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Decreased neuroplasticity in minor burn injury survivors compared to non-injured adults: A pilot study in burn injury survivors aged 45 years and older

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ABSTRACT

Objective: Neuroplasticity is the capacity of the brain to change or adapt with experience: brain changes occur with use, disuse, and injury. Repetitive transcranial magnetic stimulation (rTMS) can be used to induce neuroplasticity in the human brain. Here, we examined rTMS-induced neuroplasticity in the primary motor cortex in burns survivors and controls without injury, and whether neuroplasticity is associated with functional recovery in burns survivors.

Methods: Sixteen burn injury survivors (total body surface area of burn injury <15%) and 13 non-injured control participants were tested. Repetitive TMS (specifically, spaced continuous theta-burst stimulation[cTBS]) was applied to induce neuroplasticity 6 and 12 weeks after injury in burn survivors and in two sessions separated by 6 weeks in controls. Motor evoked potentials (MEPs) elicited by single-pulse TMS were measured before and after rTMS to measure neuroplasticity. Burns survivors completed a functional assessment 12 weeks after injury.

Results: Non-injured controls showed decreased MEP amplitude 15–30 min after spaced cTBS in both experimental sessions. Burn survivors showed a smaller change in MEP amplitude after spaced cTBS compared to controls 6 weeks after burn injury but no difference compared to controls 12 weeks after burn injury. In burn survivors, there was a significant positive association between general health outcome (Short-Form Health Survey) and the change in MEP amplitude after spaced cTBS 12 weeks after injury (r=.73, p = .01).

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Conclusions: The current findings suggest that burn survivors have a reduced capacity for neuroplasticity early in the recovery period (6 weeks after injury), which normalizes later in the recovery period (12 weeks after injury). Furthermore, the results provide preliminary evidence to suggest that burn survivors with normalized neuroplasticity 12 weeks after injury recover faster after burn injury.

1. Introduction

Rehabilitation after a burn injury is often a slow, difficult process, with physical dysfunction and quality of life is impacted long after the initial injury [1]. The proportion of elderly burns survivors is increasing with the ageing population, and the mortality rate of elderly burns victims is decreasing with improving standards of care [2]. However, age negatively affects burn survivors' morbidity: advancing age is associated with prolonged wound healing times, longer hospital stays, decreased mobility, and loss of independence [3–5]. Prior research from the State Adult Burn Unit in Western Australia has shown that a deterioration in physical function post-burn injury is greater in older adults than younger adults, with the deterioration more apparent from approximately 45–50 years of age [2]. In addition, research has shown a period of significantly elevated molecular changes in skin that occur primarily in middle-age, including downregulation of the gene expression for promotion of healing and upregulation (amplification) of pro-inflammatory pathways [6].

Neuroplasticity refers to the ability of the brain and the nervous system to change and adapt in response to intrinsic and extrinsic stimuli. The capacity for neuroplasticity is not innate but rather developed over the individual's lifetime, gradually slowing with the progression of age [7]. Neuroplasticity can be structural or functional: structural neuroplasticity refers to the physical changes in brain structure that occur with experience, such as neurogenesis and the formation of new synapses, and functional neuroplasticity refers to changes in the existing brain structure, such as the strengthening and weakening of synapses [8]. Neurotrophins, in particular, brain-derived neurotrophic factor (BDNF), are thought to underpin functional neuroplasticity that is mediated via long-term potentiation (strengthening of synapses) and long-term depression (weakening of synapses) [9]. This type of functional neuroplasticity is thought to underlie learning and memory, and form the basis of modifications in behaviour [9,10]. Given that neuroplasticity occurs continuously in response to changes in sensory input and motor output/demands, it is not surprising that neuroplasticity is observed following injury. Changes in corticospinal excitability and intracortical inhibition have been documented in response to amputation and deafferentation [11–15], as well as following a variety of musculoskeletal injuries in both acute and chronic stages [16–20]. As a result, improved outcomes are associated with rehabilitation strategies that aimed to minimize maladaptive neuroplastic changes induced by injury, rather than solely targeting the peripheral injury neural inputs [21,22].

Transcranial magnetic stimulation (TMS) can be used to both measure and induce neuroplasticity in the human primary motor cortex (M1) [23,24]. Single-pulse TMS is used to measure neuroplasticity: a coil is placed over the scalp; an electrical pulse is delivered through the coil, which induces a magnetic field; the magnetic field induces current flow in the neural tissue below the coil. If a single TMS pulse is delivered to the primary motor cortex (M1), neurons will depolarize leading to a motor evoked potential (MEP) in the target muscle [25,26]. MEP amplitude represents corticospinal excitability; a change in MEP amplitude represents a changes in corticospinal excitability, and therefore, provides a marker of neuroplasticity [23–25]. We have previously shown that minor burn injury differentially affects intracortical circuits within M1: specifically, long-latency inhibition (measured by the cortical silent period) is reduced in burn survivors compared to non-burn control participants [27] but short-latency inhibition (measured by short-interval intracortical inhibition) is not different between burn survivors and non-burn control participants [28].

Repetitive TMS (rTMS) can induce neuroplasticity by delivering trains of TMS pulses. If the trains of pulses are applied at specific intensities and frequencies, increases and decreases in corticospinal excitability can be induced: these changes in excitability last longer than the stimulation period and therefore, provide a marker of neuroplasticity [25]. Continuous theta-burst stimulation (cTBS) is an rTMS protocol that consists of patterned "bursts" of pulses: specifically, stimuli bursts are applied at 50 Hz and repeated at 5 Hz (i.e. every 200 ms) for a total stimulation period of 40 s [25,29]. Previous research applying cTBS has shown decreases in cortical excitability after cTBS application, suggesting that cTBS induces neuroplasticity via a long-term depression-like mechanism (LTD; weakening of synaptic strength) [25]. Previous research applying cTBS twice with an interval if 10 min interval (known as "spaced cTBS") has been shown longer-lasting and more reliable decreases in cortical excitability after spaced cTBS than after a single cTBS application [30]; this suggests that spaced cTBS is an ideal protocol to examine LTD-like neuroplastic responses in the human primary motor cortex. This is important because although rTMS is a promising non-invasive tool to induce neuroplasticity, some studies have shown large variation in responses to rTMS protocols (including a single application of cTBS) across individuals [31–34].

To date there are no known studies examining neuroplasticity in the motor cortex in individuals with acute burn injuries. If there are demonstrable differences in neuroplastic responses between burns survivors and non-injured controls, then strategies targeting the central nervous system to address burn-induced changes in the brain might improve

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rehabilitation outcomes [35]. Given the rapid deterioration in, and prolonged recovery of physical function after burn injury with advancing age, we investigated the relationship between acute burn injury, neuroplastic responses, and functional outcomes in individuals aged 45+ years. It was hypothesized that burns survivors would show a smaller change in MEP amplitude following spaced cTBS than non-injured, age-matched control participants. If upheld, this result would indicate a reduced neuroplastic response in burn survivors compared to non-injured control participants. It was also hypothesized that the difference between neuroplastic responses in burn survivors and controls would be greater 6 weeks after injury than 12 weeks after injury, in line with the temporal impact of burn scar maturation during functional recovery. Finally, it was hypothesized that burns survivors who showed the greater decrease in MEP amplitude following spaced cTBS (that is, the greatest neuroplastic response) would have the highest scores on the functional outcome measures.

2. Methods

2.1. Participants

The sample of burn injured and control participants tested in the current study is the same sample of participants reported in our previous work measuring short-interval intracortical inhibition following burn injury [28]: 16 burn injury participants (6 females; 56.8 ± 7.9 years; 45–71 years) who were recruited from the Western Australia State Adult Burns Unit and 13 control participants (seven females; 62.4 ± 10.3 years; 47–83 years) who were recruited from the broader community, respectively. As described in our previous work [28], inclusion criteria for burn injury survivors were: aged ≥45 years (when recruited); total body surface area (TBSA) of burn injury <20%; burn injury occurred <six weeks (when recruited). As described in our previous work [28], exclusion criteria for burn survivors included: conditions that might hinder rehabilitation beyond the burn injury or confound the measurement of recovery; heart disease (severe or recent); self-assessed sleep deficiency; contraindication to TMS [36,37]. As previously reported, burn injury survivors received routine treatment and recovery monitoring after the burn injury (Inpatient and/or Outpatient Services at the Western Australian State Adult Burn Unit). Routine treatment and monitoring include physical examination and medical history. Furthermore, at 12 weeks after burn injury, a functional assessment was completed for burn survivors.

The inclusion and exclusion criteria for control participants (non-injured) have been reported previously [28]. Inclusion: aged ≥45 years (when recruited) and no prior record of a burn injury for which they sought medical treatment. Exclusion: as per burn survivors.

All participants were informed about the study and provided written consent prior to participation. All participants screened with the TMS Safety Screen to identify contraindications to TMS [36,37].The protocol was approved by the Murdoch University Human Research Ethics Committee (2016–166), East Metropolitan Health Service (16–012), South Metropolitan Health Service (16–012) and University of Western Australia (RA/4/1/8354).

2.2. Experimental procedures

As reported above, the sample of burn injured and control participants tested in the current study is the same sample tested in our previous work measuring motor cortical function following burn injury. Specifically, our previous work investigated motor cortex inhibition (known as short-interval intracortical inhibition; SICI) in burns survivors and non-injured controls to determine whether motor cortex inhibition is altered following burn injury, and showed an association with functional recovery in burn injury survivors. The results of this previous work showed no difference in SICI between burn injury survivors and non-injured controls, and no association between SICI and functional outcome measures in burn injury survivors. Although some of the experimental procedures outlined in the current study, including TMS procedures for experimental setup, are the same as those outlined in our previously published work [28], the current study measure motor cortex neuroplasticity (not motor cortex inhibition). Below, we outline the specific procedures conducted to measure motor cortex neuroplasticity in this sample.

2.2.1. Transcranial magnetic stimulation

Two experimental sessions were conducted, separated by 6 weeks. For burn injury survivors, the sessions occurred 6 weeks and 12 weeks after injury to align with their clinical appointments and thus minimize the time commitment and likelihood of drop-out. Throughout the experimental sessions, participants were seated, resting their right hand on a pillow. The right first dorsal interosseous (FDI) muscle was identified. The skin around the muscles was cleaned with an ethanol-based solution and Ag-AgCl cup electrodes filled with a water-based lubricant were placed in a belly-tendon configuration over FDI to record surface electromyography (EMG) activity. A grounding electrode was placed over the distal ulna. The EMG signal was amplified 1000 times and band-pass filtered from 20 Hz to 1 kHz (Cambridge Electronic Design (CED) 1902 signal conditioner, Cambridge, UK). The EMG signal was digitized at 2 kHz (CED 1401 analog-to-digital converter, Cambridge, UK). EMG data were saved to a personal computer.

A figure-of-eight coil connected to a Magstim BiStim 200[2] stimulator (The Magstim Company Limited, Wales, UK) was used to deliver monophasic TMS pulses. The figure-of-eight coil was held tangentially to the scalp, with the angle of the coil 45 degrees to the sagittal plane. The handle of the coil was pointing posteriorly. The coil placement parameters were selected as this coil placement has been shown to induce a posterior-anterior current flow. The optimal stimulation site and the resting motor threshold (RMT) were determined for right FDI. Single TMS pulses that were sufficiently intense to elicit an MEP in right FDI were delivered at multiple scalp sites to identify the site that consistently elicited MEPs in right FDI: this site was determined to be the optimal stimulation site. This coil

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position was marked on a cap (tight-fitting for each individual) to ensure reliable placement of the coil in each experimental session. RMT is the minimum stimulus intensity (expressed as a % of maximum stimulator output; MSO) that produced a MEP of ≥50 μV in at least 3/6 trials in the relaxed right FDI [38–41].

2.2.2. *Continuous theta burst stimulation (cTBS)*

cTBS was applied using a Magstim Rapid (The Magstim Company Limited, Wales, UK) connected to an air-cooled figure-of-eight coil (biphasic pulses). The optimal site for stimulation and RMT were determined using the air-cooled coil and the Magstim Rapid prior to commencing cTBS. cTBS comprised a total of 600 pulses: bursts of 3 pulses delivered at 50 Hz which were repeated at 5 Hz (i.e. every 200 ms) [29]. The intensity for cTBS was 70% RMT (determined using the MagStim Rapid). In the current study, 'spaced cTBS' was applied: two applications of cTBS separated by 10 min. This protocol was demonstrated by Goldsworthy, Pitcher and Ridding [30] to be effective at inducing long-lasting decreases in MEP amplitude that were more reliable than a single application of cTBS across individuals [31].

To measure of corticospinal excitability, three blocks of TMS pulses were delivered before (baseline), and at several time points after the spaced cTBS protocol (see Fig. 1). There was a total of 14 single-pulses per block; the test stimulus intensity for single pulses was 120% RMT (determined using the MagStim BiStim). (It is important to note here that TMS was delivered in blocks of 14 single-pulse and 14 paired-pulse trials (the interval between trials was 5 s (±20% noise) and the order of single- and paired-pulse trials was randomized). The paired-pulse trials were delivered to measure short-interval intra-cortical inhibition (SICI): as noted, the SICI results have been reported previously [28]).

2.3. *Functional and quality of life measures*

Functional and quality of life measures have been reported previously [28]. Measures were obtained 12 weeks after burn injury at the second TMS experimental session and included:

- Short-Form Health Survey version 2 (SF-36) [42]
- Burn Specific Health Scale – Brief (BSHS-B) [43]
- Disabilities of the Arm, Shoulder and Hand disability measure (QuickDASH) [44,45]: upper-limb burn survivors (N = 8)
- Timed Up and Go (TUG) [46] and Lower Limb Function Index-10 (LLFI) [47]: lower-limb burn survivors (N = 8)

All assessments used in the study have been validated for use in burn survivors [42–44,47,48].

2.4. *Data analysis*

As reported previously [28], four (of sixteen) burn survivors were lost to follow-up after the first experimental session (contraindication to TMS, N = 1; unable to attend lab, N = 2; contamination of EMG recordings, N = 1); no functional measures were obtained for these four burn survivors. TMS trials with muscle activity in the EMG recording 250 ms before MEP onset were excluded: 5.8% (±5.1%) of trials were excluded, including 6.6% (±6.5%) for burn survivors and 4.8% (±2.6%) for controls (the difference was not statistically significant: independent samples *t*-test ($t_{27} = 0.96$, $p = 0.344$)). The peak-to-peak MEP amplitude (mV) was calculated from the EMG activity 15–55 ms after the TMS pulse.

2.4.1. *Baseline MEP data*

Separate two-way mixed analysis of variance (ANOVAs) were performed to test for differences in (1) RMT and (2) baseline MEP amplitude: within-subject factor of SESSION (Session 1 and 2); between-subjects factor of GROUP (burn survivors and control participants).

Three baseline blocks of MEPs were obtained to ensure reliable pre-cTBS MEPs. To test for differences in MEP amplitude in the three baseline blocks, repeated measures analysis of variance (RM-ANOVA) with within-subject factors of BLOCK were performed on the raw MEP amplitudes. Separate ANOVAs were performed for each session and each group. There was no evidence of differences between baseline blocks (burns survivors Session 1: $F_{2,30} = 0.80$, $p = .46$, $\eta_p^2 = .05$, Session 2: $F_{2,22} = 0.80$, $p = .46$, $\eta_p^2 = .07$, and control participants Session 1: $F_{2,24} = 1.76$, $p = .19$, $\eta_p^2 = .13$, Session 2: $F_{2,24} = 1.97$, $p = .16$, $\eta_p^2 = .14$); therefore, the three baseline blocks of MEPs were averaged.

2.4.2. *Spaced cTBS-induced change in MEP amplitude*

To test for differences between MEP amplitudes obtained at 0 and 5 min after spaced cTBS (after spaced cTBS is referred to simply as post-cTBS from here onwards), paired-samples t-tests were performed on the raw MEP amplitudes. Separate t-tests were performed for each session and each group. There was no evidence of differences in MEPs between the first two time-points after cTBS (0 min (i.e. immediately) and 5 min after cTBS; all $t < 1.37$, all $p > .20$); therefore, these two MEP blocks were averaged, and analyzed as 'post-cTBS$_{EARLY}$'. To test for differences between MEP amplitudes obtained at 15 and 30 min post-cTBS, paired-samples t-tests were performed on the raw MEP amplitudes. Separate t-tests were performed for each session and each group. There was no evidence of differences between MEPs at 15 min and 30 min after cTBS (all $t < 0.81$, all $p > .43$); therefore, these two MEP blocks were also averaged, and analyzed as 'post-cTBS$_{LATE}$'.

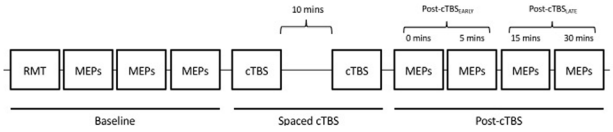

Fig. 1 – Experimental protocol for each TMS session. Abbreviations: RMT, resting motor threshold; MEPs, motor-evoked potentials; cTBS, continuous theta-burst stimulation; Post-cTBS$_{EARLY}$, averaged early blocks; Post-cTBS$_{LATE}$, averaged late blocks.

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To test for differences in MEP amplitude following spaced cTBS, two-way RM-ANOVAs were performed with within-subject factors of SESSION and TIME (baseline, post-cTBS$_{EARLY}$, post-cTBS$_{LATE}$). Separate RM-ANOVAs were performed on MEP data from burn survivors and control participants. For analyses in which Mauchly's test of sphericity was violated, Greenhouse-Geisser corrections were used.

To test for differences in MEP amplitude changes following spaced cTBS between the burn survivors and the control participants, two-way mixed RM-ANOVAs were performed, with within-subject factor of TIME (baseline, post-cTBS$_{EARLY}$, post-cTBS$_{LATE}$) and between-subjects factor of GROUP (burns, control). Separate RM-ANOVAs were performed on MEP data from Session 1 and Session 2.

To examine reliability of the neuroplastic response to spaced cTBS across sessions, Pearson's bivariate correlations were performed between post-cTBS$_{EARLY}$ and post-cTBS$_{LATE}$ for Session 1 and 2.

Statistical significance was accepted at $p < .05$. In text, data are presented as mean ± standard deviation; in figures, data are presented as mean ± standard error of the mean (SEM).

2.4.3. *Functional and quality of life measures*

Functional and quality of life measures were compared between the burn survivors and control participants using independent t-tests. Associations between functional and quality of life scores and spaced cTBS-induced change in MEP amplitude were assessed with Pearson's bivariate correlations.

3. Results

3.1. *Participant characteristics*

Participant characteristics have been reported previously [28]. Age and gender did not differ between burn survivors and non-injured control participants (Age p= .11, Gender p= .40). The average burn size in the survivors was 2.14% and burn injuries were minor with all being less than 15% TBSA [49]. Burn location included upper limb burns (N = 9), lower limb burns (N = 9; including buttocks), thorax burns (N = 3; includes chest, abdomen, pelvis (including genitals but excluding buttocks) and back), and head and neck burns (N = 3). One burn injury survivor sustained a burn injury over the area that was examined, specifically, the right hand (first dorsal interosseous muscle). This patient did not complete the second TMS session because EMG activity could not be reliably recorded from first dorsal interosseous muscle, which might have been secondary to the changes (such as maturation) in scarring over this area. Six (out of 16) burn injury survivors required surgical management of the injury due to deep dermal burns.

3.2. *Baseline corticospinal excitability*

Baseline corticospinal excitability characteristic have been reported previously: neither RMT nor baseline MEP amplitude differed significantly across sessions or between groups [28].

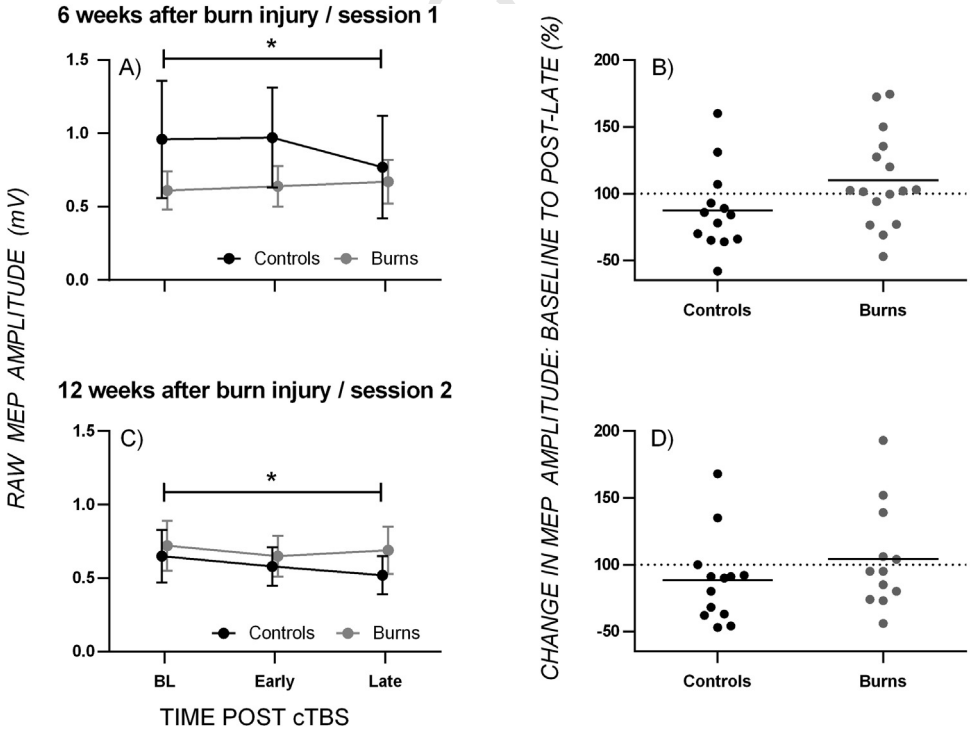

Fig. 2 – Panels (A) and (C) show MEP amplitudes (+/- SEM) at baseline (BL), post-cTBS$_{EARLY}$ (Early), and post-cTBS$_{LATE}$ (Late) in Session 1 and Session 2, respectively: there was a significant decrease in MEP amplitude from baseline to post-cTBS$_{LATE}$ in control participants but not burn survivors in both sessions. Panels (B) and (D) show the change in MEP amplitude from baseline to post-cTBS$_{LATE}$ for burns and control participants in Session 1 and Session 2, respectively: 77% of control participants show a decrease in MEP amplitude from baseline to post-cTBS$_{LATE}$ (the expected response to spaced cTBS). *P < 0.05.

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3.3. *Effect of spaced cTBS on MEP amplitude*

Fig. 2 shows MEP amplitude at baseline and post-cTBS for burn survivors and control participants for the two experimental sessions. In control participants, MEP amplitude decreased from baseline to the post-cTBS$_{LATE}$ time point in both Session 1 and Session 2 (see Fig. 2). The two-way within-subject ANOVA showed a main effect of TIME ($F_{1,12} = 11.00$, $p < .01$, $\eta_p^2 = .48$), but no main effect of SESSION ($F_{1,12} = 1.50$, $p = .25$, $\eta_p^2 = .11$) and no SESSION*TIME interaction ($F_{1,12} = 2.48$, $p = .14$, $\eta_p^2 = .17$).

To further investigate the main effect of TIME, post-hoc one-way within-subject ANOVAs were performed on MEP amplitudes, with separate ANOVAs for Session 1 and Session 2. Both ANOVAs showed a main effect of TIME (both $F_{1,12} > 5.36$, both $p < .04$, both $\eta_p^2 > .31$). Paired sample t-tests showed a significant difference in MEP amplitude from baseline to post-cTBS$_{LATE}$ in both sessions (both $t > 2.32$, both $p < .04$, $d < 0.14$), but no evidence of a difference between baseline and post-cTBS$_{EARLY}$ (both $t < 0.90$, both $p > .39$) or between post-cTBS$_{EARLY}$ and post-cTBS$_{LATE}$ (both $t < 1.57$, both $p > .14$). (Note that there was one control participant with a large MEPs (>2SD above the mean). When data from this participant was removed from the analysis, the main effect of TIME showed similar effect sizes but failed to reach statistical significance: Session 1 $F_{1,11} = 4.19$, $p = .06$, $\eta_p^2 = .28$; Session 2 $F_{1,11} = 3.87$, $p = .08$, $\eta_p^2 = .26$.)

Burn survivors showed no evidence of a systematic change in MEP amplitude following spaced cTBS at either 6-weeks after injury (Session 1) or at 12-weeks after injury (Session 2). The two-way within-subject ANOVA showed no main effect of TIME ($F_{1,11} = 1.62$, $p = .23$, $\eta_p^2 = .13$), no main effect of SESSION ($F_{1,11} = 0.02$, $p = .89$, $\eta_p^2 < .01$), and no SESSION*TIME interaction ($F_{1,11} = 1.08$, $p = .32$, $\eta_p^2 = .09$).

3.3.1. *Comparison of burns group and control group*

At 6-weeks after injury for burn survivors (and Session 1 for control participants), there was no evidence of a systematic change in MEP amplitude following spaced cTBS in burn survivors but a decrease in MEP amplitude from baseline to the post-cTBS$_{LATE}$ time point in control participants. The mixed ANOVA showed a significant TIME*GROUP interaction ($F_{1,27} = 8.00$, $p < .01$, $\eta_p^2 = .23$), but no main effect of TIME ($F_{1,27} = 2.38$, $p = .13$, $\eta_p^2 = .08$) or GROUP ($F_{1,27} = 0.56$, $p = .46$, $\eta_p^2 = .02$). A post-hoc one-way ANOVA of the burn survivors MEP amplitude data at 6-weeks after injury (Session 1) showed no effect of time ($F_{1,15} = 1.46$, $p = .25$, $\eta_p^2 = .09$); the one-way ANOVA of the control participants MEP amplitude data from Session 1, reported above, showed that there was a significant reduction from baseline to post-cTBS$_{LATE}$. These results suggest that the cTBS-induced MEP depression evident in control participants is not evident in burn survivors at 6-weeks post injury.

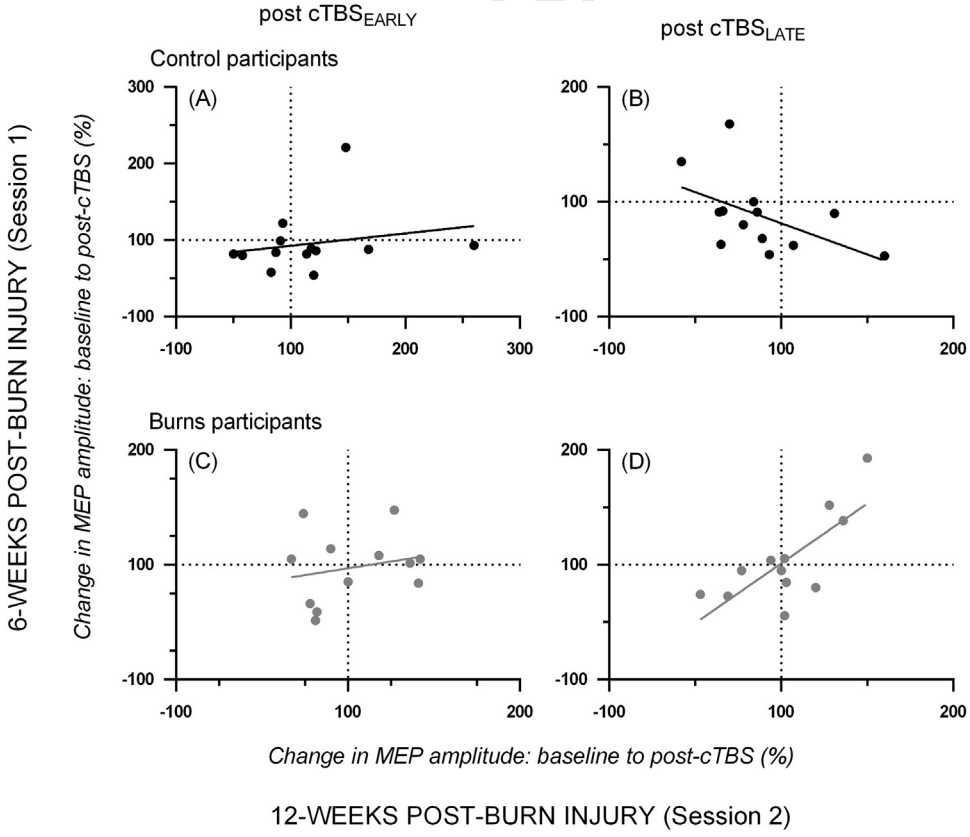

Fig. 3 – Associations between neuroplastic response to spaced cTBS across sessions for control participants (top row) and burns participants (bottom row). No associations were evident at the post-cTBS$_{EARLY}$ time point in controls (A) or burns participants (C). There was no association at post-cTBS$_{LATE}$ for controls (B) but there was a positive association at post-cTBS$_{LATE}$ for burns participants between 6- and 12-weeks post burn-injury (D). (For controls, 62% showed a decrease in MEP amplitude from baseline to post-cTBS$_{LATE}$ in both sessions, lower left quadrant panel B.).

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In contrast to the results at 6-weeks after injury, the mixed ANOVA performed on the data at 12-weeks after injury for burn survivors (Session 2 for control participants), showed no significant TIME*GROUP interaction ($F_{1,23} = 1.90$, $p = .18$, $\eta_p^2 = .08$) and no main effect of TIME ($F_{1,23} = 3.60$, $p = .07$, $\eta_p^2 = .14$) or GROUP ($F_{1,23} = 0.21$, $p = .66$, $\eta_p^2 = .01$). These results suggest no difference in cTBS-induced MEP depression between control participants and burn survivors at 12-weeks after injury, that is, further along the functional recovery time course for burn survivors.

3.3.2. *Intra-individual neuroplastic response associations between Session 1 and Session 2*

Fig. 3 shows scatterplots of post-cTBS$_{EARLY}$ and post-cTBS$_{LATE}$ normalized MEP data in Session 1 and Session 2 for burn survivors and control participants. Correlational analyses of burn survivors post-cTBS$_{EARLY}$ normalized MEP data showed no evidence of a relationship between 6-weeks after injury (Session 1) and 12-weeks after injury (Session 2) (r=.22, p=.50, 95% confidence interval [*CI*] = -.41, .70). Correlational analyses of burn survivors post-cTBS$_{LATE}$ normalized MEP data showed a significant relationship between spaced cTBS-induced neuroplastic responses at 6-weeks after injury (Session 1) and 12-weeks after injury (Session 2) (r=.75, p<.01, 95% *CI* = .30, .92), demonstrating a consistent neuroplastic response at post-cTBS$_{LATE}$ across sessions; individuals who showed a late MEP depression following spaced cTBS at 6-weeks after injury (Session 1) also showed a late MEP depression following spaced cTBS at 12-weeks after injury (Session 2) (Fig. 3, panel B). Three of the twelve burns participants showed the expected MEP suppression following spaced cTBS in both sessions, at both time points (see lower left quadrants, Fig. 3 panels A and B).

Correlational analyses of control participants normalized MEP data showed no evidence of a relationship between Session 1 and Session 2 for either post-cTBS$_{EARLY}$ (r=.21, p=.49, 95% *CI* = -.38, .68). or post-cTBS$_{LATE}$ (r=.51, p=.07, 95% *CI* = -.05, .83). Seven of the thirteen control participants showed the expected MEP suppression following spaced cTBS in both sessions at the post-cTBS$_{LATE}$ time point (see lower left quadrant, Fig. 3 panel D).

3.4. *Associations between neuroplastic responses and functional and quality of life measures*

Functional and quality of life measures recorded 12-weeks after injury in burn survivors (Session 2), prior to the TMS protocol, have been reported elsewhere [28]. At 6-weeks after injury (Session 1), there was no evidence of relationships between the change in MEP amplitude post-cTBS$_{LATE}$ and any functional or quality of life measures. At 12-weeks after injury (Session 2), there was a significant relationship between the change in MEP post-cTBS$_{LATE}$ and the SF-36 Domain General Health (r=.73, p = .01, 95% *CI* = .27, .92), as shown in Fig. 4. There was no evidence of associations between average MEP amplitude change post-cTBS and the other functional outcome measures (Burn Specific Health Scale – Brief, Lower Limb Functional Index or QuickDash measures or TUG times) in burn survivors.

4. Discussion

In this pilot study, we investigated the relationship between early burn injury recovery, neuroplastic responses, and functional outcomes in individuals aged 45+ years. Although burns survivors had minor burns (with the largest burn being 7.25% TBSA), they showed reduced rTMS-induced neuroplasticity compared to control participants 6-weeks after injury, early in the functional recovery time course, but not 12-weeks after injury, later in the functional recovery time course. These findings suggest that motor cortical neuroplastic responses might be influenced following relatively minor burn injuries, which could have important implications for rehabilitation following burn injury.

4.1. *Spaced cTBS-induced changes in MEP amplitude*

All burn injury survivors were recruited within six weeks of sustaining their burn injury and completed two experimental sessions of spaced cTBS to measure neuroplasticity at 6 and 12 weeks after injury. Six weeks after injury, early in the functional recovery time course for burn survivors, there was a

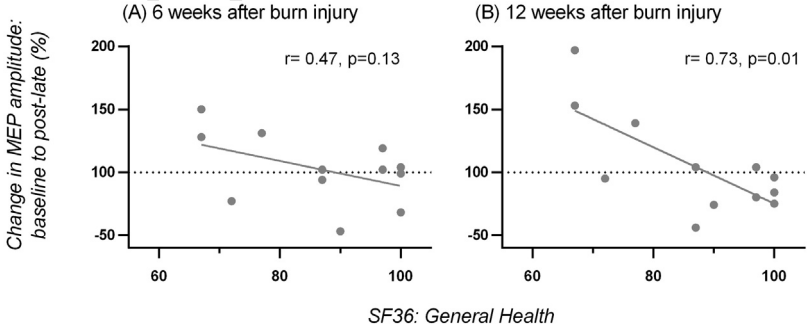

Fig. 4 – Associations between change in MEP amplitude from baseline to post-cTBS$_{LATE}$ and SF-36 Domain General Health at 6-weeks after burn injury (A) and 12-weeks after burn injury (B). A significant association at 12-weeks after burn injury shows those individuals with greater decrease in MEP amplitude following spaced cTBS (expected response) have higher functional outcome score in the general health domain.

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significant difference between the change in MEP amplitude following spaced cTBS in the two groups; the controls but not the burns survivors showed a significant decrease in MEP amplitude following spaced cTBS. Twelve weeks after injury, further into the functional recovery time course, there was no significant difference in the change in MEP amplitude in response to spaced cTBS between the two groups. These findings suggest that burn survivors have a reduced capacity for motor cortical neuroplasticity six weeks after injury compared to non-injured controls. By 12 weeks after injury, there was no longer evidence of a difference in motor cortical neuroplasticity between burn survivors and non-injured controls. Previous research has strongly suggests that cTBS induces MEP depression via LTD-like mechanisms [29,30] because the decrease in MEP amplitude post-cTBS lasts longer than the stimulation period, the change in MEP amplitude following cTBS (i.e. increase or decrease) is dependent on the temporal nature of trains of TMS pulses, and the change in MEP amplitude following cTBS is N-methyl-D-aspartate (NMDA) receptor-dependent [31,50–53]. Therefore, the current findings suggest reduced spaced cTBS-induced neuroplasticity in burns survivors compared to controls, which might reflect a reduced LTD-like neuroplasticity following burn injury that normalizes by 12 weeks after a minor burn injury. Given the role of neuroplasticity in motor learning and the importance of motor function for recovery from injury, a decreased capacity for a neuroplastic response could substantially influence the rate of recovery of functional outcomes following burn injury [10,21,54].

It is important to note, however, that we only measured neuroplasticity at two timepoints after injury. In this pilot study, which is the first to measure neuroplasticity in humans acutely after burn injury, we chose to probe neuroplasticity at an early phase of functional recovery (specifically, 6 weeks after injury) and a later phase of functional recovery (specifically, 12 weeks after burn injury). In light of these pilot findings, it is warranted that future research to comprehensively characterise the time course of changes in neuroplasticity following burn injury. For example, measure neuroplasticity at several time points within the first month of injury and continuing to measure neuroplasticity until functional recovery has plateaued (up to one year after burn injury). In addition, we only measured neuroplasticity in burn injury survivors aged 45 years and over. It is possible that the finding of reduced neuroplasticity at 6 weeks after injury in burn survivors aged 45 years and over compared to non-injured controls would also be evident in younger burn injury survivors. It is important for future research to examine neuroplasticity in burn survivors across the lifespan.

4.2. *Associations between spaced cTBS-induced neuroplastic responses and functional and quality of life measures*

At 12-weeks after burn injury, at a late stage in functional recovery after a minor burn and when neuroplastic responses to spaced-cTBS in the burn patients were not different to non-injured controls, there was a significant association between SF-36 Domain General Health and the change in MEP amplitude following spaced cTBS after a burn. Overall, burns survivors who showed a typical response to spaced cTBS (i.e. MEP suppression) scored higher on the General Health Domain than those with an atypical response (MEP facilitation) to spaced cTBS. This association was not evident at 6-weeks after injury, which is an early stage in functional recovery when neuroplastic responses to spaced-cTBS in burn survivors were reduced compared to non-injured controls. Together, these findings suggest that burn-injury survivors whose neuroplasticity response normalized 12 weeks after injury appear to recover function faster after burn injury. The General Health Domain of the SF-36 (version 2) is a sentinel sub-score and predominantly measures perception of health in general (i.e. "In general, would you say your health is: Excellent, Very Good, Good, Fair, Poor"), and the questions are not time-specific. Although speculative, the association between neuroplasticity and general health scores may reflect that individuals who showed the expected neuroplastic response during functional recovery may be able to adapt to the injury and improve their perceived general health-related outcomes faster than those with a reduced capacity for neuroplasticity. As the follow up in this study was not extended beyond 12-weeks, it is not clear whether this relationship would persist as burns survivors continue to recover. This was a pilot study with a small sample size, therefore these findings need to be replicated in future studies with larger samples. Specifically, future research should characterise the time course of changes in neuroplasticity following burn injury to determine whether the normalization of neuroplasticity following injury is associated with functional recovery at the individual level, as well as determine whether the severity of the injury and the age of the survivor influence the association between neuroplasticity and recovery.

4.2.1. *Group comparison of functional and quality of life measures*

There was no significant difference in SF-36 scores between burn survivors and control participants in this study. As these were minor burns, taken after twelve weeks of State Adult Burn Unit treatment and rehabilitation, it is expected that burn survivors would to return to baseline (i.e. comparable to non-injured control participants) in the SF-36 quality of life assessment. (It is worth noting that the SF-36 has been shown to be more sensitive to change after burn injury than the BSHS-B after approximately one month [42].) When exploring specific functional tasks, TUG times were longer in minor lower limb burn survivors, indicating poorer outcomes at 12-weeks after injury than for non-injured control participants. The TUG is a sensitive test and has been shown to provide useful clinical information regarding functional recovery up to six months after a lower limb burn injury [48]. A longer follow up period was beyond the scope of the current study; it is unclear whether the burns survivors had plateaued in their functional recovery by 12-weeks or whether the TUG time would have improved beyond this point. While no baseline TUG data is available for burn survivors, the fact that their TUG time is longer than the control participants despite no difference in quality of life (SF-36) may suggest that TUG is a more sensitive measure of recovery in lower limb burns.

It is important to note that functional and quality of life measures were only measured at twelve weeks. Future studies

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should aim to record functional and quality of life data at multiple time points, as changes in these data may correlate with changes in neuroplasticity after burn injury. Within burn survivors there was some variation in rehabilitation input; those participants who were admitted to the State Adult Burn Unit would have received more intensive rehabilitation early in their burn injury recovery than those who did not require inpatient admission. Future research may need to account for differences in rehabilitation within this cohort, and perhaps stratify these participants into separate groups to better measure the impact of neuroplasticity, rehabilitation and functional recovery.

4.3. *Delayed spaced cTBS-induced neuroplastic in non-injured control participants*

In the current study, control participants showed significant MEP amplitude suppression 15–30 min but not 0–5 min following spaced cTBS in both experimental sessions (separated by six weeks). Although we didn't have a young adult group in the current study, previous work has shown a significant MEP amplitude suppression from 0 to 120 minutes post-cTBS in young healthy adults [30]. Therefore, the current results showing a significant MEP suppression from 15 to 30 minutes post-cTBS suggests a delayed LTD-like neuroplastic response in non-injured healthy adults (aged 45 years and over). Recent research examining neuroplasticity following other forms of non-invasive brain stimulation (NIBS), including anodal transcranial direct current stimulation and the facilitatory protocol intermittent TBS, have also shown a delayed change in MEP amplitude in older compared to younger adults [55,56]. It is important to note that the primary comparison in the current study was the neuroplastic response induced by spaced cTBS in burns survivors and non-injured control participants, therefore, we did not include a non-injured control sample of adults younger than 45 years or a sham control condition. It is necessary for future studies to replicate the current findings and incorporate additional conditions to show that older adults exhibit a delayed neuroplastic response to spaced cTBS compared to younger adults and compared to sham stimulation. Nonetheless, the current results support the suggestions that the capacity for neuroplasticity might not be reduced with age, but that neuroplastic induction may follow a different time-course in younger and older adults [55,56].

4.4. *Intra-individual variability to spaced cTBS*

Control participants showed a significant MEP suppression in both Session 1 and Session 2 at the group level, however, scatterplots and correlational analysis of normalized MEP data in Session 1 and Session 2 showed no significant correlation between sessions at either post-cTBS$_{EARLY}$ or post-cTBS$_{LATE}$. At the post-cTBS$_{LATE}$ time point, 54% of participants demonstrated the expected MEP suppression across both sessions. This suggests that although there is a reliable and reproducible effect of spaced cTBS at a group level, there is still considerable variation in participants at an individual level. Although we used the spaced cTBS protocol in the current study, which has been shown to induce longer lasting and more reliable MEP depression than a single application of cTBS [30], there is evidence of high inter- and intra-subject variability following single cTBS [31] and, recently, inter-subject variability following spaced cTBS [57]. The causes of the variability in neurophysiological responses to NIBS include priming (recent synaptic activity), voluntary muscle activity, physical activity levels, attention, genetics, and time of day of testing [31,58,59]. Further, inter-individual physiological differences in the cortical network that is activated by NIBS can also influence variability [31,59]. The current study is the first to report intra-individual variability in response to spaced cTBS, and therefore it is not known whether the variability in this study is representative of a wider healthy, older population.

5. Conclusion

The findings of this study suggested that a minor burn injury can affect rTMS-induced neuroplastic brain responses up to 6-weeks after injury in burn survivors aged over 45 years, relative to controls. In burn survivors, when comparing functional and quality and life outcomes, those with reduced rTMS-induced neuroplasticity (smaller decrease in MEP amplitude post-cTBS) also had poorer General Health Domain scores. The results provide preliminary evidence to suggest that neuroplastic changes occur acutely after small burn injuries and may play a role in delaying recovery.

Disclosure statement

None of the authors have potential conflicts of interest to be disclosed.

Statement of Ethics

The research presented in the manuscript was ethically conducted in accordance with the World Medical Association Declaration of Helsinki and the appropriate guidelines for human studies. Ethical approval was granted by Murdoch University Human Research Ethics Committee (MU HREC Reference: 2016–166), East Metropolitan Health Service (EMHS HREC Reference: 16–012), South Metropolitan Health Service (SIRO HREC Reference: 16–012) and University of Western Australia (UWA HREO RA/4/1/8354). Governance approval was obtained from East and South Metropolitan Health Services. All subjects gave written informed consent prior to testing.

Author contributions

All authors designed the study. CJW collected data. CJW and AMV analysed data and prepared figures. All authors interpreted results. CJW drafted the manuscript. All authors reviewed and edited the manuscript.

Declarations of interest

None

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