# Primary Motor Area Activity in Phantom Limb Imagery of Traumatic Unilateral Lower Limb Amputees With Phantom Limb Pain

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## ABSTRACT

**INTRODUCTION:** Estimates of the worldwide increase in amputees raises the awareness to solve long-standing problems. Understanding the functional brain modifications after a lower limb amputation (LLA) is one of the first steps towards proposing new rehabilitation approaches. Functional modifications in the central nervous system due the amputation could be involved in prosthesis use failures and Phantom Limb Pain (PLP), increasing costs and overwhelming the health services.

**OBJECTIVE:** This study analyses orphan primary motor area (M1-Orphan) hemodynamic and metabolic behaviour, which previously controlled the limb that was amputated, in comparison with the M1-Preserved, responsible for the intact limb (IL) during phantom limb imagery moving during Mirror Therapy (MT), compared to Isolated Intact Limb Movement Task (I-ILMT).

**METHODOLOGY:** A case-control study with unilateral traumatic LLA with moderate PLP who measured [oxy-Hb] and [deoxy-Hb] in the M1 area by Functional Near InfraredSpectroscopy (fNIRS) during the real (I-ILMT) and MT task.

**RESULTS:** Sixty-five patients, with 67.69% of men, young (40.32 ± 12.91), 65.63% amputated due motorcycle accidents, 4.71 ± 7.38 years ago, predominantly above the knee (57.14%). The M1 activation in the orphan cortex did not differ from the activation in the intact cortex during MT ($P > .05$).

**CONCLUSION:** The perception of the Phantom limb moving or intact limb moving is metabolically equivalent in M1, even in the absence of a limb. In other words, the amputation does not alter the brain metabolism in control of phantom movement.

**KEYWORDS:** Traumatic amputation, motor cortex, disability evaluation, rehabilitation, cerebral cortex, Phantom Limb

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## Introduction

Current health trends indicate a growing need for rehabilitation, especially for people with a lower limb amputation (LLA), as ageing increases the risk exposition for noncommunicable diseases, disasters and traumatic injuries.[1-3] Rehabilitating is a challenge that is handled with limited access to services and resources as treatment and assistive products, even though it is one of the focus conditions of the World Health Organization.[1-3] Certainly, walking again through the prosthesis is a key point for independent living, preventive strategies for many chronic diseases and health promotion.[4-6] However, there are other unmet needs that need attention such as new approaches in rehabilitation, as prosthesis innovation and understanding Phantom Limb Pain (PLP), defined as any unpleasant sensation perceived in the amputated part.[3,7]

The LLA determines functional and architectural brain modifications,[7-11] and PLP is one of these markers. It translates a process that begins in the orphaned brain area (previously responsible for the amputated limb), and has repercussions throughout the nervous system, generating symptoms referred to in the absent part (PLP), impacting posture and gait engrams.[10-12]

Rehabilitation plays a central role in optimising functioning in meaningful life roles. However, when based only on prostheses, it does not address other consequences of amputation, such as this brain reorganisation.[11-13] The loss of physical limb structures and peripheral motor and sensory systems contributes, besides to brain modifications, to mobility changes, postural instability, gait asymmetries which demands more cognitive executive functions for planning, monitoring and adjustments required for every step.[14]

A greater cognitive load is observed when engaging in more complex activities or when performing multiple tasks, such as walking with crutches, prosthesis or walking with PLP.[14,15] In this way, it is important to understand what happens with the brain that houses an orphaned cerebral area from part of the afferents and efferents, to improve the approach in rehabilitation for LLA.[12,16]

Among the methods that study brain function, there is near-infrared spectroscopy (fNIRS), a technique that uses light to assess hemodynamics and cortical metabolism through the indirect measurement of oxy and deoxyhemoglobin chromophores over time, during a task.[17] There are few fNIRS studies with the amputee population, and a complete lack of data on this technique in traumatic amputees with PLP.[18,19]

This study analyses orphan primary motor area (M1-Orphan) hemodynamic and metabolic behaviour, which previously controlled the limb that was amputated, in comparison with the preserved primary motor area (M1-Preserved), responsible for the intact limb (IL) during the process of phantom limb imagery moving during Mirror Therapy (MT), compared to Isolated Intact Limb Movement Task (I-ILMT), in an extremely restricted group that shares many similar experiences: people with LLA due trauma.

## Methods

People with unilateral, traumatic LLA, with chronic PLP, with an intensity of PLP at least 40 on a visual analogue scale (VAS), which grade pain along a 100-mm line from '0' (no pain at all) to '100' (the most severe pain), were evaluated. Those with clinical functional deterioration due to no proper treatment, brain diseases or interventions, pregnancy or other disabilities were not included. The volunteers' previous medications remained stable for at least 3 months. Only patients attending Lucy Montoro Rehabilitation Center – Sao Paulo, Brazil, between January 2018 and February 2020 participated in the study.

This study was approved by the Research Ethics Committee (REC), under CAAE: 16607519.00000.0065; number: 3.467.928. Volunteers signed the informed consent form to participate for the following data to be collected: sociodemographic; amputation side, level and aetiology; time since amputation (TSA), rehabilitation phase, PLP VAS (mm), duration of pain in the injured limb before amputation (DPBA).

The volunteers were submitted to fNIRS to the analysis of primary motor area (M1) in 2 activities:

1. Real: task of moving the IL in knee or ankle flexion and extension, according with the amputation level of the other limb, named as Isolated Intact Limb Movement Task (I-ILMT).
2. Mirror Therapy (MT): imagining the phantom limb (PL) moving in flexion and extension, supported by the reflection of a mirror projecting the image of the IL moving in flexion and extension. Thus, this activity presents 2 tasks: moving the IL, called Isolated Intact Limb Movement Task during MT (MT-ILMT), which activates the M1-Preserved, and at the same time imagining the PL moving, the Phantom Limb Imaginary Movement Task (PLIMT), which activates the M1-Orphan.

The level of amputation determined the IL and PLIMT site. For below-knee amputation, only the ankle is moved in flexion and extension. In the case of above-knee amputation, the knee and ankle are both acted in real or imaginary tasks.

Each activity cycle (Real or MT) lasted 20 seconds, which followed sequentially, interspersed with a 20-second rest, repeating cyclically for 24 minutes. Each cycle had 20 repetitions of each task (1 repetition/second). The exams were performed in a controlled environment, with the volunteer seated, eyes open, without adornments or prosthesis, in the same way and with the same device, with a 0.01 to 0.2 Hz filter to remove cardiorespiratory interference and environmental and body artefacts. The [oxy-Hb] and [deoxy-Hb] values express a variation from the Rest (baseline).

In the I-ILMT, the M1-Preserved is involved with the task, and responsible for the movement of the IL. In the MT, 2 tasks take place simultaneously:

- MT-ILMT controlled by M1-Preserved
- PLIMT, controlled by M1-Orphan.

The patient during the Imagination task was considered a Case that was paired and controlled by the Real task in 2 ways. Thus, we have a Case-Control study, comparing the M1-Orphan controlling the phantom limb during MT versus the M1-Preserved controlling the IL in 2 tasks: one during MT (MT-ILMT) and the other isolated I-ILMT, regarding [oxy-Hb] and [deoxy-Hb], allowing us to discern how much of the cortical metabolism is due to phantom imagination or IL movement.

Cerebral perfusion hemodynamics is intrinsically and intimately related to neuronal activity, directly reflecting the interaction between nerve cell and blood vessel. The cell, demanding greater consumption of oxygen and glucose, determines a rapid and specific increase in cerebral blood flow to the active areas.[17] When oxy-Hb releases oxygen and is transformed into deoxy-Hb, there is a relative increase in the second and a decrease in the first, which is compensated with an increase in local perfusion that increases the clearance in deoxy-Hb and increases the presence of oxy -Hb.[17,18,20] Thus, perfusion is intrinsically related to neuronal activity, directly reflecting vascular interactions and neuronal activity.[17,19,20] Therefore, the typical hemodynamic response to cortical activity shows an increase in blood flow, determining an increase in [oxy-Hb] and a concomitant decrease in [deoxy-Hb] due to the clearance provided by local arteriolar vasodilation.[20]

### *Statistical analysis*

The sample was considered normal, after statistical assessment. Categorical variables were presented in number of observations (n), followed by their percentage (%). Numerical variables were presented both as means (*M*) with standard deviation from the mean (SD) and 95% confidence interval (95% CI), and in median (med) followed by interquartile range (IQR).Comparisons between hemodynamic and metabolic variables ([oxy-Hb], [deoxy-Hb]) between M1-Orphan versus M1-Preserved and the different Real versus Imaginary tasks were carried out using the factorial ANOVA test for repeated measures, controlled by age, gender and gender confounders. amputation level, amputation side, TSA in full years, DPBA and VAS.

A significance level of 5% ($\alpha = .05$), $P < .05$ and 2-tailed 95% CI were considered statistically relevant in all analyses. Subsequently, due to the number of variables involved, multiplicity of tests and comparisons, correction of *P* values was performed using the Holm-Bonferroni method. Statistical tests were performed using IBM SPSS Statistics® for Windows software, version 27 (IBM Corp, Armonk, NY, USA), as well as Python® and related libraries (SciPy® and StatsModels®).

## Results

The sample comprised 65 volunteers chronically amputees $4.71 \pm 7.38$ years ago, due to trauma (90.63% due traffic accident, specially motorcycle), predominantly men (67.69%), young ($40.32 \pm 12.91$ years), with a high school degree (53.85%), with PLP VAS of $65.03 \pm 15.56$ mm. There was a predominance of amputations above the knee (57.14%), on the left side (63.49%), in the post-prosthetic phase (users of prosthesis) with 38.46% not presenting pain in the injured limb before amputation, as shown in Tables 1 and 2.

The analysis of the M1 activity, reveals that [oxy-Hb] is 4.55 times (455.35%) higher in the M1-Orphan in PLIMT (phantom imagination during MT), than the M1-preserved during I-ILMT, indicating a greater metabolic demand. Congruently, [deoxy-Hb] is half the level in M1-Orphan compared to M1-Preserved, that is, imagination determines a greater hemodynamic change than IL movement. Statistical analysis controlled by confounders (age, gender, level and side of amputation, TSA, VAS and DPBA) reveals that there is statistical significance for [oxy-Hb] ($P = .012$). The same does not occur for [deoxy-Hb] ($P = .839$), as shown in Graph 1 and Table 3. Thus, phantom imagination determined a statistically significant metabolic and hemodynamic response in M1-Orphan for [oxy-Hb], but not intense enough to generate vasodilation to the point of statistically significant change in the amounts of deoxy-Hb. Graph 1 reveals the magnitude of these changes.

Graph 2 compares [oxy-Hb] and [deoxy-Hb] in PLIMT (M1-Orphan) in relation to intact limb movement during MT (MT-ILMT) and with I-ILMT (M1-Preserved activity in isolated IL movement), that is the changes in the M1-Orphan area during imagination compared with the IL movement isolated or concomitantly with imagination (MT).

The [oxy-Hb] in PLIMT is 4.55 times (455.35%) higher than the I-ILMT control and 2.81 times (281.80%) higher

**Table 1.** Sociodemographic. clinical and rehabilitation characteristics (N = 65).

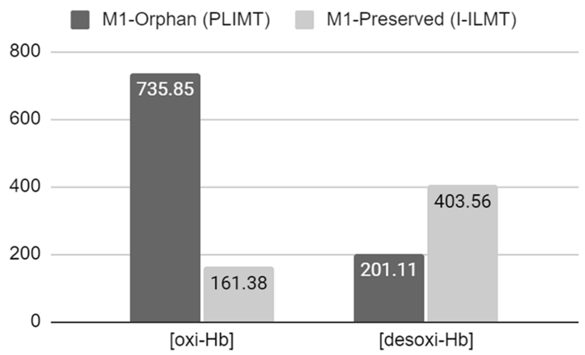
| | | |
|---|---|---|
| Gender | | |
| Women (n%) | 21 | 32.31 |
| Men (n%) | 44 | 67.69 |
| Ethnicity | | |
| White or Asian (n%) | 33 | 50.77 |
| Black or Brown (n%) | 32 | 49.23 |
| Education | | |
| Primary level (n%) | 19 | 29.23 |
| High school (n%) | 35 | 53.85 |
| Third level (n%) | 11 | 16.92 |
| Amputation level | | |
| Below the knee (n%) | 29 | 44.61 |
| Above the knee (n%) | 36 | 55.39 |
| Amputation side | | |
| Right (n%) | 23 | 33.38 |
| Left (n%) | 42 | 64.62 |
| Rehabilitation phase | | |
| Pre-prosthetic (n%) | 32 | 49.23 |
| Post prosthetic (n%) | 33 | 50.77 |
| Duration of pain in the injured limb before the amputation | | |
| Never (n%) | 25 | 38.46 |
| Less than 1 wk (n%) | 9 | 13.85 |
| 1-4 wk (n%) | 14 | 21.54 |
| 1-6 mo (n% | 7 | 10.77 |
| 6 mo-1 y (n%) | 2 | 3.08 |
| 1+ ano (n%) | 8 | 12.30 |

Abbreviations: n, observations; %, percentage of total respondents.

**Table 2.** Clinical and rehabilitative characteristics.

| | *M* | 5% CI | SD | MED | IQR |
|---|---|---|---|---|---|
| Age (y) | 40.32 | [37.12; 43.52] | 12.91 | 38 | (31-50) |
| TSA (y) | 4.71 | [2.88; 6.54] | 7.38 | 2 | (1-5) |
| VAS (mm) | 65.03 | [61.17; 68.89] | 15.56 | 67 | (50-78) |

Abbreviations: 95% CI, 95% confidence interval; IQR, interquartile range; n, number; M, mean; Med, median; SD, standard deviation; TSA, time since amputation (years); VAS, visual analogue scale for pain (mm).




**Graph 1.** Comparison of [oxy-Hb] and [deoxy-Hb] mean in M1-Orphan in PLIMT and M1-Preserved in I-ILMT.
Abbreviations: I-ILMT, Isolated Intact Limb Movement Task; PLIMT, Phantom Limb Imaginary Movement Task.

than the MT-ILMT. [Deoxy-Hb] in PLIMT (imagination) is 2.01 times (49.66%) less than MT-ILMT (IL movement in MT) and 2.01 times (49.83%) less than I-ILMT.

The comparison between the actual movements of the preserved limb (I-ILMT and MT-ILMT) revealed that there is no statistically significant difference for [oxy-Hb] and [deoxy-Hb], $P = .199$ and .745, respectively.

Due to the multiplicity of tests, it was necessary to correct the significance level (*P* value) by Holm-Bonferroni, to minimise the effect of variables that may be involved with different brain responses. Thus, the higher [oxy-Hb] during the PLIMT in relation to the movement of the IL, lost statistical significance, *P*-corrected = .348. Correlation and regression tests showed that the amputation side, TSA and age can influence this result, but comparisons, after controlling for confounders, were not statistically significant ($P > .05$).

## Conclusion

Phantom limb moving or intact limb moving are metabolically equivalent in M1, even in the absence of a limb. In other words, the amputation does not alter the brain metabolism in control of phantom movement

## Discussion

There was a predominance of left side amputations above the knee, related to the trauma mechanism in motorcycle accidents, where the left side is less likely to escape the impact due to the protection mechanisms that instinctively privilege the dominant member (in most cases, the right).[21] The amputation side did not influence the outcome.

The PLP is not one of the objectives of the study, but one of the selection criteria for gathering people who share similar traumatic experiences. In this way, the aetiology and the PLP identification are relevant for understanding the experience of acquiring a definitive body modification, which complicates with pain (PLP).[22-24]

By studying a specific population, we increase our understanding of brain functioning. All studies with this population do not mention the presence or form of diagnosis of PLP or have heterogeneity on aetiologies. This is relevant to ensure the homogeneity, decreasing possible differences involved in the experience to be turned into an amputated person.[25-28]

The representation and meaning of amputation is a point that influences brain modification. Leaving home to work and 'returning amputated' due to trauma is completely different from amputating a leg due to critical ischemia, osteomyelitis or cancer, where surgery is desired and removes the fear of death.[22,23,27,29] Different experiences that determine cortical alterations different from those where the result represents a solution and hope for continuity.[30]

Regardless of the situation, the result is amputation and then PLP, but the process of thoughts and reflections, waiting time to the surgery, the feelings involved with victimisation or guilt are different between traumatic aetiologies and those related to non-communicable diseases. The same neuroplasticity could happen in other aetiologies, but to reduce biases and variables it is important to restrict the casuistic, especially in studies with brain functionality.[22,23,27,29,30]

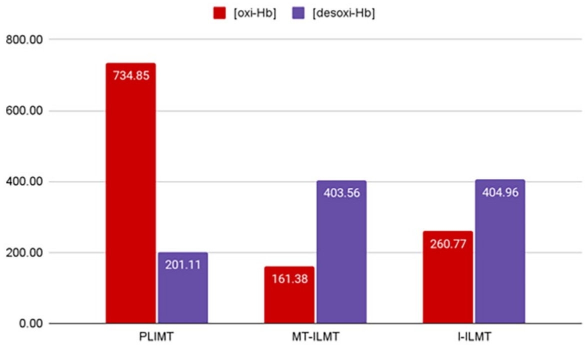
Brains are built over time, from concrete or imaginary experiences and have idiosyncratic characteristics with unique functioning patterns that differentiate and bring us together. Hence the importance of valuing these experiences in brain processing and functioning, determining different structural and functional behaviours and brain structures in a body that is definitely modified by default.[30,31] Hence the importance of having an extremely restricted group that shares similar experiences.

The brain is a dynamic and self-organised physical-chemical system, which modifies its structure and functioning in response to real or imagined, internal and external stimuli,

**Table 3.** Metabolic comparison of the M1, through the variation of oxy and deoxy-Hb, in the Phantom Limb Imaginary Movement Task (PLIMT), Isolated Intact Limb Movement Task during MT (MT-ILMT) and Isolated Intact Limb Movement Task (I-ILMT).

| | PLIMT | MT-ILMT | I-ILMT | *P* | *F* |
|---|---|---|---|---|---|
| Oxy-Hb | 734.85 | 260.77 | | .538 | 0.452 |
| Deoxy-Hb | 201.11 | 404.96 | | .896 | 0.019 |
| Oxy-Hb | 734.85 | | 161.38 | **.012*** | **19.494*** |
| Deoxy-Hb | 201.11 | | 403.56 | .839 | 0.047 |
| Oxy-Hb | | 260.77 | 161.38 | .199 | 2.362 |
| Deoxy-Hb | | 404.96 | 403.56 | .745 | 0.121 |

Abbreviations: *F*, *F* score of the repeated measures factorial ANOVA test; M1, primary motor area; MT, mirror therapy; *P*, *P* value of repeated measures factorial ANOVA test. Differences are considered statistically significant for corrected *P* values < 0.05.




**Graph 2.** M1 cortical activity, assessed by [oxy-Hb] and [deoxy-Hb] contents, during the Phantom Limb Imaginary Movement Task (PLIMT) compared to the Intact Limb Movement Task during Mirror Therapy (MT-ILMT ) and Isolated Intact Limb Movement Task (I-ILMT).

resulting in optimisation and lower energy expenditure in information processing.[22,30,31] Changes are made to survive, but something maladaptive happens that causes PLP.[11,12] The modified body needs to assume a new spatial identity and this brain needs to either exercise the 'art of forgetting' the amputation (possibly in the neoplastic cause), live with the change or alert (pain).[7,8,12] There is nothing clear in the literature about the paths that lead to one or the other neuroplastic decision making, and this answer is still an open challenge.

There was no statistical difference after adjustments and corrections, between real and Imaginary movements. Imagination was not inferior to the real and this can be explained by imagery studies in which thinking about the movement, activates both the same brain areas (including the M1)[32,33,34,35] as the same effectors (muscles) of a concrete training.[34,35] Motor imagery is the cognitive strategy of sequential mental training of a motor action, without its concrete execution (movement imagination). Activates the supplementary motor area, the cerebellum, premotor cortex, cingulate cortex, superior and inferior parietal cortex and primary motor (M1) and sensory cortex, similar to real motor action

Regardless of the type of IL movement (isolated or in the MT) both have the same metabolic and hemodynamic activation. The imagination of the PL determines an intense hemodynamic response to meet the metabolic demand. Imagination was not inferior to the real and this can be explained by imagery studies in which thinking about the movement, activates both the same brain areas (including the M1)[32,34,35] as the same effectors (muscles) of a concrete training.[34,35]

Imagining is a powerful non-pharmacological intervention that alters brain activity, producing behavioural outcomes such as cognitive and motor skill performance, improved attention and distraction and can modulate neuronal circuits related to pain perception.[30,32,34] Keeping the motor representation stable through training with imaginary exercises in amputees, and even in hemiplegic or tetraplegic patients, can preserve functional circuits during rehabilitation or prevent maladaptive brain reorganisation, particularly if started early, even before the possibility of real movement.[36]

There are gaps in pathophysiological, neurochemical, anatomical and functional knowledge of what occurs in the absence of a body part. In this universe, we are at the beginning of brain data extraction from people with disabilities. Understanding what happens to the brain of people with LLA is the first step towards proposing new rehabilitation approaches.

This study replicates reports showing that the phantom movement shares the same anatomical area and is hemodynamically and metabolically equivalent to the movement of the intact limb. Thus, it is hypothesised that helping the patient to imagine the phantom limb early, may be a strategy that minimises maladaptive neuroplasticity related to an amputation.

## Author Contributions

Sugawara, AT and Battistella contributed to the study's conceptual idea; F Fregni, M Simis, and LR Battistella contributed to the study design; AT Sugawara contributed to data acquisition; De Pretto contributed to data analysis; AT Sugawara, M Simis and LR Battistella. contributed to data interpretation; and AT Sugawara, De Pretto and LR Battistella contributed to manuscript writing. Final manuscript approval and agreement to be accountable for all aspects of the work while ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved were done by AT Sugawara, M Simis, F Fregni and LR Battistella.

## Ethical Approval

This study was approved by the Research Ethics Committee, under CAAE: 16607519.00000.0065 judgment number: 3467928.

## Informed Consent/Patient Consent

All volunteers signed the informed consent form, approved by Research Ethics Committee, to participate in the study and only after the patient agreement with a signature, data were collected

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