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Case series investigating the cortical silent period after burns using transcranial magnetic stimulation

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ABSTRACT

Objective: The study aimed to investigate intracortical inhibition following a burn injury, and to establish transcranial magnetic stimulation (TMS) as a useful and sensitive tool to investigate the cortical response to a burn injury.
Methods: Thirteen burn injured patients and 12 uninjured subjects underwent TMS to measure the cortical silent period (cSP), a marker of intracortical inhibition.
Results: In burn injury patients, cSP was similar in the burn-injured and less-injured arm (133 and 132 ms respectively; $p=0.96$). cSP was numerically shorter in burns patients than control subjects, however, these differences were not statistically significant (133 vs 148 ms, $p=0.24$). Subgroup analysis revealed cSP was shorter in the burn arm of patients compared to the uninjured control subjects in patients with upper-limb burn (cSP 120 ms vs 148 ms, $p=0.03$), those with <10% TBSA (cSP 120 ms vs 148 ms, $p=0.01$), those <2 years' post-burn (cSP 110 ms vs 148 ms, $p=0.01$), and patients with partial thickness burns (cSP 120 ms vs 148 ms, $p=0.02$).
Conclusions: These results demonstrate significantly shorter cSP in the burned arm in patients with upper limb burn sustained <2 years ago, those with partial thickness burns, those with upper limb burns only, and those with burns of less than 10% TBSA. The results are consistent with the existing literature, which demonstrates a reduction in cSP duration in patients with a range of peripheral nerve injuries. There is a strong suggestion that cortical inhibition is altered following burn injury, and that TMS is a useful and sensitive method for investigating changes in cortical inhibition in burn patients.

1. Introduction

It is known that the brain's functional anatomy is able to reorganise itself in response to injury to the peripheral nerve field. What is yet to be described is how the brain will reorganise itself in response to a burn injury, which intrinsically involves a peripheral nerve field injury. This is among the first studies to investigate the cortical response to a burn injury. The secondary purpose of this study was to establish if transcranial magnetic stimulation (TMS) is a sensitive method of measuring the cortical response to a burn injury.

To date, many burns studies have focussed on local aspects of wound healing, as these have been shown to improve aesthetic and functional outcomes through better wound

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healing [1,2]. However, recent studies suggest that following burn injury to the peripheral nerve field, repair may be driven by a contribution from the central nervous system (CNS) [3,4].

Studies suggest that following burn injury the peripheral nerve field is not only compromised at the site of injury but also remote from the site of injury [3,4]. Anderson et al. demonstrated similar changes in peripheral nerve density both at the site of an upper limb burn as well as the corresponding site on the uninjured contralateral limb. Animal studies [3] and clinical studies post burn injury [4] suggest that there may be a cortical response driving these changes in the peripheral nerve field.

The plasticity of the nervous system is such that if the cortical representation of a particular body part is deprived of its sensory input, it can be activated in response to other sensory inputs from adjacent body parts [5]. Sensory information from the skin surface projects to the sensory cortex in a topographical arrangement of the major body parts known as the homunculus. Descending control from the primary motor cortex (M1) is arranged in a similar topographical manner. Direct connections exist between the sensory cortex and M1, therefore, sensory changes at the periphery can influence M1 function. For example, if the sensory input of a hand is blocked, after amputation, or transient limb deafferentation, there is an enlarged motor cortical output targeting the upper arm muscles immediately proximal to the deafferented level [6–8]. It has also been reported that there is also an increased output of the M1 representation of the muscle distal to the deafferentation [9]. Together, these data provide strong evidence that alteration of sensory input induces plasticity in the human motor cortex. This case series aims to investigate whether similar cortical changes are seen when the peripheral nerve field is damaged in a burn injury.

In order to investigate the cortical response to a burn, a small cohort of burn injured and uninjured subjects were recruited to undergo TMS testing. TMS is a non-invasive tool which can be used to provide information regarding cortical excitability and inhibition [10]. The TMS protocol was derived from protocols described previously, however this is the first time TMS has been used in burn injured patients [11].

TMS applied over the motor cortex works by inducing descending impulses from M1, resulting in a motor evoked potential (MEP) in the target muscle. The amplitude of the MEP provides a measure of corticospinal excitability. Single-pulse TMS can be used to measure a cortical inhibitory process known as the cortical silent period (cSP). The cSP is a period of inactivity in the electromyogram (EMG) from a voluntarily contracted muscle following a suprathreshold TMS pulse [12,13]. While the early part of the cSP (<50 ms) is primarily mediated by spinal mechanisms, the later part (50–200 ms) is mediated by cortical mechanisms [14]. The cSP is likely mediated by GABAergic inhibition, with both $GABA_A$ and $GABA_B$ receptor activity possibly playing a role [15–19]. The ability to measure cortical inhibitory processes in conscious humans is important, because cortical inhibition influences plasticity induction [20].

Here we investigated the cortical response to a burn injury by using TMS to measure the cSP in 13 burn injured and 12 uninjured subjects. Given the evidence of M1 plasticity due to altered sensory input, and the role of cortical inhibition in M1 reorganisation, we hypothesise that similar cortical changes are seen in response to a burn injury compared to other peripheral nerve injuries. This pilot case series is the first to investigate the cortical response to a burn injury, using TMS as a sensitive method of measuring the cortical response. This is an important first step to determining whether cortical plasticity promotes healing and functional outcomes following burn injury.

2. Methods

2.1. Ethics statement

This study was carried out in accordance with the regulations outlined in the national statement on ethical conduct in research involving humans issued by the NHMRC and was approved by the RPH ethics committee. Written informed consent was obtained from all participants prior to commencement. Approval code EC 2008/094.

2.2. Study participants

Thirteen burns patients were recruited from the state tertiary burns centre. Subjects were all aged 18–50 years of age, and had all suffered a burn injury involving the upper limb, +/− burns involving other parts of the body. Table 1 outlines the burn injury characteristics for each patient. There were 2 females and 11 male subjects. Patients were excluded if they had a documented neurological condition or injury, electrical burn or chemical burn; cold injury; chronic pain, and documented contraindications to TMS testing [21]. Uninjured subjects were recruited as a comparison cohort. The uninjured population tested included 4 female and 8 male subjects aged 18–60. Uninjured subjects were excluded in they had any documented contraindication to TMS and no significant past medical history including burns, trauma and chronic pain [21].

2.3. TMS testing

Testing was conducted at the Centre for Neuromuscular Research (QEII Medical Centre). All assessments were undertaken as standard TMS protocol as outlined by Wilson [22].

Surface EMG was used to measure the motor evoked potential (MEP) from the first dorsal interosseous (FDI) muscle. Data were amplified by 1000, bandpass filtered 2–20 kHz, and digitised at a sampling rate of 2 kHz; 500 ms of data were saved before and after each TMS pulse (Fig. 1).

Stimuli were administered using a Magstim 200 magnetic stimulator with a 70 mm diameter figure-of-eight coil. The coil was placed tangential to the skull, at a 45° angle to the interaural central line, with the centre of the figure-of-eight over the site to be stimulated. A latex cap with latitude and longitude sites marked at 1 cm intervals was fitted to the head as a marker to identify coordinates of a stimulus site. Latitude was defined as distance over the scalp from the vertex, and longitude as the distance, along a line of latitude, from the interaural line.

The optimal site for stimulation was determined by systematically applying stimuli to sites on the pre marked

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