Research Report

Corticospinal excitability and motor representation after long-term resistance training

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Abstract

It is poorly understood how the central nervous system adapts to resistance training, especially after years of exposure. We compared corticospinal excitability and motor representation assessed with transcranial magnetic stimulation (TMS) between long-term resistance trained (LRT, ≥3 years) versus untrained (UNT) males (n = 15/group). Motor-evoked potentials (MEPs) were obtained from the biceps brachii during isometric elbow flexion. Stimulus-response curves were created at the hotspot during 10% maximum voluntary torque (MVT) contractions. Maximum peak-to-peak MEP amplitude (MEPmax) was acquired with 100% stimulator output intensity, whilst 25%−100% MVT was produced. Maps were created during 10% MVT contractions, with an individualised TMS intensity eliciting 20% MEPmax at the hotspot. LRT had a 48% lower stimulus-response curve slope than UNT (p < .05). LRT also had a 66% larger absolute map size, although TMS intensity used for mapping was greater in LRT versus UNT (48% vs. 26% above active motor threshold) to achieve a target 20% MEPmax at the hotspot, due to the lower slope of LRT. Map size was strongly correlated with the TMS intensity used for mapping (r = 0.776, p < .001). Once map size was normalised to TMS intensity, there was no difference between the groups (p = .683). We conclude that LRT had a lower stimulus-response curve slope/excitability, suggesting higher neural efficiency. TMS map size was overwhelmingly determined by TMS intensity, even when the MEP response at the hotspot was matched among individuals, likely due to larger current spread with higher intensities. Motor representation appears similar between LRT and UNT given no difference in the normalised map size.

Keywords
mapping, motor-evoked potentials, stimulus-response curve, transcranial magnetic stimulation

Abbreviations: AMT, active motor threshold; CoG, centre of gravity; CV, coefficient of variation; EMG, electromyography; LRT, long-term resistance trained; MEP, motor evoked potential; MEPmax, maximum peak-to-peak MEP amplitude; M-max, maximal muscle compound action potential; MSO, maximal stimulator output; MVC, maximum voluntary contraction; MVT, maximum voluntary torque; RT, resistance training; Slope20%MEPmax, slope between AMT and the intensity used for mapping; Slope_max, maximum slope in the full S-R curve; SP, silent period; S-R, stimulus-response; TMS, transcranial magnetic stimulation; UNT, untrained.

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1 INTRODUCTION

Resistance training (RT) is known to be the best practice for improving muscular strength, and can enhance athletic performance and/or quality of life (ACSM, 2009). RT-induced strength gain has often been suggested to be associated with muscle hypertrophy as well as changes within the central nervous system (Folland & Williams, 2007). Neural adaptation may occur within the first few weeks of RT, but cumulative or more dramatic changes can be seen after prolonged periods (e.g., >1 year) of RT (Balshaw et al., 2019; Simoneau et al., 2007). Although the specific neural loci remain opaque, the motor cortex is thought to play a fundamental role in the control of movements, from the generation of ‘low-level’ control signals such as muscle force production (Evarts, 1968; Cheney & Fetz, 1980; and see Omrani et al., 2017 for a review) to involvement in ‘high-level’ control functions such as motor skill acquisition and consolidation (Papale & Hooks, 2018). The motor cortex therefore seems a plausible site of nervous system adaptation with changes in the excitatory and/or inhibitory intracortical circuits that appear to mediate increases in force generation after RT (for reviews, see Kidgell et al., 2017; Skarabot et al., 2020) and decreases in strength after disuse (Clark et al., 2010). An enhanced understanding of the modulations in the motor cortex following RT may help to improve and refine the exercise prescription of RT, which is now part of the physical activity recommendations for the general populations as well as people with neurological disorders (Kim et al., 2019; Verschuren et al., 2016).

One way to examine systems-level changes in the motor cortex is to use transcranial magnetic stimulation (TMS) to map the motor representation for a given muscle, by stimulating at different sites across the motor cortex and identifying the excitatory area that responds with motor-evoked potentials (MEPs) (Pascual-Leone et al., 1995). For example, Pascual-Leone et al., (1995) showed that an intense period of motor practice (2 hr/day for 5 days) resulted in the expansion of the motor representation of the involved muscles. Similarly, other studies have shown expanded/contracted representations in response to prolonged training in musicians (Schwenkreis et al., 2007), braille readers (Pascual-Leone et al., 1993) and stroke patients (Liepert et al., 2000). Whilst less is known about the plasticity of motor representation in the learning of maximal/high force motor tasks, volleyballers are reported to have a greater TMS map size in the dominant arm (deltoid and forearm muscles) than their non-dominant arm or either arm of runners (Tyc et al., 2005). These results suggest that motor representation is well associated with motor learning, with increased representation likely due to long-term potentiation of synaptic efficacy and synaptogenesis (Klein et al., 2004; Monfils et al., 2005). Some evidence suggests that neural adaptations to RT share similar corticospinal changes to motor learning/skill training (Leung et al., 2015; Mason et al., 2020; Selvanayagam et al., 2011), but the effect of RT on the size of the motor representation has not been investigated and may shed light on whether RT induces long-term potentiation of synaptic efficacy and synaptogenesis.

Regarding the methodology for creating a TMS map, it is customary to use a fixed (pre-determined) stimulation intensity at a percentage (e.g., +20%) above motor threshold, which is calculated at the hotspot (i.e., most responsive site) and then applied to other sites, for all participants (Rossini et al., 2015). This simplified approach is time-saving and practically beneficial, particularly in a clinical setting (Liepert et al., 2000). However, the slope of a stimulus-response (S-R) curve of MEP responses to a series of incremental stimuli, which reflects synaptic gain (excitability) of cortical and spinal neurones as well as the synchrony of firing (Devanne et al., 1997), has been reported to change after RT by decreasing (Carroll et al., 2002; Jensen et al., 2005) or increasing (Goodwill et al., 2012; Weier et al., 2012). In this case, stimulating at a fixed intensity above motor threshold may result in a slope-dependent map size, given that some authors have proposed there may be an inextricable link between excitability and map size (Ridding & Rothwell, 1995). For example, increasing the excitability may result in a larger map because more excitable neurones at the periphery of a muscle’s cortical representation will produce a larger response more likely to exceed any given threshold (Ridding & Rothwell, 1997). In other words, individuals with a steeper slope of the S-R curve may have a larger map due to greater MEP responses at the hotspot and across the whole area of cortical representation. Therefore, to inform cortical mapping methodology, it would seem useful to first determine the S-R curve. No study has compared map sizes between different cohorts (or pre- and post-intervention) whilst also taking into account the influence of S-R curve slopes on map sizes. In the event of large differences in S-R curve slopes both between individuals and groups, we considered that the stimulation intensity should be individually set to produce a constant MEP response at the hotspot for all participants when creating/comparing a map, the approach and results of which would be useful information for future studies. One way to do this is using an individualised intensity that elicits a certain percentage (e.g., 20%) of maximum MEP amplitude (MEPmax), which reflects the overall strength of the corticospinal pathway to the muscle (Kalmar, 2018). Similar approaches of using an individualised intensity (50% MEPmax or 10%–20% M-max) have been used when comparing MEP responses to varying contraction levels (Bunday & Perez, 2012; Pearcey et al., 2014; Philpott et al., 2015) or interstimulus intervals (Cirillo et al., 2016) across groups with potentially different excitability.

The primary purpose of this study was to compare motor representation of the biceps brachii muscle, assessed with TMS map size, in long-term resistance trained (LRT) versus
untrained (UNT) individuals. The secondary purpose was to compare the corticospinal excitability (S-R curve slope) of LRT versus UNT. We hypothesised that LRT would have a larger map size than UNT.

2 MATERIALS AND METHODS

2.1 Participants

Fifteen LRT (5.6 ± 3.4 years of RT experience) and 15 UNT participants were recruited for the study. All participants were required to be healthy males aged 18–40, with no history of taking anabolic steroids or drugs for similar purposes, asymptomatic at the time of testing and with no major injuries within the last 3 months. LRT participants had an extensive history of upper arm RT with ≥2 sessions/week, ≥10 months/year, ≥3 years, elbow flexion maximum voluntary torque (MVT; assessed during the familiarisation session—see below) of >90 Nm and MVT/body mass of >1.1 Nm/kg. UNT had no systematic physical training history of any kind. Physical activity levels, assessed with the International Physical Activity Questionnaire (IPAQ, short format; Craig et al., 2003), were 6,518 ± 1,749 and 1,052 ± 449 metabolic equivalent min/week for LRT and UNT, respectively. RT routines of the LRT individuals were reported via a detailed questionnaire. All LRT participants had implemented several elbow flexor exercises (e.g., dumbbell/barbel arm curls, incline arm curls and preacher curls) with the primary aim of developing maximum strength. They typically performed repetitions using medium-to-high loads with ~maximal efforts and often until volitional failure during each set. All participants received written and verbal information about the experimental protocol, completed a TMS safety-screening questionnaire (Keel et al., 2001) before providing written informed consent. This study was approved by Loughborough University Ethical Advisory Committee (R17-P146) and was conducted according to the Declaration of Helsinki.

2.2 Overview

All participants attended the laboratory on three occasions; one session involved familiarisation and assessment of the full S-R curve, followed by two identical mapping sessions, which were averaged to improve the reliability of these measurements. All sessions were conducted in the afternoon (12–8 p.m.) at a consistent time of the day (±2 hr), separated by at least 48 hr and no more than 7 days. Participants were instructed not to perform unfamiliar strenuous physical activity, consume caffeine or food in the 36, 6 and 2 hr, respectively, before each session. All sessions involved unilateral isometric elbow flexion dynamometry of the dominant arm to assess elbow flexion torque, with EMG recordings of the biceps brachii and TMS applied to the contralateral cerebral hemisphere. The familiarisation/full S-R curve session involved the following measurements/tasks in this order: (a) maximum voluntary contractions (MVCs) to assess MVT, (b) identifying the hotspot, as well as assessment of active motor threshold (AMT) and MEPmax at the hotspot, (c) assessment of the full S-R curve and (d) measurement of maximal muscle compound action potential (M-max) in response to peripheral nerve stimulation. The two mapping sessions involved the following in this order: (a, b) same as above, (c) calibration of the stimulus intensity that elicited 20% MEPmax for mapping, (d) creating a map at the calibrated intensity and (e) measurement of M-max. All TMS stimuli were delivered whilst participants performed low level voluntary contractions (10% MVT; Weier et al., 2012; Rossini et al., 2015; Kidgell et al., 2017), except for during MEPmax measurements (Task 2 above) which also involved higher levels of voluntary contractions (25%–100% MVT: detailed below). Stimuli were delivered during voluntary contractions rather than at rest because it is functionally more relevant (i.e., state/task-specific to RT), and corticospinal excitability is known to differ between active and rested states (Kalmar, 2018). During the second mapping session, ultrasonographic assessment of muscle thickness as an additional index of training status was conducted before any other measurements (detailed below).

2.3 Force and EMG recording

Participants were seated upright (hip joint angle of 90°) in an isometric elbow flexion dynamometer with the shoulder of their dominant arm flexed to 90° (i.e., upper arm horizontal) and slight horizontal abduction (~10°), and the elbow joint fixed at ~80° and forearm in a half supinated (~45°) position (0° = anatomical position). The participants wrist was tightly strapped to a wrist brace in series with a calibrated tension/compression strain gauge (Force Logic, Swallowfield, UK) positioned perpendicular to the forearm/ulna. Adjustable straps were also tightly fastened across the pelvis and chest to prevent extraneous movement. The analog force signal from the strain gauge was amplified and sampled at 2,000 Hz using an external analog-to-digital (A/D) converter (Micro 1,401; CED), with gravity corrected by subtracting baseline force, and recorded with Spike2 computer software (CED). Lever arm (forearm) length was measured, from the elbow joint centre to the centre of the strap around the wrist, to convert force into elbow joint torque.

Surface EMG was recorded from the biceps brachii long head using a wireless EMG system (Trigno; Delsys). Following skin preparation (shaving, abrading and cleansing with 70% ethanol), a single differential Trigno Standard
EMG sensor (Delsys), with a fixed 1-cm interelectrode distance, was attached over the mid muscle belly at a set percentage of upper arm length (67% between the medial acromion and fossa cubit) and parallel to the presumed orientation of the underlying fibres. EMG signals were amplified at source (×300; 20- to 450-Hz bandwidth) and sampled at 4,000 Hz via the same A/D converter and computer software as for the force signal to enable data synchronisation.

2.4 | Maximum voluntary contractions

The warm-up protocol prior to MVCs involved voluntary contractions of ~3-s duration at 50% (×3), 70% (×3) and 90% (×1) of perceived maximum, with the rest periods of 10 s (50%) and 20 s (70%–90%). After ≥30-s rest, participants were instructed to flex the elbow as hard as possible and complete three MVCs of ~3 s (≥30-s rest) with verbal encouragement. Visual feedback of the force signal was provided on a monitor placed directly in front of the participants, with a cursor used to mark the level achieved during each successive contraction. The highest peak value was taken as MVT.

2.5 | Transcranial magnetic stimulation

Single-pulse TMS was delivered by using a BiStim stimulator (Magstim Co. Ltd.), triggered via the running Spike2 software and A/D converter which allowed for data synchronisation, through a flat figure-of-eight coil (70 mm diameter). Participants wore an inelastic neoprene swim cap, on which a 7 × 7 square grid of points (15-mm square spacing) was displayed over each hemisphere (although only the contralateral hemisphere was used for TMS), to allow for locating the stimulation points (Figure 1a). The length between the edge of the cap and the nasion was recorded, and a marker was placed on the forehead during the test sessions so that the cap position could be checked and maintained. The centre of the coil was

FIGURE 1 The 7 × 7 grid of points over each hemisphere used for TMS motor mapping (a). The grid was positioned based on anatomical landmarks, with each point 15 mm apart. Mapping was conducted with the one cerebral hemisphere controlling the dominant arm and did not cross the centre line. Example 2D (b) and 3D (c) data from one UNT participant for the TMS map based on MEP responses normalised to MEPmax
positioned over a specific coordinate on the grid of the cap, and the handle was oriented backwards at ~45° with respect to the mid-sagittal line in order to induce current flow approximately perpendicular to the central sulcus (Rossini et al., 2015).

2.5.1 Hotspot, AMT and MEPmax

The hotspot was systematically identified, by delivering constant-intensity stimuli over the cortex, as the point that elicited the highest peak-to-peak MEP amplitude for a given TMS intensity (detailed in Supporting Document). AMT at the hotspot was then determined during voluntary contractions at 10% MVT as the minimum TMS intensity that elicited MEPs of ≥200 μV in at least three of five stimuli (Rossini et al., 2015) by increasing or decreasing stimulator output by increments of 1% of maximal stimulator output (MSO). Then, to assess MEPmax, TMS stimuli were delivered at 100% MSO, whilst participants performed constant-force voluntary contractions at 25%, 50% and 75% MVT (five, five and three stimuli, respectively). In some participants, MEP did not plateau at 50% MVT (22% of all sessions showed an increased MEP from 50% to 75% MVT, in contrast to some previous reports; Martin et al., 2006; Pearcey et al., 2014; Philpott et al., 2015). In this case, participants performed constant-force voluntary contractions at 25%, 50% and 75% MVT (five, five and three stimuli, respectively). During the voluntary contractions at 10% MVT, performed here and in the subsequent tasks, five stimuli each 5 s apart were successively delivered during a sustained contraction (i.e., ~25–30 s). For the higher levels of voluntary contraction (25%–100% MVT), only one stimulus was delivered during each of a series of brief contractions (2–3 s) at the target level, separated by ≥10, ≥20 and ≥30 s rest for 25%–50%, 75%–90% and 100% MVT, respectively, to minimise fatigue. Peak-to-peak MEP amplitudes of all stimuli at each contraction level were measured and the middle three out of five stimuli by amplitude (excluding the highest and lowest; for 10%–50% MVT), or all three stimuli (for 75%–100% MVT), were averaged. From the same MEP responses measured for amplitude, silent period (SP: the time from the start of the MEP to the resumption of muscle activity; Damron et al., 2008) was also calculated at each contraction level. In this study, SP was then calculated as the ratio of SP/MEP amplitude (from the same MEP response) to remove the influence of MEP amplitude, which is known to strongly influence SP duration (Orth & Rothwell, 2004).

2.5.2 Full S-R curve

In the familiarisation and assessment of the full S-R curve session, TMS was delivered at six incremental steps from AMT up to 100% MSO (i.e., AMT+20%, 40%, 60%, 80% and 100% of the difference between AMT and 100% MSO) during voluntary contractions at 10% MVT (five stimuli for each intensity). The TMS intensities were thus individual (e.g., for an AMT of 45% MSO, increments were 45%, 56%, 67%, 78%, 89% and 100% MSO). One hundred percent MSO was chosen as the end point of the S-R curve to ensure maximal/near maximal MEP. Our approach of six incremental steps from AMT to 100% MSO was therefore deemed the most efficient for achieving this and assessing the full SR curve (Figure 3a,c). Measurements at each intensity included MEP amplitude (peak-to-peak) and the SP/MEP amplitude ratio and were averaged over the middle three of five MEPs by excluding those with the highest and lowest amplitudes. To enable comparisons at the same relative TMS intensities as % above AMT between groups, individual S-R curves for the MEP amplitude were interpolated at +5%, +10%, +15%, etc. up to +40% AMT (Figure 3b) by fitting the curve to the following Boltzmann sigmoidal equation (Devanne et al., 1997):

\[ \text{MEP} (S) = \frac{\text{MEP}_{\text{peak}}}{1 + \exp \left( \frac{(S_{50} - S)}{K} \right)} , \]

where MEP (S) is the MEP amplitude for a given stimulus intensity S (as % above AMT), MEP_{peak} is the peak MEP amplitude or plateau of the S-R curve (at 10% MVT), S_{50} is the stimulus intensity (as % above AMT) required to obtain a response of 50% of the MEP_{peak}, and K is the slope parameter. The inverse of the slope parameter (1/K) is directly proportional to the maximal steepness of the function, which occurs at S_{50}. For the SP/MEP amplitude ratio, individual S-R curves were fitted with a cubic equation (as this provided the best fit, highest R²), and interpolated at +5%, +10%, +15%, etc. up to +40% AMT (Figure 3d). R² values of the S-R curves for the MEP amplitude and the SP/MEP amplitude ratio in the whole cohort were 0.921 ± 0.088 and 0.918 ± 0.100, respectively, without differences between the groups (p = 0.630–0.940). From the full interpolated S-R curve for the MEP amplitude, the maximum slope (Slope_{max}) was obtained by calculating the derivative of the Boltzmann sigmoidal equation and plotting it against the stimulus intensities as % above AMT (Hassanlouei et al., 2017).

2.5.3 Calibration of mapping stimulus intensity

In the two mapping sessions, once MEPmax had been established, TMS intensity was calibrated to elicit 20% MEPmax at the hotspot during voluntary contractions at 10% MVT. More specifically, five stimuli were first delivered at an intensity of ~10% above AMT, with the middle three MEP amplitudes averaged and expressed as % MEPmax. TMS intensity was adjusted to the nearest 1% and the process was repeated to
achieve stimuli responses of 20% MEPmax. This stimulus intensity (eliciting 20% MEPmax) for the TMS mapping was selected to exceed AMT intensity in all participants (Figure 3b), without causing excessive participant discomfort or overheating of the coil. We chose to adjust to a % MEPmax (Bunday & Perez, 2012; Cirillo et al., 2016) rather than a % M-max (Pearcey et al., 2014; Philpott et al., 2015) because we found better reproducibility for the former in our pilot testing, which was confirmed by the reproducibility data from the two duplicate sessions in this study (see Reproducibility and Statistical Analysis below). This calibration also facilitated a measure of the slope between AMT and the intensity used for mapping (Slope20%MEPmax), which was calculated as ΔMEP/ΔTMS intensity (where ΔMEP = % MEPmax used for mapping – % MEPmax at AMT and ΔTMS intensity = individualized TMS intensity used for mapping as % above AMT), that was averaged across the two mapping sessions. Here, we did not use the Boltzmann equation to calculate the slope because the full S-R curve was not created in the mapping sessions and also because the Slope20%MEPmax was considered relevant to examine the relationship between map size and excitability at the stimulation intensity used for mapping.

2.5.4 Mapping

To determine the size of the map, we used the fixed intensity stimuli (i.e., the one eliciting 20% MEPmax at the hotspot calibrated as described above) at a range of grid points during voluntary contractions at 10% MVT; firstly at the hotspot and then adjacent (including diagonal) grid points in a random order, with >10-s rest before moving to the next point. This was repeated until all active points had been identified within the 7 × 7 grid points, by demonstrating that all surrounding/adjacent points were non-active (see Figure 1b,c). The size of the map was quantified as the number of active points. An active point was defined as one in which the MEP amplitude exceeded 200 μV. For each grid point, five stimuli were delivered (as described above), and when all MEPs exceeded 200 μV, the middle 3 values (excluding the highest and lowest) were averaged. When only three or four of five stimuli were >200 μV, then all values were averaged. In offline analysis, active points exhibiting MEP amplitudes less than 11% MEPmax were excluded from the map size calculation, as the lowest common % MEPmax in active points, based on the cut-off amplitude (200 μV) divided by the lowest MEPmax amplitude among all participants/sessions (1,818 μV), was 11%. MEP amplitude at each active grid point of an individual was ranked in order of MEP size to facilitate averaging for grid point rank, first across the two sessions of each individual and then within groups. As an additional index of map size, map volume was calculated as the sum of the mean MEP at each active point, normalised to the mean MEP at the point of largest response (Rossini et al., 2015). Centre of gravity (CoG) of the map was also calculated as CoG-x = (ΣMEPi × xi)/ΣMEPi; CoG-y = (ΣMEPi × yi)/ΣMEPi, where MEPi is the mean amplitude of the MEPs produced at each active point, and xi and yi represent the x (medio-lateral) and y (antero-posterior) coordinates of the point normalised to the nasion (Plow et al., 2014).

2.6 M-max

To control for peripheral factors (e.g., muscle-electrode distance) that can influence MEP amplitude (Kalmar, 2018), M-max was evoked from the biceps brachii by peripheral electrical stimulation with a constant-current variable voltage stimulator (DS7AH; Digitimer) for the purpose of normalisation. The stimulation was applied to the brachial plexus with a cathode probe (1-cm diameter; Electro-Medical Supplies) positioned in the supraclavicular fossa and an anode electrode (7 × 10-cm carbon rubber electrode; Electro-Medical Supplies) on the deltoid. Both electrodes were coated with electrode gel and cathode location was determined by delivering single electrical impulses (square wave pulses of 0.2-ms duration, >10 s apart) to identify the position that elicited the greatest submaximum M-wave response. The cathode was taped in place and M-max was determined by increasing the stimulus intensity until M-wave amplitude plateaued. A supramaximal current (+50% above plateau current) was used to elicit three supramaximal responses 15 s apart. These three responses were averaged and taken as M-max. A clear M-max was not obtained from one participant in UNT, and thus this participant was excluded from the analysis related to M-max. It is reported that M-max amplitude of the biceps brachii does not differ at rest versus 10% MVT (Collins & Button, 2018; Collins et al., 2017) or between chronically resistance trained and untrained controls at 10%–100% MVT (Pearcey et al., 2014).

2.7 Muscle thickness

Muscle thickness of the elbow flexors at rest was measured using ultrasonography whilst participants were positioned in the isometric elbow flexion dynamometer. An ultrasound probe (5- to 10-MHz linear array transducer, B-mode, scanning width of 92 mm and depth of 65 mm, EUP-L53L; Hitachi EUB-8500) was placed longitudinally at two locations over the biceps brachii and perpendicular to the skin surface. The two recorded images were one of the biceps brachii long head and brachialis, centred at the position of the long head EMG electrode location (lateral), and one of the biceps brachii short head and brachialis, centred at 67% of the distance from the medial acromion and fossa cubit along the short head (medial). By using public domain image analysis software (https://physlets.org/tracker/; Tracker, version...
4.97), the muscle thickness of the elbow flexors was determined as the distance from the subcutaneous adipose tissue–muscle interface to the muscle–bone interface in the centre of each image. Values from the two images were averaged to provide a mean elbow flexor value. We have previously found the within-participant inter-day coefficient of variation (CV) for this measurement to be 1.2% (Maeo et al., 2014).

### 2.8 Reproducibility and statistical analysis

All raw data, except for those reported in the results section, are shown in Table 1. The mean between-session within-participant CV and intraclass correlation coefficient (ICC) for the primary outcomes were calculated from the two duplicate mapping sessions for all participants in
each group \((n = 15/\text{group, Table 2})\). It can be seen that MEP amplitude normalised to MEPmax had better reproducibility than when normalised to M-max. Data from the two mapping sessions were averaged to produce criterion values for each individual, and are presented as mean ± SD for each group.

Responses (MEP amplitude and SP) between groups during submaximal contractions at different \%MVT were compared with two-way ANOVA (level of contraction [10\%, 25\%, 50\% and 75\% MVT] × group [LRT, UNT]). From the full S-R curve, MEP amplitude and the SP/MEP amplitude ratio at TMS intensities at and above AMT between groups were also compared with two-way ANOVA (TMS intensity [AMT (+0\%), +5\%, +10\%, +15\% etc. up to +40\% AMT] × group [LRT, UNT]). From the mapping, MEP amplitudes at each ranked grid point (i.e., 1 being the highest etc.) were compared between groups with two-way ANOVA (ranked grid point [49 points in total] × group [LRT, UNT]). Unpaired \(t\) tests were used to compare between groups for all other variables. Data were checked for normality using Shapiro–Wilk tests. If the data set included non-normally distributed data, non-parametric Mann–Whitney \(U\) tests were used to compare between groups for that data set. Sphericity was checked by Mauchly’s test in ANOVA, and statistics \((F, df\) and \(P\) values) were modified with Greenhouse–Geisser correction when necessary. Bivariate correlations were assessed with Pearson’s product moment correlations. Correlation coefficients were compared with William’s test by using R-based software (Diedenhofen & Musch, 2015). Statistical significance was set at \(p < .05\). Effect sizes of between-group differences were calculated as Cohen’s \(d\) values and interpreted as large (≥0.80), medium (0.50–0.79), small (0.20–0.49) or trivial (<0.20).

### TABLE 2  
Between-session reproducibility for the primary outcomes

| Variable | CV (%) | ICC |
|----------|--------|-----|
|          |        | LRT | UNT |
|          | MVT    | 3.4 | 3.7 |
|          | MEPmax | 13.2| 23.1|
| MEP normalised to MEPmax at 10\% MVT and 100\% MSO | 17.7 | 14.9 | 0.868 | 0.897 |
| MEP normalised to MEPmax at 25\% MVT and 100\% MSO | 5.2 | 13.0 | 0.919 | 0.912 |
| MEP normalised to MEPmax at 50\% MVT and 100\% MSO | 4.0 | 7.3 | 0.844 | 0.892 |
| MEP normalised to MEPmax at 75\% MVT and 100\% MSO | 8.6 | 9.7 | 0.902 | 0.873 |
| MEP normalised to MEPmax at 10\% MVT and AMT | 24.4 | 23.1 | 0.605 | 0.720 |
| Slope\(20\%\)MEPmax | 34.2 | 44.9 | 0.579 | 0.411 |
| Number of active map points | 33.4 | 46.7 | 0.462 | 0.523 |
| Map volume | 36.8 | 52.3 | 0.628 | 0.603 |
| M-max | 9.8 | 14.9 | 0.911 | 0.803 |
| MEPmax normalized to M-max | 13.7 | 18.6 | 0.702 | 0.442 |
| MEP normalised to M-max at 10\% MVT and 100\% MSO | 22.9 | 33.1 | 0.805 | 0.491 |
| MEP normalised to M-max at 25\% MVT and 100\% MSO | 16.7 | 33.4 | 0.774 | 0.502 |
| MEP normalised to M-max at 50\% MVT and 100\% MSO | 18.0 | 26.0 | 0.595 | 0.310 |
| MEP normalised to M-max at 75\% MVT and 100\% MSO | 19.7 | 27.5 | 0.716 | 0.563 |
| MEP normalised to M-max at 10\% MVT and AMT | 24.8 | 32.9 | 0.639 | 0.383 |

Note: \(n = 15/\text{group except for the M-max and MEPs normalised to M-max (n = 15 for LRT and 14 for UNT). CV: mean within-participant coefficient of variation; ICC: intraclass correlation coefficient.}
3 | RESULTS

3.1 | Group characteristics

No differences were observed between groups in age (LRT vs. UNT, 21.9 ± 3.8 vs. 21.9 ± 3.3 years, \(p = .959, d = 0.02\) ‘Trivial’) and height (1.79 ± 0.07 vs. 1.76 ± 0.10 m, \(p = .331, d = 0.36\) ‘Small’), but body mass was 29% larger for LRT than UNT (89.0 ± 11.4 vs. 69.1 ± 10.5 kg, \(p < .001, d = 1.81\) ‘Large’).

3.2 | Muscle size and strength

LRT had 59% thicker muscles (36.5 ± 5.4 vs. 23.0 ± 3.8 mm, \(p < .001, d = 2.87\) ‘Large’), 73% higher absolute MVT (121.1 ± 15.7 vs. 70.2 ± 13.8 Nm, \(p < .001, d = 3.44\) ‘Large’) and 34% higher relative MVT (1.36 ± 0.07 vs. 1.02 ± 0.13 Nm/kg, \(p < .001, d = 3.17\) ‘Large’) than UNT.

3.3 | MEPmax and the voluntary force-MEP and -SP relationships

MEPmax normalised to M-max did not differ between groups (81.7 ± 25.0% vs. 80.5 ± 20.9%, \(p = .891, d = 0.05\) ‘Trivial’). The main statistical findings were the same when expressed as either % MEPmax or % M-max, and therefore to avoid redundancy, data are only reported as % MEPmax. The voluntary force–MEP relationship for contractions over the range 10%–75% MVT is shown in Figure 2a (for stimuli at 100% MSO). A two-way ANOVA found a significant main effect of contraction level (\(F[2.3, 64.4] = 22.207, p < .001\)), but no main effect of group (\(F[1, 28] = 0.211, p = .649\)) and no interaction effect (\(F[2.3, 64.4] = 1.863, p = .162\)), indicating no difference between groups. Post hoc Bonferroni comparisons on pooled whole cohort data revealed MEP amplitude was 44%–59% lower during voluntary contractions at 10% MVT than at higher levels of contraction (\(p < .001, d = 1.24–1.84\) ‘Large’), but there were no differences in MEP amplitude between 25%, 50% and 75% MVT (\(p = 1.000, d = 0.17–0.61\) 'Small').

FIGURE 2 MEP amplitude (a) and SP/MEP amplitude ratio (b) in response to stimuli at 100% MSO during isometric elbow flexion voluntary contractions at 10%, 25%, 50% and 75% MVT for LRT (\(n = 15\)) and UNT (\(n = 15\)) groups. Data are mean ± SD.

FIGURE 3 Measured MEP amplitude (a) and SP/MEP amplitude ratio (c) at AMT and at five incremental TMS intensities up to 100% MSO for LRT (\(n = 15\)) and UNT (\(n = 15\)) groups. To enable comparisons at the same TMS intensities, MEP and SP/MEP amplitude ratio at +5%, +10%, +15%, etc. up to +40% AMT were interpolated by using a Boltzmann equation for MEP amplitude (b) and a cubic equation for SP/MEP amplitude ratio (d) fitted to individual S-R relationships. Data are mean ± SD. An asterisk indicates a significant difference between groups (\(p < .05\)).
indicating a plateau in mean MEP at ≥25% MVT.

The SP/MEP amplitude ratio (Figure 2b) had a significant main effect of contraction level \(F[1.5, 42.0] = 14.267, p < .001\) and a tendency towards significance for a main effect of group \(F[1, 28] = 3.872, p = .059\), without an interaction effect \(F[1.5, 42.0] = 0.128, p = .820\), indicating that the SP/MEP amplitude ratio tended to be lower for LRT than UNT at all contraction levels.

3.4 The full S-R curve

Figure 3 shows measured MEP amplitude and the SP/MEP amplitude responses to six incremental stimulation intensities from AMT up to 100% MSO (Figure 3a,c), as well as interpolated responses at +5% increments from AMT to 40% above AMT (Figure 3b,d) during voluntary contractions at 10% MVT. AMT was not different between groups (40.3 ± 7.8% vs. 43.9 ± 5.7% MSO, \(p = .162, d = 0.53\) ‘Medium’, Figure 3a). A two-way ANOVA of interpolated MEP amplitude (Figure 3b) revealed a TMS intensity × group interaction effect \(F[1, 29] = 9.153, p = .005\), as well as a main effect of group \(F[1, 29] = 9.548, p = .004\). Subsequent post hoc analysis found 36%–50% lower MEP amplitudes for LRT than UNT at all interpolated TMS intensities at and above AMT \(p = .003–0.044, d = 0.77–1.18\) ‘Medium–Large’, Figure 3b). Consequently, the S-R curve Slope max was 48% lower for LRT than UNT (0.52 ± 0.33 vs. 1.00 ± 0.62, \(p = .013, d = 0.97\) ‘Large’; Figure 3b).

The interpolated SP/MEP amplitude ratio (Figure 3d) had a significant TMS intensity × group interaction effect \(F[1.6, 45.9] = 4.951, p = .016\), as well as a main effect of TMS intensity \(F[1.6, 45.9] = 28.004, p < .001\) without a main effect of group \(F[1, 28] = 0.031, p = .862\). However, subsequent post hoc analysis did not find differences between groups at any of the TMS intensities \(p = .129–0.968, d = 0.02–0.57\) ‘Trivial–Medium’, Figure 3d).

3.5 Motor representation with TMS mapping

During the mapping task, the MEP amplitude at the hotspot was very close to the target value of 20% MEPmax and was similar for both groups (19.8 ± 0.9% vs. 19.3 ± 0.7%, \(p = .151, d = 0.63\) ‘Medium’). Achieving this similar response (% MEPmax) involved a higher TMS intensity (% above AMT) for LRT than UNT on average across both mapping sessions (48.2 ± 27.8% vs. 26.3 ± 12.8% above AMT, \(p = .009, d = 1.02\) ‘Large’; 55.4 ± 14.8% vs. 51.3 ± 6.7% MSO, \(p = .334, d = 0.36\) ‘Small’), which was consistent with lower Slope 20%MEPmax for LRT than UNT (0.37 ± 0.20 vs. 0.63 ± 0.42, \(p = .024, d = 0.78\) ‘Medium’).

As shown in Figure 4a, LRT had a 66% greater number of active points than UNT \((p = .008, d = 1.05\) ‘Large’), but with large variability within each group. Map volume was also 62% greater for LRT than UNT (6.0 ± 2.6 vs. 3.7 ± 1.2 AU, \(p = .005, d = 1.13\) ‘Large’). Neither CoG-x (33.3 ± 4.7 vs. 35.0 ± 4.7 mm, \(p = .328, d = 0.56\) ‘Small’) nor CoG-y (186.0 ± 10.7 vs. 183.6 ± 6.5, \(p = .466, d = 0.27\) ‘Small’) differed between groups. For each individual, % MEPmax values at all grid points of their TMS map were ordered by the size of the MEP responses from left to right (rank order by magnitude shown up to 30 points, Figure 5a) before averaging within each group, and this revealed a group × ranked grid point interaction effect (two-way ANOVA; \(F[48, 1344] = 3.962, p < .001\)). Whilst MEP amplitude did not differ between groups for the grid point with the largest response (first ranked grid point), significant differences were found at points 5–11 \((p = .005–0.036, d = 0.74–1.13\) ‘Medium–Large’). Figure 5b shows the number of participants with an active response for each ranked grid point, and clearly shows the higher number of participants in LRT that had active grid points from rank 4 onwards compared to UNT.

Given the differences between the groups, and variability within the groups, in the map size, TMS intensity (% above AMT) used for the mapping and S-R curve slope (excitability),

**FIGURE 4** The number of active points in the TMS map (a) and the number of active points normalised to the TMS intensity as % above AMT used for mapping (b) for LRT (n = 15) and UNT (n = 15) groups. Data are mean ± SD with the individual data overlaid. An asterisk indicates a significant difference between groups \((p < .05)\). The difference in Figure 4b remained non-significant \((p = .451)\) when the potential outlier in LRT was excluded.
we investigated if there was a relationship between these phenomena. In the whole cohort, the number of active points ranged widely from 3 to 17, TMS intensity from 8.5% to 112.1% above AMT and Slope20%MEPmax from 0.14 to 1.56. The TMS intensity used for the mapping (% above AMT) was strongly correlated with the number of active points within both groups (LRT $r = 0.749$, $p = .001$; UNT $r = 0.543$, $p = .035$) and the whole cohort ($r = 0.776$, $p < .001$, Figure 6a). The Slope20%MEPmax (i.e., excitability) was also correlated with the number of active points in both groups (LRT $r = -0.603$, $p = .017$; UNT $r = -0.546$, $p = .035$) and the whole cohort ($r = -0.548$, $p < .001$, Figure 6b). For the whole cohort, the strength of the correlation between the TMS intensity and the number of active points was significantly greater than the correlation between the Slope20%MEPmax and the number of active points (i.e., 0.776 vs. 0.548, $p = .044$). Subsequently, when the number of active points was normalised to the TMS intensity (% above AMT), there was no difference between the groups ($p = .683$, $d = 0.22$ ‘Small’, Figure 4b).

4 | DISCUSSION

This study aimed to compare motor representation of the biceps brachii, assessed with TMS map size, in LRT versus UNT, which also involved determining the S-R curve slope to inform the method for the mapping. The S-R curve Slope_max was substantially lower for LRT versus UNT (~48%) and was also highly variable between individuals. This necessitated using an individualised TMS intensity
% above AMT) for the mapping, which was on average higher for LRT than UNT, to achieve a consistent MEP response (20% MEPmax at the hotspot). LRT had a larger absolute map size than UNT; however, a surprising finding was that map size was strongly correlated with the relative TMS intensity (% above AMT; \( r = 0.776 \)), and statistically more so than excitability (Slope\( \% \)MEPmax; \( r = -0.548 \)) which had been hypothesised as the major determinant of map size (Ridding & Rothwell, 1995). Subsequently, when map size was normalised to TMS intensity, there were no longer any differences in map size. These results suggest that (a) LRT had a lower S-R curve slope, (b) whilst TMS map size was related to excitability (slope) as expected, map size was more strongly determined by the relative TMS intensity used for mapping even when the MEP response at the hotspot was matched among individuals and (c) given that the normalised map size did not differ between groups (i.e., when the influence of TMS intensity was removed), motor representation size appears similar between LRT and UNT.

4.1 S-R curve

We found the MEP amplitude response at all stimulus intensities to be lower by 36%–50% for LRT versus UNT (Figure 3b) and thus demonstrated a 48% lower S-R curve Slope\( \max \). Previous studies have reported the slope, or the MEP amplitude in response to a given stimulus at % above AMT, to be decreased (Carroll et al., 2002; Jensen et al., 2005), increased (Goodwill et al., 2012; Weier et al., 2012) or unchanged (Christie & Kamen, 2014; Coombs et al., 2016; Hortobagyi et al., 2009) after 2–4 weeks of RT. This inconsistency might be because of variations in protocols and/or muscle groups studied (Carroll et al., 2011) or because the training interventions were too short to induce sufficient or distinct changes, leading athletes, visuo-spatial task in table tennis athletes (Guo et al., 2017) and cycling task in cyclists/triathletes (Ludyga et al., 2016). Although the S-R curve in this study was created only with TMS, which cannot locate the site of neural changes along the corticospinal tract, Carroll et al., (2009) found decreased MEP and cervicomedullary-MEP amplitudes at 50% MVT after 4 weeks of RT. Collectively, these results suggest that RT reduces corticospinal excitability/activity (i.e., increases corticospinal transmission) during low-to-medium force productions, which involves modulations at subcortical levels. It is also worth noting that 14 weeks of RT increased H-reflex amplitude during maximum contractions, reflecting enhanced excitability of spinal \( \alpha \)-motoneurons and transmission efficiency (i.e., reduced presynaptic inhibition) (Aagaard et al., 2002). The potential influence of such RT-induced changes at the spinal level on the corticospinal transmission is yet to be examined, as there is currently no study that has conducted comprehensive assessments of the above parameters and examined their interactions. Further research is warranted to better identify the site(s) of neural adaptations to RT and whether changes in one site affect others.

From the MEP responses in the S-R curve created at 10% MVT, we also measured SP (Figure 3c,d), which is reflective of corticospinal inhibition (mediated through gamma-aminobutyric acid-B receptors) and reported to be decreased (i.e., less inhibition) following RT by some (Christie & Kamen, 2014; Coombs et al., 2016; Mason et al., 2017) but not all (Kidgell et al., 2011) studies. However, we did not find any differences in SP between the groups at any TMS intensities during contractions at 10% MVT (i.e., S-R curve measurements; Figure 3d). At higher contraction levels (≥25% MVT; Figure 2b), SP tended to be lower for LRT than UNT, implying that there may be a difference between LRT and UNT in corticospinal inhibition at higher contraction levels routinely performed by LRT individuals (thus more state/task specific). However, it should be noted that measurements during these higher levels of contraction were primarily designed in order to assess MEPmax, and thus TMS intensity was 100% MSO stimuli for all participants (i.e., an absolute rather than relative TMS intensity) (Figure 2a). We are confident that MEPmax was achieved in each individual in this study, by showing a plateau in MEP amplitude at ≥25% MVT which is in line with previous studies (Martin et al., 2006; Pearcey et al., 2014; Philpott et al., 2015), with good reproducibility (Table 2). However, the use of an absolute TMS intensity may not be ideal for determining MEP and SP responses (i.e., S-R curves) at several contraction levels, and a more robust examination with relative TMS intensity (% above AMT) is necessary in future studies to substantiate whether differences between LRT and UNT are dependent upon voluntary contraction levels.
4.2 | TMS map size

There was a substantial difference in absolute map size between the groups with LRT having 66% more active points (Figure 4a) and 62% greater map volume. These values were much greater than the intersession CVs of these variables (33%–52%, Table 2) calculated across the duplicate mapping sessions. Thus, we consider that the observed difference in absolute map size was a systematic effect and appears to support our hypothesis of a greater map size for LRT versus UNT. However, due to the difference in the S-R curve slopes, achieving a consistent 20% MEPmax at the hotspot required a higher TMS intensity, quantified as % above AMT, for LRT than UNT (48% vs. 26% above AMT). When the number of active points was normalised to the TMS intensity, there was no difference between the groups (Figure 4b). This indicates that the larger absolute map size of LRT was a consequence of the higher TMS intensity used for the mapping.

Due to the large individual variability in the S-R curve slopes and the difference between the groups and a previous suggestion that excitability and map size may be inextricably linked (Ridding & Rothwell, 1995), we considered it logical to create the map using an individualised TMS intensity (% above AMT), to achieve a consistent MEP response (20% MEPmax) at the hotspot. We were concerned that the alternative approach of using a fixed TMS intensity (i.e., non-individualised at a constant % above AMT) may (a) introduce bias due to greater excitability and thus MEP responses in one group leading to a larger map and (b) result in large individual variability in MEP responses within each group, potentially obscuring any differences in map size between groups. Indeed, there was a substantial difference between the groups and wide variability within each group in the S-R curve slopes, and Slope20%MEPmax was found to be moderately correlated with absolute map size ($r = -0.548$ for the whole cohort, Figure 6b). This suggests that excitability/slope has an influence on map size as previously proposed (Ridding & Rothwell, 1995).

However, a novel finding of this study was that TMS intensity was statistically more strongly correlated with map size ($r = 0.776$ for the whole cohort; Figure 6a) than excitability. There is some evidence that within-individual map size is concomitantly dependent on stimulation intensity and MEP response (van de Ruit & Grey, 2016), but the distinct importance of these two factors to map size has not been known. Ridding and Rothwell (1995) suggested that response size/slope (excitability) and map size are linked to one another. Theoretically, for example, if the excitability of a given projection area increases, then the apparent area from which corticospinal responses can be obtained with TMS also will increase, because it will be possible to activate the neurons more readily by current spread from distant sites (Ridding & Rothwell, 1995). Conversely, if there is an increase in the area of a motor representation, it will also increase the slope of the S-R curve because current spread from a stationary stimulator will have access to a larger number of cortical cells so that a given intensity of stimulus will evoke a larger response (Ridding & Rothwell, 1997). However, we found map size was overwhelmingly related to stimulus intensity rather than excitability, even when the MEP response at the hotspot was matched among individuals.

A likely explanation for the strong relationship of map size and stimulus intensity is the influence of the size of the electric field (current spread). The figure-of-eight coil used in this study is recommended for mapping, as it provides a focused stimulation (Rossini et al., 2015), although there still is some current spread the extent of which is known to increase proportionally with stimulation intensity (Thielscher & Kammer, 2004). We were aware of this issue and thought that the influence of larger current spread concomitant with using a higher stimulation intensity would be counteracted by the lower excitability/slope. However, based on the strong correlation of TMS intensity and map size that does not seem to have been the case. Further, some studies (Hoef et al., 2008; Opitz et al., 2014) implicitly show that whilst the electric field is most concentrated at the centre of the coil, it is also distributed around the circular parts of the coil (see Figure 1 of Opitz et al., 2014). Thus, although it is unknown precisely how the distribution of the current spread in the brain changes with stimulation intensity, it is possible that larger current spread with the higher TMS intensity, not only from the centre but also from the circular parts of the coil, brought about the larger map of LRT versus UNT. Such a confounding factor seems to have obscured the true indication of the motor representation size.

On the other hand, it should be pointed out that the induced field is affected by skull thickness, cortical morphology and excitability (Aberra et al., 2020), and this is why the same absolute intensity (% MSO) elicits MEPs of different sizes in different individuals. The current results indicate that it is not just the absolute stimulus intensity that is an important influence of map size, because % MSO used in mapping on average was similar across groups. Rather, the relative intensity as % above AMT, i.e., the relative induced field strength, is critical for producing the larger map size. In other words, many of the differences that might be a confounding factor for mapping can be accounted for by establishing AMT, and simply using a set relative intensity as % above AMT may be fine/less confounding. We take the result that the normalised map size did not differ between the groups (i.e., when the influence of TMS intensity/current spread was removed) as suggesting that motor cortical representation is similar between LRT and UNT.

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No difference in (normalised) map size between LRT and UNT refutes our hypothesis of a greater map size of LRT. Whilst extensive practice of complex skill and dexterity tasks
has been found to be associated with expanded motor representation (Nudo et al., 1996; Pascual-Leone et al., 1993; Schwenkreis et al., 2007; Tyc et al., 2005), it has been unknown if systematic exposure to gross motor tasks such as RT might increase map size. Our findings might be taken to suggest that the expansion of motor representation is specific to the learning of complex dexterity skills, rather than the enhanced muscular force production of RT. A previous study (Jensen et al., 2005) suggested that skill training and RT are associated with different plastic changes in the nervous system, by showing an S-R curve slope/MEP response to increase after skill training and to decrease after RT, which is in line with the current study. There is also some evidence from direct (invasive) stimulation of the cortex in monkeys, a technique that offers better spatial resolution, of expanded motor representation after skill training but not after RT (Remple et al., 2001). Collectively, these results suggest that RT induces a decrease in the S-R curve slope but does not change map size. Nevertheless, future studies should further examine the interaction of slope and map size, as well as the effect of RT on map size by creating a map with a traditional methodology (i.e., stimulate at a set % above AMT) to avoid the confounding influence of relative TMS intensity. Finally, it should be mentioned that we measured the S-R curves and maps only at 10% MVT, as often conducted in related studies (Hassanlouei et al., 2017; Tyc et al., 2005; Weier et al., 2012), because it was more feasible (particularly when creating maps) considering the potential influence of fatigue compared to the higher contraction levels, although higher contractions levels are arguably more relevant to RT. On the other hand, van de Ruit & Grey, 2016 showed that maps could be acquired at contraction levels up to 40% MVT with an advanced methodology using a TMS device (Magstim Rapid®) that allows for repetitive stimuli but was not available within the current experiment. Thus, contraction levels such as 40% or higher, if possible, should be selected/added in future studies when examining the effect of RT on map size and/or S-R curves.

5 | CONCLUSIONS

In summary, we found a substantially lower S-R curve slope in LRT versus UNT and high variability between individuals. Subsequently, TMS maps were created with an individually calibrated TMS intensity that elicited the same MEP response (20% MEPmax) at the hotspot for all individuals. Although LRT had a larger absolute map size than UNT, the difference between groups disappeared when the map size was normalised to the TMS intensity. This was because of the surprising finding that map size was very strongly related to TMS intensity between individuals even when the MEP response at the hotspot was matched and more so than excitability/slope, contrary to expectation. We conclude that (a) LRT had a lower S-R curve slope, suggesting higher neural efficiency, (b) TMS map size was moderately affected by the S-R curve slope (excitability) but more strongly determined by relative TMS intensity and (c) motor representation appears similar between LRT and UNT given no difference in the normalised map size.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

SM and JPF designed the study, reviewed by TGB, MBL and RH. Data were collected and analysed by SM, TGB and MBL and interpreted by SM, JPF and RH. SM drafted the work, reviewed by JPF, RH, TGB and MBL. All authors approved the final version of the report and agreed to be accountable for all aspects of the work.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15197.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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