



Reorganization of sensorimotor representations of the intact limb after upper but not lower limb traumatic amputation

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ABSTRACT

It is becoming increasingly clear that limb loss induces wider spread reorganization of representations of the body that are nonadjacent to the affected cortical territory. Data from upper extremity amputees reveal intrusion of the representation of the ipsilateral intact limb into the former hand territory. Here we test for the first time whether this reorganization of the intact limb into the deprived cortex is specific to the neurological organization of the upper limbs or reflects large scale adaptation that is triggered by any unilateral amputation. BOLD activity was measured as human subjects with upper limb and lower limb traumatic amputation and their controls moved the toes on each foot, open and closed each hand and pursed their lips. Subjects with amputation were asked to imagine moving the missing limb while remaining still. Bayesian pattern component modeling of fMRI data showed that intact ipsilateral movements and contralateral movements of the hand and foot were distinctly represented in the deprived sensorimotor cortex years after upper limb amputation. In contrast, there was evidence reminiscent of contralateral specificity for hand and foot movements following lower limb amputation, like that seen in controls. We propose the cortical reorganization of the intact limb to be a function of use-dependent plasticity that is more specific to the consequence of upper limb loss of forcing an asymmetric reliance on the intact hand and arm. The contribution of this reorganization to phantom pain or a heightened risk of overuse and resultant maladaptive plasticity needs investigating before targeting such reorganization in intervention.

1. Introduction

Nearly 60 million people worldwide were living with the affliction of a traumatic limb amputation around the time of a recent report (McDonald et al., 2021). Following amputation, deprivation of peripheral sensory input and motor output results in cortical plasticity or reorganization, the extent and potential functional consequences of which continue to be considered as targets of clinical intervention (Gunduz et al., 2021; Zink and Philip, 2020). Localized cortical reorganization is well-documented (Merzenich et al., 1983; Merzenich et al., 1984; Pons et al., 1991; Donoghue et al., 1990; Sanes et al., 1990; Calford and Tweedale, 1988; Kew et al., 1994; Chen et al., 1998; Cohen et al., 1991; Hamzei et al., 2001; Irlbacher et al., 2002; Pascual-Leone et al., 1996), with an expansion of somatotopically-neighboring representations into and around the sensorimotor cortical territory devoted to representing the affected limb. Mechanisms driving this cortical reorganization are likely multifactorial

and operating at multiple timescales (Harding-Forrester and Feldman, 2018), one of which might serve to unmask usually inhibited cortical connections (Jacobs and Donoghue, 1991; Li et al., 2014), with a more slowly developing activity-dependent potentiation following the reduction in inhibition (Muret and Makin, 2021).

In addition to local functional reorganization, there is growing support for the hypothesis that limb loss induces more widespread cortical reorganization of representations of body parts that are nonadjacent to the affected cortical territory. Magnitude-based fMRI data from studies with upper extremity amputee human subjects compared to controls showed increased activation in the deprived sensorimotor cortex contralateral to the amputated limb during movement (Makin et al., 2013; Bogdanov et al., 2012; Philip and Frey, 2014) and cutaneous stimulation (Valyear et al., 2020) of the intact limb. This suggests an intrusion of representations of the intact limb into the amputated limb's former territory (*i.e.*, ipsilateral to the intact moving limb). Similar

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effects are seen in animal models of deafferentation and subsequent motor disuse, with activity in response to intact forepaw stimulation in the ipsilateral deafferented somatosensory zone (Pelled et al., 2007; Pelled et al., 2009) as rapidly as one-hour post-injury (Han et al., 2013). This reorganization of the ipsilateral intact limb has been attributed to increased firing rates of inhibitory neurons in layer V of somatosensory cortex that are likely mediated by an unmasking of typically silent transcallosal synaptic input (Han et al., 2013).

Despite amputation of a lower limb occurring far more often than that of an upper limb (particularly from trauma (Ziegler-Graham et al., 2008)), previous work on cortical reorganization has predominantly been investigated following upper limb amputation, leaving a major gap in considering the neural reorganization that is specific to lower limb loss. Whether magnified ipsilateral sensorimotor representations of intact movements are specific to the neural reorganization of the upper limbs or reflect large scale adaptations triggered by any unilateral limb loss is unknown. This gap is relevant for ultimately implementing appropriate interventions that target plasticity, if present and maladaptive, but it might also restrict insight into the driving force of cortical reorganization. For example, if magnified cortical rerepresentations of the ipsilateral side is in any way activity-dependent, it might be less pronounced following lower limb amputation than upper limb amputation. Individuals with a lower limb amputation continue to have use of both of their upper limbs and might not necessarily use their intact foot more than before the amputation, whereas upper limb amputees might be forced to use their intact hand more for all hand-based environment interactions.

Using Bayesian pattern component modeling (vRSA (Friston, 2019)) of fMRI data, we determine whether amputation of the lower and upper limb, respectively, modulates the extent of ipsilateral intrusive representations in the affected sensorimotor cortex (*i.e.*, former territory of the lost limb). This vRSA approach identifies evidence of spatial activity pattern differences between conditions of interest, which are not

necessarily driven by magnitude-based differences. We survey primary somatosensory and motor regions since these regions support planning and executing movement (Gale et al., 2021; Ariani et al., 2022), and have previously shown the above-described reorganized intrusion of representations of ipsilateral movement following upper limb amputation (Makin et al., 2013; Philip and Frey, 2014; Valyear et al., 2020). These analyses are run in samples of individuals with traumatic upper limb amputation and lower limb amputation and their controls.

Based on previous work, we predict that during movements of the intact limb, we should observe representations in cortex ipsilateral to the intact limb (*i.e.*, in the cortex contralateral to a missing limb), at least following upper limb amputation (Makin et al., 2013; Bogdanov et al., 2012; Philip and Frey, 2014; Valyear et al., 2020). In addition, and based on accumulating evidence for the persistence of representations of the missing limb in the deprived cortex (Kikkert et al., 2016; Wesselink et al., 2019; Bruurmijn et al., 2017), we also predict that during imagined movements of the missing limb, we should observe sensorimotor representations of the contralateral missing limb. Combined, these predictions form our core hypothesis, *i.e.*, that regions of cortex showing “intrusive” ipsilateral representations should therefore be primarily sensitive to the limb performing the reach (hand vs. foot), but not the laterality of that limb (*i.e.*, similar patterns whether the former limb is imagined or the intact limb is used), nor any interaction that suggests a limb-specific laterality of representations. Results yielded this exact pattern of effects, but only for the upper limb amputation group. We found no evidence of “intrusive” representations in the lower limb amputation group, suggesting that cortical reorganization of the ipsilateral intact limb is specific to upper limb amputation. Results were in line with this prediction, showing enhanced ipsilateral cortical representations of the intact limb is specific to upper limb amputation. Cortical reorganization differences driven by site of amputation are critical to highlight considering that most unilateral amputations recorded are in the lower limb, whereas most research on cortical

Table 1
Demographic information.

Upper Limb Amputees					Controls		
	Sex	Age	Handedness	Amputation Location (Age)	Sex	Age	Handedness
1	F	51	Right	Below Left Elbow (3)	F	50	Right
2	M	23	Right	Above Right Elbow (9)	M	23	Right
3	M	54	Right	Below Right Elbow (16)	M	53	Right
4	M	34	Right	Below Right Elbow (33)	M	36	Right
5	M	28	Right	Below Left Elbow (21)	M	31	Right
6	F	51	Right	Above Right Elbow (21)	F	54	Right
7	F	58	Left	Above Right Elbow (21)	F	61	Left
8	M	48	Right	Below Left Elbow (41)	M	52	Right
9	M	73	Right	Above Right Elbow (65)	M	69	Right
10	M	66	Right	Above Right Elbow (46)	M	67	Right
11	M	42	Right	Above Left Elbow (19)	M	46	Right
12	M	62	Right	Above Right Elbow (36)	M	61	Right
13	M	56	Right	Above Right Elbow (22)	M	60	Right
14	M	61	Right	Below Left Elbow (21)	M	61	Right
15	M	61	Right	Below Right Elbow (20)	M	64	Right
16	M	65	Right	Below Right Elbow (21)	M	69	Right
17	M	66	Right	Below Right Elbow (21)	M	67	Right
Lower Limb Amputees					Controls		
	Sex	Age	Handedness	Amputation Location (Age)	Sex	Age	Handedness
1	F	44	Right	Below Right Knee (36)	F	48	Right
2	M	67	Right	Above Left Knee (67)	M	67	Right
3	M	46	Right	Above Left Knee (44)	M	46	Right
4	M	50	Right	Below Left Knee (46)	M	52	Right
5	M	27	Right	Above Right Knee (21)	M	23	Right
6	M	52	Right	Below Left Knee (45)	M	53	Right
7	M	54	Right	Below Right Knee (45)	M	52	Right
8	F	58	Left	Below Left Knee (58)	F	61	Right
9	M	57	Right	Above Left Knee (24)	M	54	Right
10	F	44	Right	Below Right Knee (39)	F	45	Right
11	M	58	Right	Above Right Knee (24)	M	60	Right
12	M	65	Right	Above Right Knee (30)	M	64	Right
13	F	52	Right	Below Right Knee (47)	F	50	Right

reorganization following amputation has been conducted on those with upper limb loss.

2. Materials and methods

2.1. Participants

Thirty subjects with traumatic unilateral amputation of an upper limb ($n = 17$; $M = 53$; range: 23–73) and a lower limb ($n = 13$; age mean = 50; age range: 27–65 years old) and the same number of age, sex, and handedness-matched healthy adults for each group were recruited for this study. See Table 1 for demographic information and details of amputation (age of amputation, location of amputation). Ages were similar between groups with upper and lower limb amputation ($p > .05$), but time since amputation was longer in the group with upper limb amputation ($p = .02$).

2.2. Materials, design, and procedure

Subjects were asked to move the toes on each foot, open and close each hand, and purse their lips. When cued to move the missing limb, those with amputation were asked to imagine moving the missing limb while remaining still. Controls were asked to move all limbs. All movements were cued in pseudorandom order by audio instructions and paced by a 1 Hz tone. Each body part was moved for 16 s, followed by a 12-s rest. Each body part was cued six times, for a total scan time of 12.8 min.

Paced movements were performed while undergoing MRI in a Siemens Allegra 3 T head-only scanner (Siemens Medical, Erlangen, Germany) equipped with a circularly polarized birdcage coil. The imaging protocol included a high-resolution 3D MPRAGE T1 structural scan (TR/TE = 2500/4.38 ms, flip angle = 8°, FOV = 256 × 256 × 176 mm; matrix size 512 × 512 × 176), a double echo field map (flip angle = 55°, TR/TE1/TE2 = 500/2.53/4.99 ms), and a BOLD T2* weighted echo-planar (EPI) scan (flip angle = 80°, TR = 2 sec, FOV = 200 × 200 mm, matrix size 64 × 64, slice thickness = 4 mm, 32 slices). The EPI scan used prospective acquisition motion correction (Thesen et al., 2000). The slices were acquired axially, transverse to the main magnetic field, to minimize the signal from oblique Nyquist ghosts.

2.3. Data analysis

MRI data were pre-processed and analyzed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK) and FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). The data from amputees missing the left arm or left leg were left–right flipped in order to place the deprived cortical territory in the same hemisphere for all participants (*i.e.*, left hemisphere) (Valyear et al., 2020). Data from matched controls for left-sided amputees was also flipped. Using SPM, subjects' functional images were spatially realigned to a mean image using 2nd degree B-spline interpolation, coregistered to the T1, and normalized. Head motion mean rotations and translations (with minimum and maximum values in parentheses) were minimal: x: 0.016 mm (−0.049, 0.384); y: 0.068 mm (−0.206, 0.320); z: 0.067 mm (−0.069, 0.514); pitch: 0.0005° (−0.007, 0.006); roll: 0.0001° (−0.005, 0.003); and yaw: 0.0001° (−0.007, 0.005). All functional images were visually inspected for distortions due to B0 inhomogeneities. In one control subject, we observed such distortion near the superior sagittal sinus, which we remediated using fieldmap distortion correction using SPM. All other aspects of the pre-processing pipeline remained the same.

Following preprocessing of fMRI data, we assessed condition-specific patterned activity distributed over voxels in pre-specified primary sensorimotor regions of interest from SPM's Anatomy toolbox (Eickhoff et al., 2005; Eickhoff et al., 2006; Eickhoff et al., 2007) (BA4a; BA4p; BA1; BA3b). The motivation behind surveying patterned activity broadly in primary motor and somatosensory regions (rather than the

hand and foot area) was three-fold. First, constraining the ROI based on voxels that are active during a body part movement requires deciding which of the four body parts to use. Since we are interested in the reorganization of ipsilateral intact limbs, a reasonable approach might be to limit the ROI based on activity in voxels during intact limb movements. That said, this constrains and assumes a priori overlapping activity of contralateral and ipsilateral movement. Even if there is overlapping activity between contralateral and ipsilateral movements, there might be pattern dissimilarity in other regions (*e.g.*, distinct patterned activity related to contralateral movements beyond the ipsilateral region). Second, sampling patterned activity relating to foot and hand movements in a more global way is based on strong evidence that spatial activity patterns for movements by different body parts vary greatly between subjects (whereas spatial activity pattern differences between body parts are robust between subjects) (Ejaz et al., 2015). We increase the potential to lose subject-specific patterned activity by constraining analyses to smaller sub-regions that need to be matched in voxel size for the purposes of our Bayesian pattern component modeling approach. Critically, each of these concerns can be dealt with by decomposing second-order statistics (see below) of broadly defined primary motor and somatosensory regions. Finally, our approach is computed from the second order matrix after removing the averaged intensity from each pattern of voxels, hence spatial pattern similarity can be observed independent of magnitude-based differences (Friston, 2019). There is not necessarily a one-to-one mapping between pattern dissimilarity and magnitude-based differences, which is assumed by an activity-based constrained ROI approach.

We assess spatial patterned activity differences between conditions of interest in ROIs using a Bayesian implementation of representational similarity analyses, vRSA (Friston, 2019) with an adaptation of the Matlab script DEMO_CVA_RSA.m available in SPM12. First, we computed a convolution-based general linear model (GLM), selecting each of the onsets for each of the experimental conditions. The RobustWLS Toolbox in SPM (Diedrichsen and Shadmehr, 2005) was used to down-weight functional images with high noise variance to account for movement artifact. The GLM was set up with 5 conditions: left foot, right foot, left hand, right hand and lip movements, the latter of which was modelled but not used in further analysis. Like other studies using multivariate approaches (Wesselink et al., 2019; Wesselink et al., 2022; Sadnicka et al., 2023; Berlot et al., 2020; Berlot et al., 2019), we combine trials to estimate a condition's contribution to BOLD activation instead of modeling single trials as separate regressors. We choose this approach in an effort to minimize effects of diverse sources of noise and unwanted variability of fMRI data that limit the robustness and interpretability of data analyses (Liu, 2016). Aggregating event-related data for multivariate analyses greatly optimizes classification accuracy compared to other methods, including that from single trial estimates (Stehr et al., 2023). GLM-derived beta values for each of the conditions were extracted from ROIs using FSL's `fslmeants`.

Similar to more traditional RSA and pattern component modeling approaches, vRSA compares between-condition dissimilarity in spatial activity patterns in a given ROI, by decomposing second-order statistics. In the case of our analysis, the procedure begins with each participant's condition (*i.e.*, four)-by-voxel U matrix, describing each conditions' voxel activity patterns, *i.e.*, the mean activation in each voxel elicited by each separate condition calculated with the above GLM. We then compute a four-by-four second-order similarity (covariance) matrix (G) with $G = UU^T$, which describes the relationship between these activity patterns, *i.e.*, higher values of the off-diagonals reflect higher pattern similarity between relevant conditions. We then test hypotheses regarding the composition of the second-order statistics by inferring the contribution of 'components' to G. In our case, these components test for (1) a main effect of laterality, where voxel patterns are dissimilar for contralateral than ipsilateral movements, regardless of the performing limb; (2) a main effect of limb, where patterns are dissimilar for movements performed by hand relative to foot, regardless of laterality

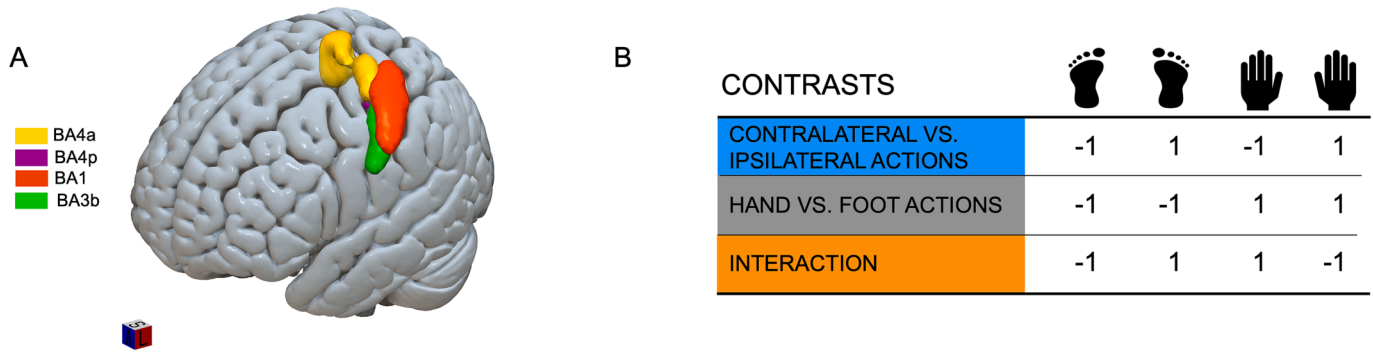


Fig. 1. Bayesian pattern component modeling of fMRI data examined the evidence that multivoxel spatial pattern activity in primary sensorimotor regions (A) contralateral to the lost limb were dissimilar for 1) contralateral than ipsilateral movements, regardless of the performing limb (*i.e.*, effect of laterality); 2) foot than hand movements, regardless of laterality (*i.e.*, effect of limb), and 3) an interaction between laterality and limb effects (B). Rows in panel B containing -1 and 1 values reflect the base vectors for components used to model second-order statistics (see Data Analysis).

and (3) the interaction between these two factors (Fig. 1B) in primary sensorimotor ROIs (Fig. 1A). By ordering the rows of U (conditions) as described in the GLM section of the previous paragraph, these components are respectively the outer product of each row vector (v) described in Fig. 1B with itself ($v^T v$), following orthonormalization. vRSA uses variational Bayesian inference to test for the contribution of these components to the second-order G matrix in a manner analogous to a multiple regression, *i.e.*, where an ROI can be sensitive to more than one component. Thus, the method evaluates the contribution of multiple contrasts to a region's activity pattern, while taking into account all specified contrasts and their interactions. Note that the relations described in the G matrix will be the same no matter what way the columns of U are ordered (much like a regression coefficient will not change if you shuffle the order of contributing pairwise x - y data). In addition, pattern similarity can be identified even if not every column contributes to the covariance. These two key features are relevant to the arguments in the above paragraph, regarding our use of broad sensorimotor ROIs. By modeling second-order statistics, we can test pattern similarities relevant for specific limb movements without prespecifying restrictive sub-areas of motor or somatosensory cortex, while also allowing the specific location of these patterns to vary across subjects.

vRSA performed with SPM functions returns log evidence (marginal evidence) values enumerating each component's contribution to the

second-order matrix (G) for a given ROI at the group level, whereby more negative values are greater evidence of a component's contribution.

To establish a criterion that sufficient log evidence is observed, we take an extra conservative step of calculating a null distribution of log evidence for each component in each ROI, by shuffling condition labels (note - not voxel order) 1000 times, each time computing G from the shuffled data and enumerating the component contributions. In Figs. 2 and 4 (for lower amputees and their controls, and upper amputees and their controls, respectively), we depict the log evidence values of correct (*i.e.*, unshuffled) labels, relative to these null distributions. Next, we formally test the normalized distance between the real and null distribution (*i.e.*, imaginary) data where we combine information in the violin plots into distributions of Bayes factors (dBf). We do so by subtracting the log evidence of the correct condition labels (*i.e.*, the real data) from each of the shuffled log evidence values (*i.e.*, the imaginary data). This creates a distribution of log Bayes factors, where higher values now communicate a strong effect. These distributions of Bayes factors are summarized in Figs. 3 and 5 (for lower amputees and their controls, and upper amputees and their controls, respectively). We report whether 0.95 or 0.80 highest density interval (HDI; analogous to a confidence interval) of this resulting distribution of log Bays factors exceeds $\log(3)$, which we take as the effect being strongly credible (with little to no overlap between the null

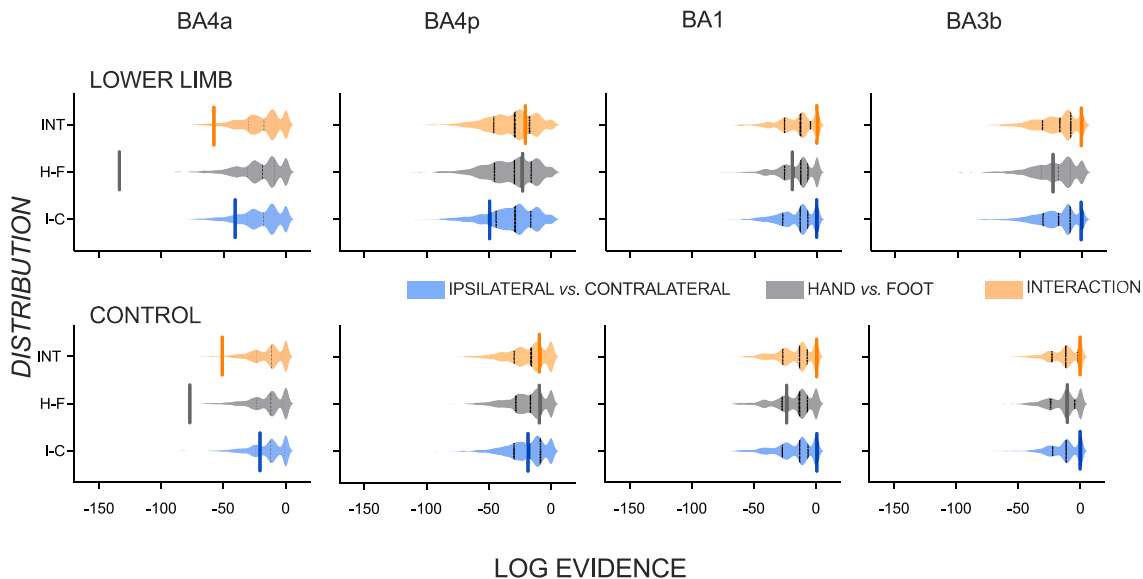


Fig. 2. Log evidence (solid lines) assessing the extent to which patterned activity in a region of interest (ROI) is explained by hypothesis-related components, plotted against a null distribution of log evidence (violin plots), for the group with lower limb amputation and their age-matched controls, respectively. Lower values on the x -axes reflect greater evidence of a component's contribution to the multivoxel patterned activity for the given ROI.

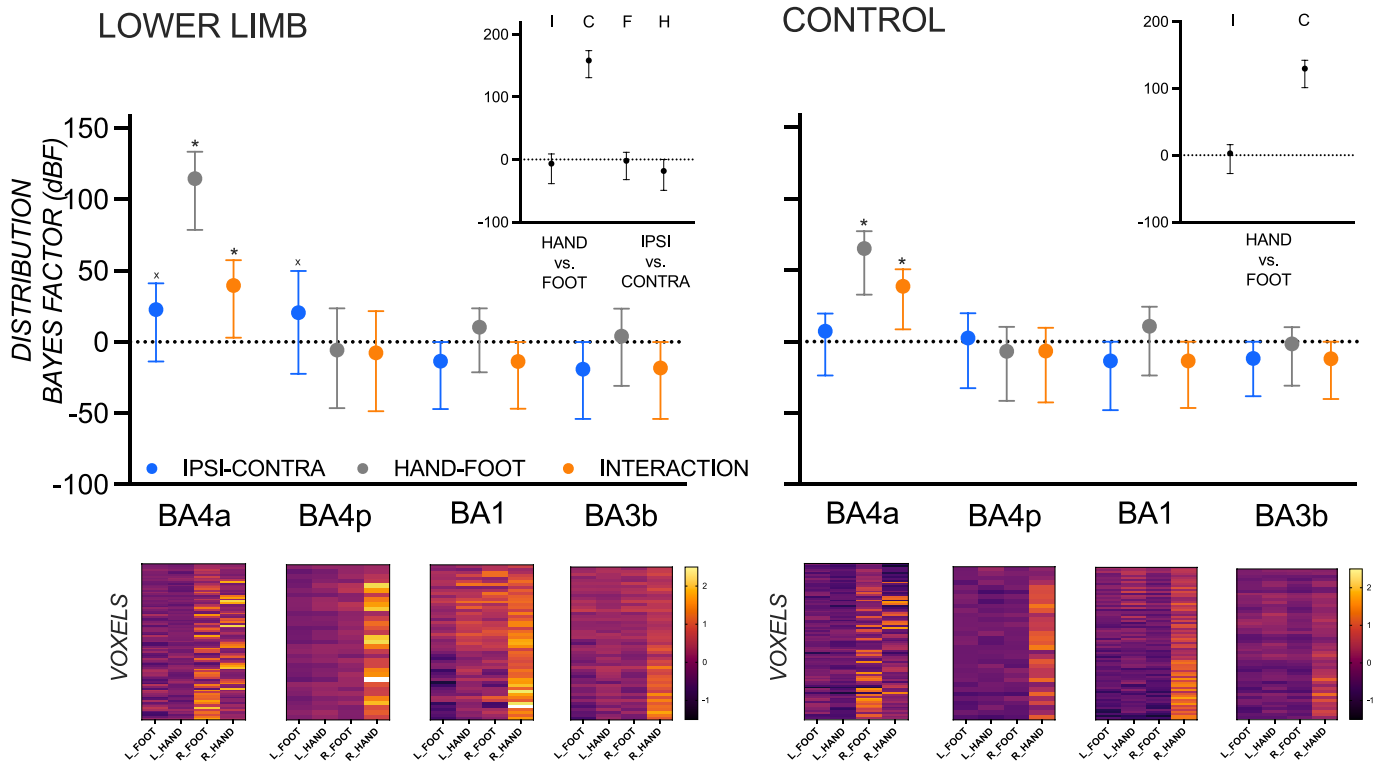


Fig. 3. Top panel. Summaries of distributions of log Bayes factors (dBF, *i.e.*, comparing log evidence from the actual data to each element of empirical nulls) for each component/contrast and region for groups with lower limb amputation (left) and their controls (right). Circular markers indicate the median of dBF. Error bars indicate the highest density interval of dBF. Asterisks (*) indicate proportion of dBF > log(3) exceeds 0.95; Cross (x) indicates proportion of dBF > log(3) between 0.80 and 0.95. Top panel insets show the evidence for BA4a voxel-pattern dissimilarity between hand (H) and foot (F) movements are predominantly driven by contralateral movements in both groups. There is no evidence of voxel-pattern dissimilarity between ipsilateral (I) and contralateral (C) foot movements or between ipsilateral and contralateral hand movements in the lower limb amputee group. Bottom panel. General linear model-derived beta distribution maps.

distribution and model evidence). In other words, our test requires that the evidence for an effect being present in the real data is at least 3 times more credible than the evidence for that effect being in each of 95% of datasets created with shuffled condition labels.

The Bayes factor is frequently employed when testing hypotheses using Bayesian statistics and offers a continuous measure of the ratio of evidence for H1 (*i.e.*, a component is contributing to the second-order matrix) relative to H0 (*i.e.*, a component is not contributing to the second-order matrix). Log Bayes factor values above log(3) (*i.e.*, ~1.1) favor H1 over H0. Similar to that provided for effect sizes, rough guidelines have been put forth to interpret the magnitude of Bayes factor (Jeffreys, 1998). A Bayes factor of ~3 has been suggested to match a “substantial” amount of evidence that a contrast of interest contributes to a region’s observed spatial activity pattern.

Regarding multiple comparisons, our approach offers two advantages. First, for each ROI, we first use a hierarchical model, constrained by the same set of priors, and test three hypotheses (*i.e.*, for the presence of three components in G) in parallel within the same model. Each model is therefore an independent test of a region’s pattern composition, constrained by sensible priors. Second, we have taken a step beyond the standard vRSA approach, and generated ROI-specific null distributions that all effects are compared against. This extra step is inherently conservative and mitigates the need for any additional multiple comparison correction within and across ROIs. In brief, a standard Bayes factor compares H1 with an arbitrary H0 and assumes “substantial” evidence if H1 is 3 times more likely. We instead compare likelihood of H1 to the likelihood of multiple H1s, computed on re-ordered trials (*i.e.*, appreciating the underlying nature of region-specific data). We only assume “substantial” evidence if H1 is 3 times more likely than the most likely top 5% of these bootstrapped H1s. Further details of the vRSA implementation, its rationale over more traditional univariate and multivariate fMRI

analyses, its relation to RSA and PCM, and why multiple comparisons are not needed can be found in (Marneveck and Grafton, 2020; Gelman et al., 2016; Kruschke, 2015; Gelman et al., 2012).

Our primary aim was to test if representations “intruding” sensorimotor cortex ipsilateral to intact limbs is unique to upper limb amputation. In our analyses, evidence of such intrusion would be indicated by distinct sensorimotor cortical patterns for foot and hand movements (contrast 2 in Fig. 1B) but without effects of laterality or an interaction (contrasts 1 and 3). This would mean that the cortex is sensitive to the limb performing the action but shows heightened similarity in contralateral and ipsilateral movement representations. For more typical representations (*i.e.*, either in controls or in an amputee group showing no evidence of “intrusion”), we would also expect this main effect of limb, however this would be combined with lateral specificity for hand and foot actions, reflected in an accompanying interaction effect (contrast 3). Note that our approach does not allow a mixed design incorporating a between-group factor, however much like frequentist approaches, you can evaluate Bayesian evidence of an effect in one group (*e.g.*, interaction effect in controls) and the lack of an effect in another group (*e.g.*, no interaction effect in a particular amputation group). More generally, for ROIs with an interaction and a limb effect, we additionally ran a contrast examining the extent to which that interaction effect was a result of the ROI showing pattern dissimilarity for hand vs. foot movement on the ipsilateral or on the contralateral side. For ROIs with an interaction effect and a laterality effect, we additionally ran a contrast examining the extent to which that interaction effect was due to distinct patterns of ipsilateral and contralateral foot movements or hand movements, respectively. Such an effect might have been a consequence of pattern differences related to executing and imagining a movement in either amputee groups. As seen below, our results were not consistent with such effects, therein minimizing the possibility for

activity pattern differences predominantly due to imagining executing and executing a movement. Finally, to check whether any effects are driven by time since amputation, we extracted subject-specific estimates of the three weights on the components that make up the G matrix. We found no difference between subject-specific estimates of sub-groups below or above the median time since amputation, and no correlation in either group between these subject-specific weights and time since amputation. This result suggests effects described below are independent of time since amputation, at least in the chronic stage of amputation.

3. Results

We used Bayesian pattern component modeling (vRSA) of fMRI data (Friston, 2019) to evaluate whether magnified ipsilateral representations of movement in sensorimotor cortex contralateral to amputation are specific to the cortical reorganization following upper limb loss. Specifically, we determined in groups of subjects with upper limb and lower limb traumatic amputation (and their controls) whether voxel pattern similarity is modulated by main effects of laterality (ipsilateral vs. contralateral), limb (hand vs. foot), and their interaction. We checked if relevant components (see Fig. 1B) were credibly present in the second-order statistics of voxel activity in primary sensorimotor regions, and if the credibility of their presence surpassed empirical null distributions derived by shuffling condition labels. Violin plots depict these null distributions and vertical lines depict the log evidence from the actual data, separately for components and ROIs (see Fig. 2 for the lower limb group and their controls and Fig. 4 for the upper limb group and their controls). More negative values mean more evidence that a component is present in the second-order matrix. When the vertical line (log evidence) is lower than the null distribution, this suggests an effect is present beyond what is expected based on noise. In Figs. 3 and 5, we summarize the effects of the lower and upper amputee groups, respectively, and their controls, using distribution of Bayes Factors where higher values support the presence of an effect. We denote when 0.95 or 0.80 of dBF exceeded $\log(3)$, which gives strong evidence for an ROI to be sensitive to an effect.

3.1. No evidence for distinctive representations of ipsilateral movements in the sensorimotor cortex contralateral to a missing lower limb

Both the control group and the lower limb amputee group showed an effect of limb, in addition to an interaction, in BA4a (see Fig. 2 showing least overlap with null distribution and this model evidence, and Fig. 3 showing the proportion of $dBF > \log(3)$ surpassing 0.95 in BA4a). Limb effects in BA1 were trending in both groups. BA4a therefore likely discriminates between hand and foot movements (limb effect; consistent with classic homunculus literature).

To further explore the limb effect combined with an interaction effect in BA4a in both groups, we additionally ran a contrast examining the extent to which that interaction effect was a result of the ROI showing pattern dissimilarity for hand vs. foot movement on the ipsilateral or on the contralateral side. In both the groups, distinctive hand and foot movements were specific to magnified representations of contralateral movements (Fig. 3, top panel insets for amputee and control groups respectively). Critically, ipsilateral representations of the intact side were not pronounced in the lower limb group.

As is seen in Figs. 2 and 3, the lower limb group additionally showed weaker effects of laterality (than the limb and interaction effects) in BA4a and BA4p. With the BA4a effect observed in conjunction with an interaction effect, we additionally ran a contrast examining the extent to which that interaction effect was due to distinct patterns of ipsilateral and contralateral foot movements or hand movements, respectively. An effect in the former contrast would suggest activity pattern differences between executing an ipsilateral foot movement and imagining a contralateral foot movement. Results were not consistent with such an effect (see Fig. 3 top panel inset, ipsi vs. contra contrast) thus minimizing the possibility that imagining compared to executing a movement to be the predominant driver of the laterality effect.

Summary from group with lower limb amputation and controls. The lower limb data give strong evidence for patterns in BA4a to be sensitive to all three contrasts, which in conjunction with follow up contrasts, shows, similar to the control group, effects that are driven predominantly by pattern dissimilarity between the execution of contralateral right hand and right foot movements (and between right-hand and left-

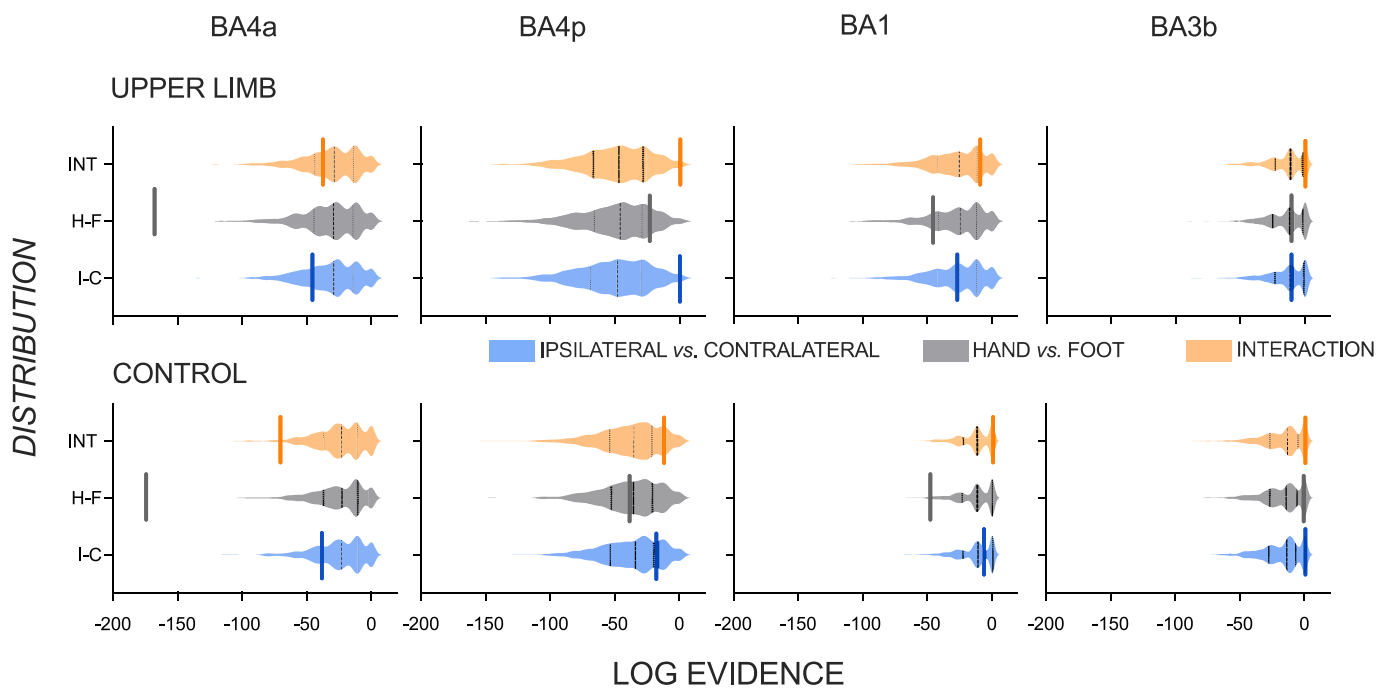


Fig. 4. Log evidence (solid lines) assessing the extent to which patterned activity in a region of interest (ROI) is explained by hypothesis-related components, plotted against a null distribution of log evidence (violin plots), for the group with upper limb amputation and their age-matched controls, respectively. Lower values on the x-axes reflect greater evidence of a component's contribution to the multivoxel patterned activity for the given ROI.

foot movements and right-foot and left-hand movements; the latter two comparisons are present and predominant drivers of both limb and laterality contrasts). It is possible that activity pattern differences at least between right foot (imagined) and other movements are in part driven by different sensorimotor experience associated with imagining a contralateral foot movement compared to executing another movement. Results from the additional contrast, showing no spatial activity differences between executing an ipsilateral foot movement and imagining a contralateral foot movement in BA4a minimize the possibility that imagining vs. executing a movement was the predominant driver of the laterality effect. Critically, there was no compelling evidence for ipsilateral movement representations to be pronounced following lower limb amputation as has previously been documented following upper limb amputation.

3.2. Evidence for distinctive representations of ipsilateral movements in the sensorimotor cortex contralateral to a missing upper limb

Both the upper limb amputee group and their controls showed a limb effect, i.e., distinct patterns for hand vs. foot movements, in BA4a and weaker to trending effects in BA1. See Fig. 4 showing little to no overlap of log evidence and the null distribution for this model evidence, and Fig. 5 showing the proportion of $\text{dBF} > \log(3)$ surpassing 0.95 in BA4a in both groups, and additionally in BA1 in the control group (and a trending BA1 effect in the amputee group). BA4a and BA1 therefore likely discriminate between hand and foot movements. However, only the control group additionally showed an interaction effect (Fig. 4, and Fig. 5), i.e., similar to the lower limb group and its controls. Replicating that seen in control and lower limb groups, distinctiveness of voxel activity patterns for hand and foot movements were magnified for that performed on the contralateral than ipsilateral side in the control group (see Fig. 5 top panel inset). Unlike all other groups, (i.e., lower limb controls, lower limb amputees and their controls), the upper limb amputees showed no interaction effect in BA4a (Figs. 4 and 5), suggesting

hand and foot movements on both the ipsilateral and contralateral side were distinctly represented. A limb effect combined with weak evidence for a laterality effect in the upper limb group suggests similar spatial activity patterns for movements performed by ipsilateral and contralateral side. The beta distribution map of BA4a (bottom panel of Fig. 5) corroborate the interpretation of ipsilateral patterns as weaker versions (in magnitude) of contralateral ones.

Summary from group with upper limb amputation and controls. The upper limb data show strong evidence for patterns in BA4a to be sensitive to the hand vs. foot effect, and unlike that seen in the control groups and the lower limb group, the upper limb group showed no interaction, suggesting pronounced representations of ipsilateral movement. Without an ipsilateral vs. contralateral effect, this suggests that magnified representations of ipsilateral movement are spatially similar but weakened versions of those from the contralateral side.

4. Discussion

We investigated the extent to which ipsilateral movement representations in sensorimotor cortex contralateral to amputation are specific to the cortical reorganization following traumatic amputation of an upper limb or reflect large-scale adaptation triggered by any unilateral deafferentation and resulting motor disuse. In line with our expectations, ipsilateral representations of movement were especially pronounced in the group with upper limb amputation, and not in the group with lower limb amputation. To our knowledge, we are the first study to document specific effects of reorganization following upper limb loss that is absent following lower limb loss.

Upper limb amputees showed distinct spatial activity patterns for hand and foot movements without an interaction effect in sensorimotor cortex. This suggests that movements by the hand and foot were distinguishable in their spatial activity patterns irrespective of whether these movements were performed on the side that is contralateral or ipsilateral to the deprived sensorimotor ROIs. Evidence of a

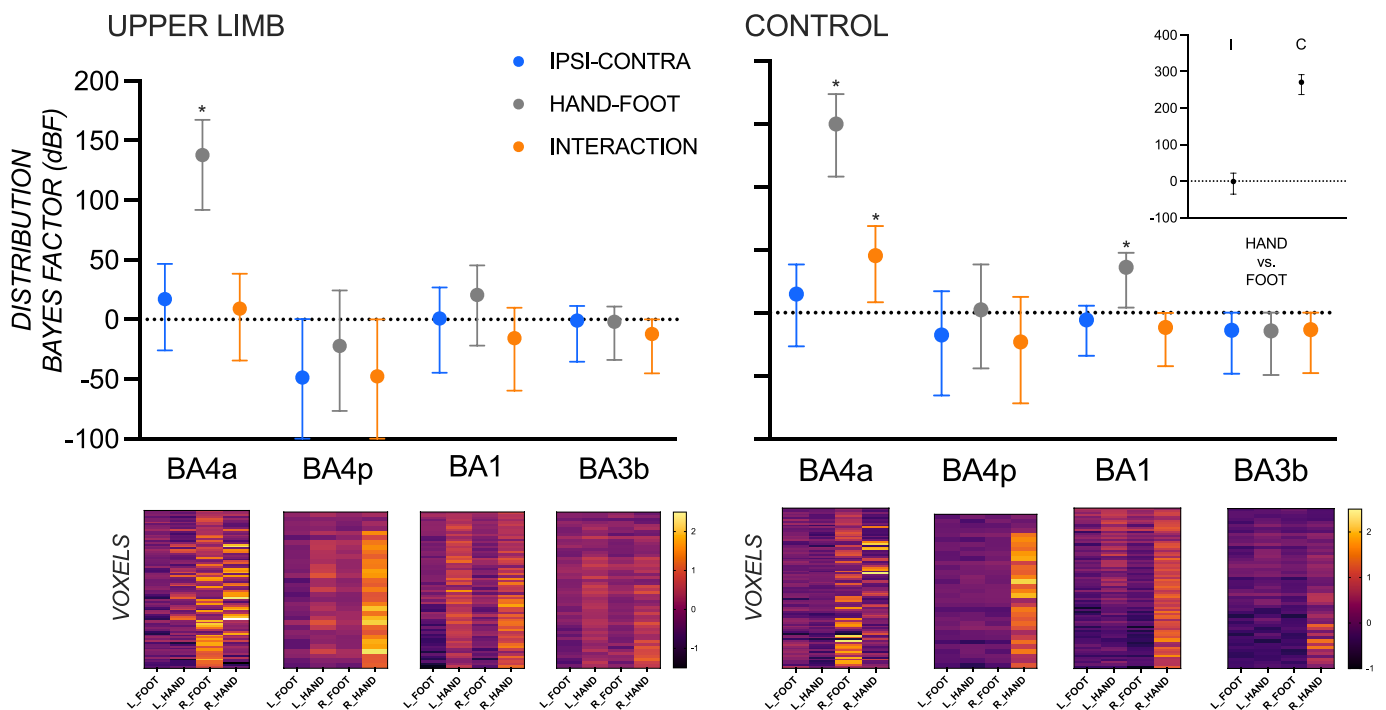


Fig. 5. Top panel. Summaries of distributions of log Bayes factors (dBF, i.e., comparing log evidence from the actual data to each element of empirical nulls) for each component/contrast and region for groups with upper limb amputation (left) and their controls (right). Circular markers indicate the median of dBF. Error bars indicate the highest density interval of dBF. Asterisks (*) indicate proportion of $\text{dBF} > \log(3)$ exceeds 0.95. Inset in the top panel shows evidence that BA4a voxel-pattern dissimilarity between hand (H) and foot (F) movements are predominantly driven by contralateral movements in the control group. Bottom panel. General linear model-derived beta distribution maps.

contralateral representation in the deprived cortex fits with accumulating evidence for the persistence of representations of the missing hand (Kikkert et al., 2016; Wesselink et al., 2019; Bruurmijn et al., 2017). Ipsilateral movement representations in the deprived cortex fit with previous data in upper extremity amputees (Makin et al., 2013; Bogdanov et al., 2012; Philip and Frey, 2014; Valyear et al., 2020) and in deafferentation animal models (Pelled et al., 2007; Pelled et al., 2009; Pawela et al., 2010) revealing reorganized representations of the ipsilateral intact limb. Ablation of the non-deprived healthy S1 completely eliminated fMRI ipsilateral responses in the deprived cortex when the intact limb was stimulated (Pelled et al., 2007; Li et al., 2011), which suggests that pronounced ipsilateral movement representations in the deprived cortex are principally mediated through interhemispheric communication. Since pyramidal and interneurons receive direct glutamatergic inputs from the contralateral homologue area (Karayannis et al., 2007), long range excitatory projections via the transcallosal pathway might activate inhibitory neurons and facilitate the magnification of ipsilateral responses in the deprived cortex. Our results suggest that these interhemispheric effects are specific to the cortical reorganization following upper limb amputation.

Representational specificity for both contralateral and ipsilateral movements in the deprived cortex were not seen in the lower limb amputee group. Like that seen in control groups, the limb effect was seen in conjunction with an interaction in the lower limb group, qualified by strong evidence for representational distinguishability of hand and foot movements contralaterally. These results are in line with what would be predicted based on Penfield's pioneering observations during direct electrical stimulation among 126 patients that different cortical loci triggered movements and sensations in different parts in pre- and post-central gyri (Penfield and Boldrey, 1937). The famously coined 'homunculus' highlights the key finding that has since been supported by numerous neuroimaging and electrophysiological studies in humans (Grafton et al., 1993; Lotze et al., 2000; Plow et al., 2010; Hluštík et al., 2001; Alkadhi et al., 2002; Yang et al., 1993) confirming the existence of gross-scale somatotopic representations of body parts in sensorimotor cortex despite representational overlap (Grafton et al., 1993; Plow et al., 2010; Hluštík et al., 2001). Thus, reorganization related to representations of the intact limb following upper limb amputation is not similarly present following lower limb amputation.

Our findings suggest that reorganization patterns of the intact side that are unique to upper limb amputation are largely a function of use-dependent plasticity. Individuals with a lower limb amputation continue to have use of both of their upper limbs and might not necessarily use their intact foot more than before the amputation. Compared to lower limb amputees, upper limb amputees might be exposed to more complex training of upper limbs that drives reorganization. Upper limb amputees are forced to use their intact hand more for all hand-based environment interactions. Compensatory ipsilateral reorganization unique to upper limb amputation might be driven by an adaptation similar to that experienced by forced right-handers. Studies in forced right-handers (e.g., Klöppel et al., 2010) give clear evidence that macrostructural differences such as central sulcus depth typically observed in dominant and non-dominant hemispheres (White et al., 1994; Hopkins et al., 2010; Amunts et al., 2000) are in fact the result of use-dependent plasticity. Here, it is thus conceivable for the forced skilled use of one hand (and the disuse of another) to lead to more compensatory reorganization following upper limb than lower limb amputation. Future work might consider the extent to which this effect is magnified when amputation results in loss of the dominant hand. In our sample, the proportion of upper limb subjects reporting their dominant hand to be on the amputated side was far greater ($n = 11$) than on the non-amputated side ($n = 6$). Larger sample sizes would reliably test whether hand dominance, and its relationship to the amputated side, modulates ipsilateral reorganization following upper limb amputation.

The extent to which ipsilateral representation reorganization is behaviorally favorable, maladaptive, or functionally irrelevant remains

unclear. As mentioned above, akin to use-dependent sensorimotor reorganization in musicians (Elbert et al., 1995), distinct ipsilateral representations following upper limb loss might reflect a functional adaptation to long-term forced and thus refined use of the remaining limbs. Consistent with this hypothesis, greater use of a residual upper limb correlated moderately and negatively with ipsilateral fMRI activity, suggesting that plasticity in the deprived cortex might reflect behaviorally favorable adaptive experiences. In contrast, others have found no difference between amputees and controls in tactile acuity of the intact hand (Valyear et al., 2020). This result raises the possibility that cortical reorganization of the intact hand in response to a chronic reduction in afferent input and motor disuse may have minimal impact on function (at least in the sensory domain), which if proven to be true would mean that any intervention aimed at reversing reorganization to be misguided. Alternatively, it is possible that intact ipsilateral representations that are spatially overlapped with contralateral ones contribute to the incidence of phantom limb pain. Evidence is mixed on whether upper limb amputation, and not lower limb amputation, is a risk factor for phantom limb pain (Bosmans et al., 2010; Limakatso et al., 2020).

In the upper limb group, activity pattern differences in BA4a between the hand and the foot, irrespective of the side performing these movements (or imagining the performance of one of the movements) does not imply representations of imagined hand and real hand movements are the same. However, this effect in conjunction with a lack of an ipsilateral vs. contralateral effect suggests that ipsilateral (real) movements are weakened versions of a spatially similar activity patterns during imagined movements. Inspection of the beta distribution maps generally corroborate this interpretation, and broadly fits with other studies that have shown ipsilateral activity patterns as weaker but otherwise identical versions of the pattern elicited by movement of the contralateral hand (Diedrichsen et al., 2013; Diedrichsen et al., 2018). Importantly, our results are computed from the second order matrix after removing the averaged intensity from each pattern of voxels, hence spatial pattern similarity can be observed independent of magnitude-based differences (Friston, 2019).

The presence of an ipsilateral vs. contralateral effect in the lower limb group and the lack of this effect in the upper limb group (and control groups) points to another potential difference in cortical reorganization depending on the amputation site. Representations of imagining a foot movement might be more distinct from representations of executing that movement than the same imagine vs. execute contrast with hand movements. A foot movement task might be harder to imagine than a hand movement task since humans might not spend as much time curling their toes as opening and closing their hands. Thus, imagining a foot movement might give way to a more distinct spatial activity pattern than executing that same movement, compared to what is seen with executing and imagining hand movements. In line with this, hand movement tasks showed more similar activation patterns between imagining and executing movements than foot movement tasks (Batula et al., 2017). To this end, we considered the extent to which differences between imagining and executing a foot movement might be driving ipsilateral vs. contralateral effects present only in the lower limb group.

In the lower limb amputee group, the three effects in conjunction with follow-up contrasts show that effects are predominantly driven by pattern dissimilarity between the execution of contralateral right hand and right foot movements (and between right hand and left-foot movements and right-foot and left-hand movements, the latter two comparisons are present and the predominant drivers of both limb and laterality effects). It is possible that activity pattern differences at least between the right foot (imagined) and other movements are in part driven by different sensorimotor experience associated with imagining a contralateral foot movement compared to executing another movement. The additional contrast showing no evidence of distinct patterns of ipsilateral and contralateral foot movements (imagined vs. executed) minimize the role of imagining vs. executing as a predominant driver of the effects described. Overlap in spatial activity patterns between

imagining and executing movements has generally been leveraged by brain computer interfaces (BCI). BCI takes advantage of the capability of cortex to generate neural activity that controls upper limb motion when imagining that movement after spinal cord injury, which then to a certain extent restores lost upper limb function (Hochberg et al., 2012; Collinger et al., 2013; Wodlinger et al., 2015). Nevertheless, the critical result here showing heightened ipsilateral representations following upper limb amputation that is not observed following lower limb amputation is not confounded by possibility of representational differences between imagining and executing a movement.

Future work should address the extent to which cortical reorganization of ipsilateral movements are modulated by muscle contractions of the stump while imagining movement, which could not be verified here. In addition, peripheral vascular disease is a major contributor to lower limb amputation (Fosse et al., 2009), whereas amputations were traumatically acquired in our lower limb group (to match better with the group with upper limb amputation, the latter of which are nearly always due to trauma) (Østlie et al., 2011). Whether the results observed in the lower limb amputation group extend to situations where sensory loss is more gradual with peripheral vascular disease, which might drive different adaptations centrally, is yet to be tested. Finally, the relationship between the presence of phantom limb pain and our current pattern of results are not currently known.

To our knowledge, this is the first study giving evidence that neural reorganization following upper limb amputation is not consistent with that seen in following lower limb amputation, with heightened representational specificity of intact ipsilateral movements contralateral to upper limb loss. Cortical reorganization differences driven by site of amputation are crucial to highlight considering that most unilateral amputations recorded are in the lower limb, whereas most research on cortical reorganization following amputation has been conducted on upper limb amputees. The functional relevance of ipsilateral representations (or lack of them) following a unilateral amputation are unclear at present. Given our results, we propose a functional model that links behavioral changes (hand loss and forced reliance of the other hand) with brain function (specifically, ipsilateral representational reorganization) that is seen following upper limb amputation. The extent to which this reorganization contributes to phantom pain or heightens the theoretical risk of overuse and resultant maladaptive plasticity needs to be investigated before targeting such reorganization in intervention. Due to poor understanding of the relevance of reorganization, it is not known if such interventions are genuinely targeting plasticity that is maladaptive, adaptive or has no effect on function whatsoever. The above-described differences in reorganization patterns between upper and lower limb amputees also caution against a *one size fits all* intervention approach.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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