>Participant number</th>
<th>Group (CON/TMW/TBE)</th>
<th>Age (years)</th>
<th>Gender (M/F)</th>
<th>Time post stroke (months)</th>
<th>Lesioned hemisphere (R/L)/stroke type (I/H)</th>
<th>FMLE (max. 34)</th>
<th>SSWS (m s(^{-1}))</th>
<th>Treadmill FWS (m s(^{-1}))</th>
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<tr>
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<td>CON</td>
<td>57</td>
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<td>0.9</td>
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<td>R/I</td>
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<td>1.6</td>
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</table>

CON N = 13 57 ± 9 9 M 54 ± 31 7 L/7 I 22 ± 7 0.85 ± 0.30 1.00 ± 0.25
TMW N = 12 55 ± 16 7 M 66 ± 60 7 R/10 I 24 ± 7 1.02 ± 0.29 1.18 ± 0.26
TBE N = 12 62 ± 10 7 M 85 ± 84 8 R/8 I 24 ± 7 0.85 ± 0.23 1.13 ± 0.23

P value NA 0.336 0.835 0.800 0.773/0.381 0.733 0.247 0.194

Group data are means ± SD. CON, control; TMW, treadmill walking; TBE, total body exercise; M, male; F, female; R, right; L, left; I, ischaemic; H, haemorrhagic; FMLE, Fugl-Meyer lower extremity; SSWS, self-selected walking speed; FWS, fast walking speed; NA, not applicable.

Exercise did not improve the retention of the locomotor task during experimental session 2, regardless of its intensity and timing. Compared to the CON group and to each other, the high-intensity groups neither retained significantly (F(2,36) = 0.488; P = 0.618; \( \eta^2 = 0.03 \); Fig. 3D) more from session 1 to session 2 (magnitude of retention: difference between the average of the first 10 strides of session 1 from the average of the first 10 strides of session 2) nor relearned significantly faster in session 2 (i.e. re-adaptation rate; H(2) = 2.43, P = 0.297; Fig. 3E).
Table 2. Exercise-related measures

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Significance</th>
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<tr>
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<td>CON (N = 13)</td>
<td>TMW (N = 12)</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>4.7 ± 0.8</td>
<td>4.7 ± 0.8</td>
</tr>
<tr>
<td>Average intensity at high intensity (% max. intensity)</td>
<td>0 ± 0</td>
<td>70 ± 22*</td>
</tr>
<tr>
<td>Time at high- intensity (% total time)</td>
<td>0 ± 0</td>
<td>64 ± 22*</td>
</tr>
<tr>
<td>ΔLactate (mmol l(^{-1}))</td>
<td>−0.05 ± 0.31</td>
<td>1.81 ± 0.97*</td>
</tr>
<tr>
<td>ΔBDNF (ng ml(^{-1}))</td>
<td>−2.35 ± 13.93</td>
<td>−1.66 ± 7.14</td>
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</tbody>
</table>

Group data are means ± SD. ∆, change. *Significant difference from CON; †significant difference from TMW. Value 0 indicates that no subject in the CON group reached and exercised at the target intensity. SD, standard deviation; CON, control; TMW, treadmill walking; TBE, total body exercise. Significance by either a one-way independent ANOVA or Kruskal-Wallis H test of the main effect of group.

Modelling data. As seen in Fig. 4, the dual-rate model provides qualitatively good fits to the behavioural data of each group (Fig. 4A, CON; Fig. 4B, TMW; Fig. 4C, TBE). The median \( R^2 \) value for the model fits to bootstrapped samples was 0.66 (95% CI, 0.30–0.81). Consistent with our behavioural analyses, there were no differences in any of the learning or retention parameters across groups (all overlapping confidence intervals; see Table 3). Collapsing across groups, we calculated the following parameter values (median (95% CIs)): \( A_{\text{fast}} = 0.949 \) (0.660–0.980); \( A_{\text{slow}} = 1.000 \) (0.995–1.000); \( B_{\text{fast}} = 0.069 \) (0.035–0.199); \( B_{\text{slow}} = 0.006 \) (0.002–0.033).

![Figure 4. Group model fits (A–C) and model comparison (D)](image-url)

A–C, a linear time invariant dual-rate model of adaptation captures characteristic features of locomotor adaptation in stroke survivors. The group averaged behavioural data (mean ± shaded SEM) are shown together with mean functions from the bootstrapped model fits. Note how the fast state (\( x_{\text{fast}} \); green) on day 1 captures the rapid rate of initial adaptation, whereas day 2 is dominated by the slow state (\( x_{\text{slow}} \); dark purple). This is due to the large proportion of long-term retention (dots with black error bars at start of day 2) which is attributed to the slow state. D, we fitted the data with both linear time invariant (LTI; i.e. constant parameters for days 1 and 2) and time-varying parameters (VP; i.e. different parameters for days 1 and 2) and compared \( \text{AIC}_C \) scores from both model fitting procedures. Here we show the null distribution of \( \text{AIC}_C \) scores (see Methods). The red vertical line indicates the mean of this distribution, and the blue vertical lines represent this mean ± the absolute value of the calculated mean difference in LTI and VP \( \text{AIC}_C \) scores.
These parameter estimates were derived using the same learning and retention parameters across both days (i.e. using the LTI model, which assumes no change in underlying learning processes across sessions or days). We assumed that since there were no differences in relearning or retention in our behavioural analyses, one set of parameters for both days should successfully characterize the data. To test this prediction more rigorously, we also fitted the 2-day data with parameter values that could change across days (i.e. VP model), as others have suggested this may better characterize learning phenomena, such as faster relearning (i.e. savings) (Mawase et al., 2014), when multiple perturbations are involved. However, model comparisons between the LTI version of the dual rate model and the VP version revealed no strong evidence to favour one model over the other. Specifically, under the null hypothesis that the AIC_C scores for both LTI and VP parameters come from the same distribution, we found that the mean difference between LTI and VP AIC_C scores had a corresponding P value of 0.810 (see Methods). That is, although the time varying version of the dual process model (VP) had yielded a slightly lower mean AIC_C score, suggesting a better model even after considering the additional parameters, there was an 81% chance that this difference in scores was due to chance alone (Fig. 4D). We thus conclude that in the case of locomotor adaptation following stroke, there is insufficient evidence to support the VP model over the LTI model.

The last model-based analysis was performed to better understand the underlying source of long-term retention. In a prior study of force field adaptation, long-term retention of adaptation was accurately predicted by the magnitude of learning reached at the end of initial training by the slow state (Joiner & Smith, 2008). Here we applied the same model as used by Joiner & Smith (see Methods) to determine whether the slow state is also responsible for long-term retention of locomotor adaptation in stroke subjects. Like the dual process model parameters, there were no differences in long-term retention parameters across groups (see Table 3). Importantly, our results show that the slow state was responsible for 91.5% (49.9–99.2%) of what was retained during the 24 h period between the end of training on day 1 and the start of training on day 2. In contrast, the proportion of retention attributable to the fast state was not different from zero (median (95% CI): 4.6% (0–45.4%)). These findings are consistent with the earlier study of force field adaptation in healthy adults (Joiner & Smith, 2008) and suggest that long-term retention in locomotor adaptation following stroke is primarily dictated by the slow process.

**Discussion**

Given that the capacity to learn is impaired after stroke and the recent promising evidence that exercise may ‘prime’ the central nervous system to promote learning, in the present study we sought to investigate whether a single exercise bout, whose intensity and timing was manipulated, would increase the retention of a novel locomotor task in chronic stroke survivors. In contrast to our hypotheses, an acute exercise bout, regardless of its intensity and timing, did not increase locomotor learning tested 24 h after the first exposure to split-belt walking in people post stroke. This finding agrees with recent work from our lab that found that high intensity exercise also did not promote locomotor learning in neurologically intact adults (Helm et al., 2017). Moreover, these findings, in both those with stroke and neurologically intact adults, differ from previous studies of the effect of exercise on upper extremity skill learning. The differences in findings between our work and previous studies is probably due to several factors that will be discussed in the following sections and, taken together, provide important insight into the role of exercise for enhancing motor learning after stroke.

**Effect of exercise on learning may be context specific**

The neural and behavioural processes of motor learning may vary depending on the type of learning and the characteristics of the motor task to be learned; therefore,
the exercise effect may depend on these variations. All previous studies that reported gains in motor learning due to exercise shared two similarities that may be important to understanding the effects of exercise on learning (Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a, b, 2017; Nepveu et al. 2017). First, in all previous studies, the task was either a visuomotor tracking task or time-on-target motor task. Subjects in those studies were given (1) explicit instructions how to perform the task, (2) online feedback about their performance, and (3) rewards based on their performance. In these tasks, therefore, the form of learning is probably a combination of strategy-based (i.e. explicit) (Taylor & Ivry, 2012) and reinforcement (i.e. reward-based) (Doya, 2000) learning. Conversely, during split-belt treadmill walking the main form of learning is implicit sensorimotor adaptation (Doya, 2000; Bastian, 2008), with neither instruction nor feedback/reward provided. Thus, the forms of learning in the previous studies of upper extremity visuomotor tracking or time on target (Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a, b) are probably quite different compared to the primarily implicit motor learning occurring during split-belt treadmill walking. One explanation, then, for the difference in the effect of exercise on motor learning in the different studies could be that exercise differentially affects motor learning depending on the type or form of learning (Ferrer-Uris et al. 2017).

This differential effect could be related to the different neural bases of different forms of learning. While sensorimotor adaptation, including that occurring during split-belt walking, is thought to be heavily cerebellar dependent (Morton & Bastian, 2006), visuomotor tracking tasks are thought to depend on cortical substrates (Sanes, 2003). While consolidation of the learning in both tasks probably relies heavily on primary motor cortex (M1) (Muellbacher et al. 2002; Luft et al. 2004), recent evidence suggests that a complex network involving not only M1 but also the cerebellum is involved in the consolidation of sensorimotor adaptation-based learning (Della-Maggiore et al. 2017). This is not the case for consolidation of a visuomotor tracking task, which relies heavily on the premotor cortex along with M1 (Boyd & Lindsell, 2009; Kantak et al. 2010; Meehan et al. 2013). The different neural pathways involved in consolidation of different forms of learning may be differentially influenced by a short bout of high intensity exercise. This is an important consideration in the application of high intensity exercise as a ‘primer’ of motor learning and must be explored further.

A second similarity in the previous studies showing gains in motor learning due to exercise is the motor learning task itself. In all previous studies the task was performed using one upper extremity while seated and required only isometric or grip force to perform the motor task (Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a, b; Nepveu et al. 2017). Learning a simple task that requires few effectors and little to no challenge to postural stability is quite different from learning a task that requires motor control of multiple effectors to accomplish a complex movement with significant postural stability challenges, such as walking. Though the control of upper extremity action and locomotion may share certain similar neural processes (Georgopoulos & Grillner, 1989; Yakovenko & Drew, 2015), there are still substantial differences in the basic neural control of each task. Thus, it is plausible that the benefits of high intensity exercise for motor learning observed in simpler, upper extremity tasks may not generalize to more complex tasks such as locomotion.

In summary, the exercise effect on motor learning may heavily depend on the intrinsic properties of the motor task used for motor practice and on the type or form of motor learning that is occurring. Future studies should investigate the effect of exercise on locomotor tasks which engage forms of motor learning (e.g. online feedback, reward) similar to those used in the previous work showing enhancement of motor learning with exercise to understand whether differences in learning are due primarily to the type of learning or also to differences in motor control of the upper extremity versus locomotion.

Among the exercise parameters that past studies have examined, gains in motor learning in neurologically intact subjects are greater when the exercise performed is at high intensity (Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a, b) and immediately after motor practice (Roig et al. 2012; Thomas et al. 2016a). Interestingly, the type of exercise (e.g. strength training, circuit training, indoor hockey) coupled with motor practice has no effect on motor learning (Thomas et al. 2017). In this study, we had stroke survivors exercise either before or after practice of the motor task to understand whether the effect of exercise timing would be similar after stroke. An early study in neurologically intact subjects demonstrated that either timing could increase retention (Roig et al. 2012), yet more recent studies showed that exercise after motor task practice may promote greater gains in motor learning (Skriver et al. 2014; Roig et al. 2016; Thomas et al. 2016a). A potential hypothesis for this strong effect of post-practice exercise on motor learning is that exercise after a motor task occurs during memory consolidation, a stage in the permanent formation of memory, which now is less susceptible to disruption (Brashers-Krug et al. 1996; McGaugh, 2000). The present study did not find an effect of exercise on the retention of the novel walking task; therefore, we were unable to discern any effect of exercise timing or further understand whether exercise during the period of consolidation positively or negatively influences motor learning after stroke.
Exercise has no effect on BDNF, but it may interact with the BDNF Val66Met gene

At a cellular level, BDNF has been proposed to be the linkage between exercise and learning (Cotman et al. 2007; Mang et al. 2013). In addition to the potential limitations of measuring BDNF in humans (Charalambous et al. 2018), findings on whether exercise-induced BDNF changes are correlated with gains in motor learning in neurologically intact adults are mixed (Mang et al. 2014; Skrifer et al. 2014). Including the potential effects of age, gender and neurological condition on the peripheral measures of BDNF (Knaepen et al. 2010; Szuhany et al. 2015; Santos et al. 2016), the fact that our stroke subjects did not reach comparable levels of high intensity exercise (lactate > 10 mmol/l) to healthy adults who participated in the previous priming studies may have also influenced the BDNF secretion (Mackay et al. 2017).

Given that gains in motor learning might be associated with upregulation of BDNF secretion due to exercise, any factors that negatively influence this activity-dependent secretion may have an indirect negative effect on motor learning. One of those factors can be genetic variation. Such a genetic variation is the presence of a single-nucleotide polymorphism of the BDNF Val66Met gene, which may detrimentally influence the capacity of learning (Lamb et al. 2015). In our previous work we found that post stroke subjects who are BDNF Val66Met carriers (MET) require more time to learn split-belt treadmill walking in a single session (i.e. slower adaptation rate) than the non-carriers (VAL) (Helm et al. 2016). In addition to the collection of neurophysiological and behavioural data, in our lab we also acquire saliva samples to determine the presence of BDNF Val66Met; the experimental procedures for data acquisition and analysis were exactly the same as in our previous recent work (Helm et al. 2016, 2017). Adding data from nine subjects, who experienced the same procedures as the subjects in the CON group, we have the results of 45 subjects (CON: 21, 5 MET; TMW: 12, 3 MET; TBE: 12, 3 MET). Given the small number of METs per group, we assessed the effect of BDNF Val66Met gene on the change of rate between sessions (i.e. adaptation rate – re-adaptation rate) using only descriptive statistics (Fig. 5). TMW and TBE have been combined (HIGH: 24, 6 METs). These data showed that in the CON group, METs (N = 5) had a slower change of rate between sessions than VALs (N = 16), while in the HIGH group, METs (N = 6) had a faster change of rate between sessions than METs in the CON group and a similar change of rate between sessions to VALs in both CON and HIGH (N = 18) groups. The results from this small sample suggest that (1) the presence of Val66Met after stroke may decrease the capacity to relearn the motor patterns of the split-belt treadmill walking, and (2) high-intensity exercise may ameliorate this effect, while not affecting the change of rate between sessions in the subjects without the polymorphism (i.e. VALs). Therefore, it might be possible that an overall effect of exercise on locomotor learning after stroke was not detected in the present study because of the differential effect of exercise in those with and without the polymorphism. Future studies should investigate whether these findings hold true in a larger sample.

Computational modelling can be feasibly applied in learning studies after stroke

While there is growing appreciation within the neuro-rehabilitation community of the utility of computational approaches (Reinkensmeyer et al. 2016), the application of computational modelling of motor behaviours of neurological patients, particularly locomotion, is still rare. To further our understanding of the learning processes underlying split-belt locomotor adaptation in stroke survivors, we applied computational modelling to the current behavioural data. The use of modelling was to provide finer grained analyses of the behaviour, with a special emphasis on long-term retention.

To this end, two versions of the dual-rate process model of adaptation developed by Smith and colleagues (2006) were used to fit the data. This model has been shown by others to effectively characterize locomotor adaptation in healthy subjects (Mawase et al. 2014; Roemmich et al. 2014). In addition to the potential limitations of computational approaches on long-term retention, factors such as the presence of BDNF Val66Met; the experimental procedures in our lab we also acquire saliva samples to determine the collection of neurophysiological and behavioural data, the use of modelling was to provide finer grained analyses of the behaviour, with a special emphasis on long-term retention.

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Computational modelling can be feasibly applied in learning studies after stroke

While there is growing appreciation within the neuro-rehabilitation community of the utility of computational approaches (Reinkensmeyer et al. 2016), the application of computational modelling of motor behaviours of neurological patients, particularly locomotion, is still rare. To further our understanding of the learning processes underlying split-belt locomotor adaptation in stroke survivors, we applied computational modelling to the current behavioural data. The use of modelling was to provide finer grained analyses of the behaviour, with a special emphasis on long-term retention.

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Figure 5. Effect of BDNF Val66Met polymorphism on the change of rate between sessions

In the CON group, rate of change between sessions was slower in METs than in VALs. In the HIGH group (all subjects from TMW and TBE groups), rate of change between sessions was similar in both METs and VALs. Compared to METs in the CON group, rate of change between sessions was faster in METs, who exercised at high intensity. Black and grey symbols denote individual data of VALs and METs, respectively, while the error bars indicate group mean and SD. Positive values denote faster rate in session 2 compared to session 1, whereas negative values denote slower rate in session 2 compared to session 1.
Effect of exercise on locomotor learning in chronic stroke survivors

2016). Interestingly, in contrast to a previous study of locomotor adaptation in healthy subjects (Mawase et al. 2014), here we did not find strong evidence to suggest that the learning processes, upon reintroduction of a given perturbation, change or improve across perturbations or sessions. Specifically, allowing parameter values to change across days did not measurably improve the model fits. As learning and retention are thought to increase in healthy subjects upon re-exposure to a split-belt perturbation, we suspect that the lack of improvements observed in the present study may be due to the neurological injury sustained by our subjects.

An additional benefit of applying a model-based approach to these data was that we were able to determine which of the two learning processes, fast or slow, underlies the 24 h long-term retention. Consistent with a previous study of force field adaptation in healthy subjects (Joiner & Smith, 2008), we found that long-term retention was due to the slow learning process. This finding, in combination with the finding that a linear time invariant version (i.e. LTI) of the dual process model was as appropriate as a time varying version (i.e. VP), suggests an interesting dichotomy. On the one hand, for our subjects with stroke the underlying learning processes did not appear to share similar characteristics (Krakauer & Shadmehr, 2006; Ranganathan et al. 2014). In the present study, the TBE group pedalled an ergometer with both arms and legs after the motor task and the TMW groups walked on the treadmill before practice of the motor task. In the case of the TBE group, retrograde interference, if it occurred, would be observed in retention on day 2. In the case of the TMW groups, anterograde interference, if it occurred, would be observed during the learning on day 1. Learning on day 1 and retention on day 2 were the same across all groups (e.g. those who exercised before or after practicing the motor task and regardless of exercise intensity), thus making interference in either case unlikely; however, this possibility cannot be ruled out.

Limitations of the study

This study has some methodological features that must be considered when interpreting the results. The most robust finding from all past exercise priming studies was that the effects of exercise on 24 h retention were even greater when the post-practice retention was measured after 7 days, regardless of the exercise parameters (Roig et al. 2012; Thomas et al. 2016a, b; Lundbye-Jensen et al. 2017). While it is unlikely that an effect of exercise on locomotor learning would be observed at 7 days when no effect was found at 24 h in the present study, this possibility cannot be ruled out. Future studies should therefore examine retention at both 24 h and 7 days after motor practice.

Subjects in the present study assigned to the high intensity groups exercised at a high intensity and significant changes in lactate were observed compared to those in the low intensity group. By design, however, exercise duration was shorter than in previous studies of neurologically intact subjects (Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a, b). As discussed in our previous work (Charalambous et al. 2018), exercise durations used in neurologically intact subjects are not feasible in subjects with stroke, if the exercise is to be coupled with neurorehabilitation involving walking and whole body movements, due to the significant fatigue and time constraints associated with these long-duration high-intensity protocols. However, it is possible that the duration of the high intensity exercise is important and may have influenced our findings. This would be important to ascertain in future studies because if longer duration high intensity exercise is necessary to observe the effects on motor learning previously found in both healthy adults (Roig et al. 2012; Skriver et al. 2014; Thomas et al. 2016a, b) and people post stroke (Nepveu et al. 2017), this will limit the type of motor practice that can be coupled with exercise in those with stroke.

Finally, we cannot rule out the potential effect of interference in the present study due to the use of the legs in both the exercise and learning tasks. Interference of one learned task on another occurs when the second task is practiced before or after the first task, but in close temporal proximity and when the two tasks share similar characteristics (Krakauer & Shadmehr, 2006; Ranganathan et al. 2014). In the present study, the TBE group pedalled an ergometer with both arms and legs after the motor task and the TMW groups walked on the treadmill before practice of the motor task. In the case of the TBE group, retrograde interference, if it occurred, would be observed in retention on day 2. In the case of the TMW groups, anterograde interference, if it occurred, would be observed during the learning on day 1. Learning on day 1 and retention on day 2 were the same across all groups (e.g. those who exercised before or after practicing the motor task and regardless of exercise intensity), thus making interference in either case unlikely; however, this possibility cannot be ruled out.

Conclusion

In the present study, we investigated whether high-intensity exercise, administered either before or after a novel locomotor task, would increase the locomotor learning of that task in people post stroke. Though all subjects exercised successfully at the target range and duration, a single high-intensity exercise bout, regardless of its timing, did not increase either the magnitude of retention (i.e. how much they remembered from day 1) or re-adaptation rate (i.e. how fast they reached the final adapted state on day 2). We postulated several factors that may have affected our findings. Preliminary analysis of genetic variation suggests that rate of change between sessions after stroke in those with the BDNF Val66Met may be impaired and high-intensity exercise may potentially ameliorate this effect. Future studies should quantitatively assess the interaction of genetic variation and exercise in larger sample of those post stroke. Lastly, in this study we demonstrated the feasibility of applying well-developed computational models of motor learning to a neurological population. In combination with the behavioural analyses, our modelling approach yielded two important insights:

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first, for subjects with stroke, learning processes did not appear to measurably improve across sessions, suggesting a specific impairment in re-learning of a previously experienced perturbation; second, long-term retention of what was learned from an initial training session was attributable to the slow learning process of adaptation, consistent with what has previously been observed in healthy subjects on a different task. This dissociation between relearning and long-term retention in stroke will be a fruitful area for further investigation.

References


Additional information

Competing interests

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

Author contributions

C.C.C., S.M.M. and D.S.R. were responsible for the conception and experimental design of the study; C.C.C., C.C.A., M.A.F. and X.L. performed experiments; C.C.C., X.L., H.E.K., S.M.M. and D.S.R. analysed and interpreted the data; C.C.C., H.E.K. and D.S.R. drafted the article; and C.C.C., C.C.A., M.A.F., X.L., K.S.M., H.E.K., S.M. M. and D.S.R. revised the article critically for important intellectual content. All authors have approved the final version of the manuscript and greed to be accountable for all aspects of the work. All persons designated authors qualify for authorship, and all those who qualify for authorship are listed.

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