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Motor cortical excitability and inhibition in acquired mirror pain

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HIGHLIGHTS

- Motor cortex excitability and inhibition were explored in acquired mirror pain.
- Motor cortex excitability and inhibition changes were not related to mirror pain.
- Alternative target sites may be critical in future investigations.

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ABSTRACT

'Mirror pain' describes when the observation of another's pain experience induces a personal experience of pain. It has been suggested that mirror pain could result from changes in neural excitability or inhibition. In this study we used transcranial magnetic stimulation (TMS) to investigate motor cortical excitability in lower-limb amputees who experience mirror pain. Using paired-pulse TMS to assess motor cortical inhibition (CI) and cortical facilitation (CF), recordings were taken from the right first dorsal interosseus in lower-limb amputees who experience mirror pain (MP+), lower-limb amputees who do not experience mirror pain (MP−), and non-amputee controls. No differences in CI or CF were observed between the MP+ and both control groups. Thus, when not paired with a pain-related stimulus, changes in motor cortical excitability do not appear to contribute to the experience of mirror pain in lower-limb amputees.

1. Introduction

For some people the observation of pain in another can induce an actual experience of pain in the absence of noxious injury: 'mirror pain' (also known as synaesthetic pain [13]). In one report, approximately 30% of an undergraduate sample stated experiencing mirror pain seemingly from birth [25]. Mirror pain is also known to be acquired following pain-related trauma, particularly in amputees who experience 'phantom limb pain' (PLP [15]): a type of neuropathic pain experienced in the absence of nociceptive stimulation [14] in approximately 80% of amputees [20,29]. In fact, our recent findings suggest that around 16% of amputees experience mirror-pain [12].

It has been proposed that mirror pain, like the similar experience of mirror-touch (see [3]), may be mediated by hyperactivity of sensorimotor mirror systems: overlapping brain regions involved in experiencing pain/touch and observing another's experience of pain/touch [13]. Indeed, recent brain imaging studies have shown increased neural activation in mirror areas for touch and pain when observing these sensations in individuals who experience mirror-touch/pain compared to controls [5,25]. This hyperactivity may override inhibitory control mechanisms thought to be involved in mirror systems. For instance, a large proportion of mirror-like corticospinal neurons identified in area F5 in the macaque brain were shown to be suppressed during action observation [21], perhaps reflecting inhibitory mechanisms that prevent the carrying out of observed actions.

One method used to investigate excitability and inhibition in the brain is transcranial magnetic stimulation (TMS): a technique whereby a magnetic field passes through the scalp inducing an electrical current that alters neural excitability in superficial areas of the brain. TMS used to measure putative mirror system activity is administered while simultaneously presenting visual stimuli and is typically targeted to the primary motor cortex (M1). This is because stimulation of M1 produces an observable motor

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response in the contralateral extremity muscle called a motor evoked potential (MEP), thought to indicate corticospinal excitability (CSE) with larger MEPs suggesting a greater number of motor neurones activated [17]. In the first example to use TMS to measure mirror system activity, the depiction of an action elicited greater MEP amplitudes thought to reflect putative mirror system activity via connections to M1 from premotor regions [8]. In contrast, MEP response to painful images typically results in reduced MEP response [1]. In people who experience acquired mirror pain, however, the presentation of painful images has been shown to result in an enhanced MEP response compared to controls [11]. Thus, TMS to the motor cortex represents a suitable target for investigating neuropathophysiology in acquired mirror pain.

While mirror pain may be the result of a breakdown in mirror system inhibitory processes, it is also possible that mirror pain is mediated by ongoing changes in the cortical excitability of the brain. Mirror pain may therefore be a consequence of a more widespread neurophysiological process effecting cortical excitability and inhibition that is not unique to mirror system function. If this is the case, such a mechanism would presumably be observable in the absence of stimuli depicting another experiencing pain. One way of examining this involves paired pulse TMS (ppTMS) [22], a technique that investigates both cortical inhibition (CI) and cortical facilitation (CF) by altering the time between a conditioning and a test TMS pulse. This paradigm is considered a putative measure of neurotransmitter function as CI and CF are thought to be generated by GABA-mediated processes [9] and glutamatergic neurotransmitters [35] respectively. Here, we carried out a preliminary exploration of motor CI and CF in lower-limb amputee participants who experience acquired mirror pain compared to lower-limb amputees who do not experience mirror pain, and non-amputee controls. By doing so, we hoped to determine the role of cortical inhibitory and excitatory mechanisms, and neurotransmitters involved in the mediation of these, in the production of mirror-pain.

2. Methods

2.1. Participants

Participants included 7 lower-limb amputees who experience mirror pain (MP+), 7 lower-limb amputees who do not experience mirror pain (MP−), and 11 non-amputee healthy controls who do not experience mirror pain (HCs) (see Table 1 for demographics; see Supplementary material for medication used by each amputee participant). As there is currently no accepted standardised measure of mirror pain, participants were considered to experience mirror pain, or not, following a brief interview. First, participants were asked about their PLP including frequency, intensity, and duration. Participants were then asked about triggers of their PLP. Participants classified as experiencing mirror pain described having the previous experience of pain when seeing another injured. Most commonly, mirror pain participants described instances where violence on TV or in film triggered their PLP, such as one participant who stated a trigger being "seeing accidents likely to result in pain, like on Funniest Home Videos", or another who experienced mirror-pain in response to "violence, especially with a knife!" Participants were excluded if they had a diagnosis of mental illness or neurological condition, had epilepsy (or any history of seizures), a history of serious head injury, or metal in the head (outside of mouth). No amputee participants had received a clinical diagnosis of clinical depression or anxiety, however two participants were taking low doses of antidepressants as prescribed by their general practitioner. Right hemisphere data could not be obtained for one MP+ participant due to injury sustained to the left hand (thereby restricting electrode placement). Informed consent was obtained by all participants prior to commencement of the study. The study was approved by Monash University Ethics Committee and the Alfred Hospital Ethics Committee.

2.2. Procedure

TMS was administered to the motor cortex via a hand-held, 70 mm figure-of-eight coil positioned over the scalp. Single-pulse (SP) TMS was administered using a Magstim 200 stimulator (Magstim Company Ltd., Carmarthenshire, Wales, UK). ppTMS was administered using two Magstim 200 stimulators linked with a bistim device. The coil was held above the scalp, with the handle angled backwards and 45° away from the midline. Motor-evoked potentials, elicited via TMS to the motor cortex, were measured at the right first dorsal interosseous (FDI) using surface electrodes.

First, participants' resting and active motor threshold (RMT/AMT) was determined for each hemisphere. RMT was defined as the minimum stimulation intensity required to evoke a peak-to-peak motor-evoked potential (MEP) of >50 μV in at least three out of five consecutive trials [30]. AMT was defined as the minimum stimulation intensity required to produce an MEP of 100 μV in at least one out of five trials during voluntary FDI muscle contraction where the participant actively contracted their contralateral thumb muscle by pressing down the lever of a weight scale to 600 g.

Similar to the paradigm used by Kujirai and group [22], ppTMS involved the administration of a subthreshold TMS pulse (i.e., below a participant's RMT: 90% of AMT), followed (i.e., 2 or 15 ms later) by a suprathreshold TMS pulse (i.e., above a participant's RMT: 125% of RMT). This ppTMS paradigm was administered to each hemisphere in two blocks, and involved a randomised sequence of 90 trials, comprising a total of 30 of each of the following three conditions: SP TMS, ppTMS with a 2 ms interstimulus interval, and ppTMS with a 15 ms interstimulus interval. There was a 5 s interval between each trial. In healthy populations, a time interval of 2 ms between TMS pulses typically produces CI demonstrated by reduced MEP amplitude known as short intracortical inhibition (SICI [32]). A time interval of 15 ms between TMS pulses typically produces CF as demonstrated by an increase in MEP amplitude known as intracortical facilitation (ICF [36]).

2.3. Analysis

Data were analysed using SPSS version 19 (SPSS Inc., Chicago, IL, USA). Data were inspected to ensure adherence to the assumptions of ANOVA; extreme outliers (3 or more standard deviations) within individual trials were deleted. Extreme outliers identified within each group were transformed to .01 above the next highest or lowest data point to reduce their effects [34]. A 2 (hemisphere: left vs. right) × 3 (group: MP+ vs. MP− vs. HCs) mixed-model ANOVA was used to investigate differences in RMT and AMT.

To analyse ppTMS, we carried out a 2 (hemisphere: left vs. right) × 3 (group: MP+ vs. MP− vs. HCs) mixed-model ANOVA for the 2 ms and 15 ms condition as expressed as a percentage of the MEP size in response to SP TMS:

$$\frac{2/15\,\text{ms} - \text{SP}}{\text{SP}} \times 100 = \text{percentage change}$$

One way ANOVAs were used to further explore any interaction effects with least significant (LSD) analyses used to examine main effects. Partial eta squared (η_p^2) was used to determine effect size throughout.