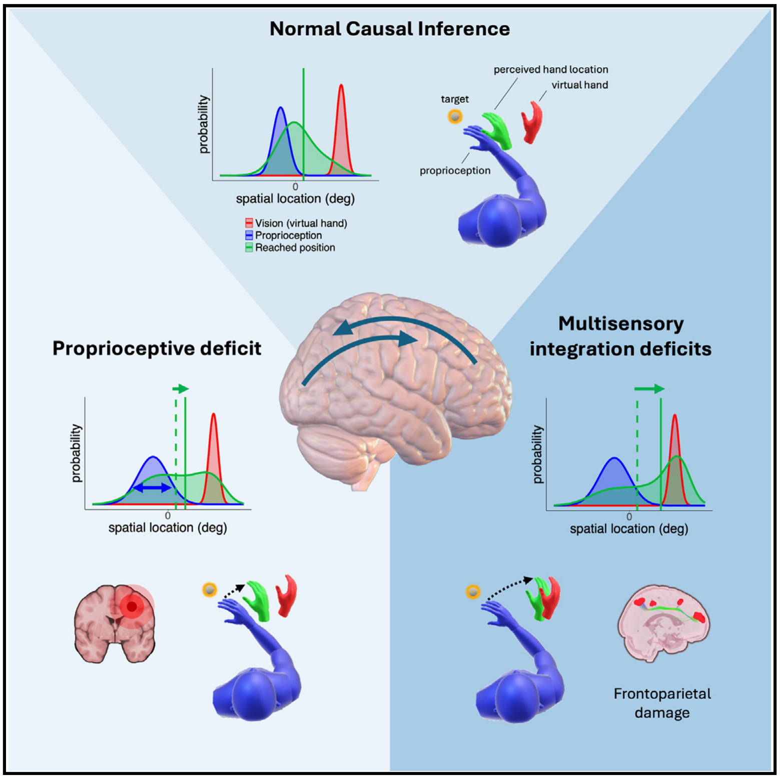
Med

Article

Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network

Graphical abstract



Highlights

- Brain stroke alters limb ownership and motor planning based on visual feedback
- Unisensory and multisensory components of these alterations can be disentangled
- Probabilistic inference accounts for these alterations in terms of proprioceptive loss
- Higher-level multisensory integration deficits are linked to frontoparietal damage

Translation to Patients

Authors

Giulio Mastria, Tommaso Bertoni, Henri Perrin, ..., Patric Hagmann, Michela Bassolino, Andrea Serino

Correspondence

giuliomastria@msn.com

In brief

Stroke patients experience alterations in their subjective feeling of ownership for the affected limb, which can hinder motor function and interfere with rehabilitation. Using computational modeling and lesion analysis, Mastria et al. show that these alterations result from the combination of proprioceptive and high-level multisensory integration deficits due to frontoparietal damage.

Mastria et al., 2025, Med *6*, 100536
April 11, 2025
https://doi.org/10.1016/j.medj.2024.10.013

CellPress

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

Med

CellPress
OPEN ACCESS

Article

Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network

Giulio Mastria,[1,6,7,*] Tommaso Bertoni,[1,6] Henri Perrin,[1] Nikita Akulenko,[1] Gaia Risso,[2,3] Michel Akselrod,[1]
Eleonora Guanziroli,[4] Franco Molteni,[4] Patric Hagmann,[5] Michela Bassolino,[1,2,3] and Andrea Serino[1]
[1]MySpace Lab, Department of Clinical Neurosciences, Lausanne University Hospital, University of Lausanne, 1011 Lausanne, Switzerland
[2]Institute of Health, School of Health Sciences, HES-SO Valais-Wallis, 1950 Sion, Switzerland
[3]The Sense Innovation & Research Center, 1950 Sion and Lausanne, Switzerland
[4]Valduce Hospital "Villa Beretta" Rehabilitation Center, 23845 Costa Masnaga, Italy
[5]Connectomics Lab, Department of Radiology, Lausanne University Hospital, University of Lausanne, 1011 Lausanne, Switzerland
[6]These authors contributed equally
[7]Lead contact
*Correspondence: giuliomastria@msn.com

https://doi.org/10.1016/j.medj.2024.10.013

CONTEXT AND SIGNIFICANCE Stroke patients can experience alterations in their subjective feeling of ownership for the affected limb, which can hinder motor function and interfere with rehabilitation. Mastria et al. show that patients are more likely to integrate incongruent visual feedback about their affected limb (i.e., a displaced virtual hand) into their motor plans and feel ownership for it. Modeling body ownership as the result of causal inference on multisensory stimuli, these alterations can be explained as emerging from proprioceptive deficits. Damage to the frontoparietal network can further disrupt the causal inference process , leading to higher-level multisensory integration and body ownership deficits. Disentangling components of body ownership alterations can help to better understand these deficits and tailor rehabilitation strategies.

SUMMARY

Background: Stroke patients often experience alterations in their subjective feeling of ownership for the affected limb, which can hinder motor function and interfere with rehabilitation. In this study, we aimed at disentangling the complex relationship between sensory impairment, body ownership (BO), and motor control in stroke patients.
Methods: We recruited 20 stroke patients with unilateral upper limb sensory deficits and 35 age-matched controls. Participants performed a virtual reality reaching task with a varying displacement between their real unseen hand and a visible virtual hand. We measured reaching errors and subjective ownership ratings as indicators of hand ownership. Reaching errors were modeled using a probabilistic causal inference model, in which ownership for the virtual hand is inferred from the level of congruency between visual and proprioceptive inputs and used to weigh the amount of visual adjustment to reaching movements.
Findings: Stroke patients were more likely to experience ownership over an incongruent virtual hand and integrate it into their motor plans. The model explained this tendency in terms of a decreased capability of detecting visuo-proprioceptive incongruences, proportionally to the amount of proprioceptive deficit. Lesion analysis further revealed that BO alterations, not fully explained by the proprioceptive deficit, are linked to frontoparietal network damage, suggesting a disruption in higher-level multisensory integration functions.
Conclusions: Collectively, our results show that BO alterations in stroke patients can be quantitatively predicted and explained in a computational framework as the result of sensory loss and higher-level multisensory integration deficits.
Funding: Swiss National Science Foundation (163951).

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

INTRODUCTION

Functional recovery after stroke is hindered not only by loss of sensory and motor functions but also by a broad spectrum of neuropsychological deficits affecting body representation and bodily awareness entangled with basic sensorimotor deficits. Following a stroke, patients may deny the ownership of the affected limb,[1] or recognize other people's limbs as their own.[2,3] During the acute phase, mild forms of body ownership (BO) alterations such as limb misidentification are present in more than half of patients suffering hemi-spatial neglect and are strongly associated with unawareness of acquired motor deficits (anosognosia for hemiplegia).[4] Upper limb perception deficits persist also in the chronic phase and ameliorate together with sensory and motor recovery induced by intense *ad hoc* training.[5,6]

In normal conditions, the feeling of BO is thought to emerge online from the continuous integration of multisensory bodily signals (e.g., visual and somatosensory inputs) based on the fact that these are congruent in space and time.[7–9] Seminal experiments on healthy participants have shown that a fake or virtual body part can be illusory, perceived as one's own, as long as it is congruent with the pattern of sensory stimuli normally arising from the body.[7,10,11] This mechanism has been described as a form of probabilistic reasoning, whereby the brain constantly infers the probability that the observed limb belongs to the body based on multisensory congruence. Conversely, loss of limb ownership in stroke patients might depend on a perceived incongruency between bodily stimuli. This may simply be the result of deficits in unisensory processing, as suggested by the fact that BO alterations are almost invariably associated with severe somatosensory deficits.[12] However, not all patients with somatosensory deficits also show clinically overt BO alterations. Therefore, it has been suggested that deficits in BO may further depend on other factors, such as a direct impairment of the process integrating multisensory bodily inputs.[12–14] A few studies have investigated this hypothesis[12–14]; however, results are divergent and not conclusive.[15–17]

The role of BO is not limited to the cognitive domain but is closely related to motor functions. Indeed, BO can influence motor planning and execution[18–22] and can modulate the activity of the motor system even when no actual movement is performed.[23] Self-attribution of visually perceived body parts, underlying BO, might be implicitly required for visual guidance of movements. A recent study directly tested this hypothesis in a case series of patients with pathological embodiment, who mistakenly attribute the hand of another individual to themselves. Results showed that the misattributed "alien" hand tends to replace the own hand in patients' motor plans, biasing their reaching.[24] As the experience of owning an alien hand implies disembodiment of the real, affected one,[25] self-attribution of an alien hand can be seen as an indicator of BO deficits. In the long term, BO deficits might contribute to a "learned non-use," whereby patients unconsciously fail to integrate the contralesional limb in their activities.[26] Thus, mild or even sub-clinical alterations of BO could have measurable effects on motor behavior and might play a role in patients' recovery and neurorehabilitation.

In sum, converging evidence suggests that both somatosensory and multisensory integration deficits may contribute to BO alterations in stroke patients. BO alterations may in turn affect motor behavior by altering the integration of visual information in motor plans. Although present to various extents in previous experimental and theoretical works,[12,13,15,21,24,27] this idea is limited by the lack of empirical data and a quantitative theoretical framework, able to generate testable predictions in clinical populations.

Here, we aim at filling this gap by measuring BO alterations in stroke patients through a novel quantitative assessment, based on the modulation of BO and reaching movements induced by variable visuo-motor rotation of a virtual hand.[28] We modeled our BO assessment within a computational probabilistic framework to estimate the contribution of unisensory inputs and multisensory integration processes to BO alterations.[22,29–31] It is well known that reaching toward a target, while visual feedback about hand position is shifted, induces an opposite error in the actual reached position.[24] Recent studies applied this idea to the study of BO by asking healthy participants to reach a target while seeing a hand in virtual reality (VR) with variable levels of displacement with respect to their real (not visible) hand (visuo-proprioceptive disparity) and rate their subjective ownership for the virtual hand (Figure 1A).[22,29] The relative reaching errors (ratio between the error and the disparity, referred to as reaching bias from now on) induced by the virtual hand and subjective ownership ratings were high at low levels of disparity and low at high disparities (Figures 1B and 1C). This means that the virtual hand was perceived as one's own when it was congruent with the real hand (low disparities) and progressively less so as the incongruence increased (Figure 1D). This behavior is well explained by a probabilistic causal inference model of BO (Bertoni et al.[29]; see also Fang et al;[22]) in which the probability of a limb belonging to the body is computed online based on the congruency of visual and proprioceptive inputs (Figure 1C). The model describes the statistically "optimal" way to integrate noisy sensory information. Importantly, it predicts that the level of visuo-proprioceptive incongruency beyond which a sharp decline in the ownership probability is observed (ownership window) depends on the precision in unimodal sensory processing (i.e., proprioceptive and visuo-spatial precision). The less precise vision and proprioception are, the less discrepancies can be detected, causing the virtual hand to be perceived as one's own and to bias reaching movements up to large levels of disparity.

This theoretical framework can be readily transposed to brain-damaged patients. Indeed, BO alterations induced by stroke may depend on failure to process coherence (or conflict) in visuo-proprioceptive information, which can originate at different stages of the multisensory integration process. Congruency detection can be impaired by a reduced precision in unisensory processing—i.e., a somatosensory deficit in an otherwise functional integration process—and/or by direct impairment of the multisensory integration mechanism itself (i.e., sub-optimal integration). In the first case, the causal inference model predicts a larger ownership window as the result of an adequate optimal response to the partial sensory loss (low-level unisensory deficit). in the second case, the larger ownership windows would depend on a significant deviation from optimal behavior

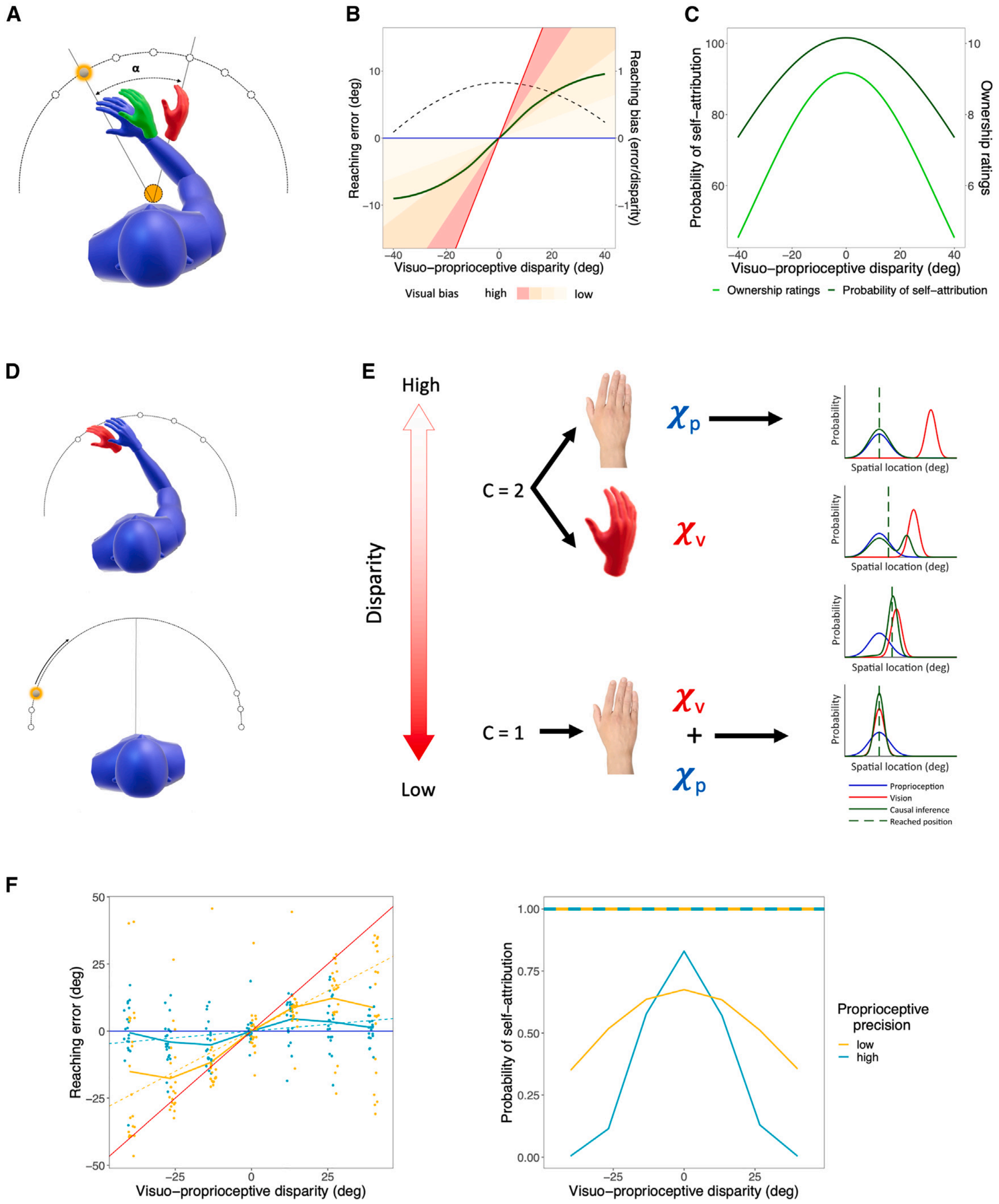


Figure 1. Behavioral tasks and model predictions

(A) In the VPD task (see also Video S1), a variable angle of disparity α is introduced between the real and the virtual hand during reaching movements toward a set of visual targets. The red hand represents the visual feedback from the virtual hand, the blue hand the proprioceptive feedback from the real hand, while the green hand is the final estimate resulting from visuo-proprioceptive integration.

(B) Average reaching error (green solid line) as a function of disparity in healthy subjects (data from Bertoni et al.[29]). The x axis indicates visuo-proprioceptive disparities, defined as the virtual-hand angle minus the real-hand angle. The left y axis reports the reaching errors as the target's angle minus the real hand's angle. The expected errors in the case of a total visual (error = disparity) or proprioceptive (error = 0) dominance are represented by the red and blue lines, respectively. The reaching error is closer to the red line at lower disparities (visual dominance) and curves toward the blue line at higher levels of disparity. The dashed black line shows the reaching bias (error/disparity), which constantly decreases as disparity increases.

(C) Subjective ownership ratings and probability of self-attribution of the virtual hand according to the causal inference model (P_{com}) as a function of disparity data from Bertoni et al.[29]).

(legend continued on next page)

Table 1. Demographic and clinical data

	Stroke patients	Healthy controls
Number of participants	*N* = 20	*N* = 35
Mean age (years)	60.7 ± 13.6	55.7 ± 23.7
Age range (years)	26–85	25–88
Right side affected	65%	N/A
Time since stroke (days)	73.15 ± 47.03	N/A
Spasticity	30%	N/A
Motor deficit	100%	N/A
Light touch	95%	N/A
Pressure	75%	N/A
Pinprick	65%	N/A
Temperature	70%	N/A
Joint position	75%	N/A
Attention	15%	N/A
Tactile extinction	10%	N/A

The table shows demographic and clinical data of the participants recruited for the study. The table reports the prevalence (%) of spasticity (Ashworth modified scale), motor deficits (motricity index), and sensory deficits (Nottingham sensory assessment) in patients' upper limbs. More details can be found in Tables S1 and S2. N/A, not applicable.

(higher-level multisensory integration deficit). We tested these non-mutually exclusive hypotheses by applying our behavioral-computational framework to a cohort of 20 stroke patients with sensorimotor deficits and 35 age-matched healthy controls.

Participants performed the VR-based reaching task and two unisensory tasks assessing proprioceptive and visuo-spatial precision. Our causal inference model predicted that stroke patients should experience ownership for a virtual hand at a higher level of visuo-proprioceptive incongruency compared to the intact limb and to healthy controls. This should also lead to a higher tendency to integrate the incongruent virtual hand in motor plans (i.e., higher reaching errors under visuo-proprioceptive disparity). Crucially, these concurrent indices of BO alteration should be quantitatively related to patients' proprioceptive impairment, as measured through an appropriate behavioral task (i.e., proprioceptive judgment; see STAR Methods). Furthermore, according to model predictions, the increased tendency to embody an incongruent alien limb should go hand in hand with a decreased ownership for a congruent own limb, thus explaining limb misidentification and ownership deficits in stroke patients through a common mechanism. In the present framework, this can be measured as a reduced ownership for congruent visuo-proprioceptive conditions. Finally, we analyzed patients' brain lesions and their effect on large-scale brain networks to study the component of BO alteration not explained by unisensory deficits. We expected such components to be related to lesions affecting multisensory-motor networks, in line with the idea that it might originate from deficits in higher-level multisensory integration functions.

RESULTS

Demographic and clinical data about participants are summarized in Tables 1, S1, and S2. Participants' information on sex, age, and race was self-reported. Information on gender and socioeconomic status was not collected. No patient showed clinically overt BO alterations at a simple clinical assessment or reported having experienced such symptoms during the acute phase after stroke.

Lateralized BO alterations in stroke patients

As a first step, we aimed at assessing whether subjective feelings of BO are reflected in the reaching bias induced by the incongruent virtual hand (behavioral measure of ownership) in the visuo-proprioceptive disparity (VPD) task in our cohort of stroke patients. With this aim, we investigated the relation between reaching errors and subjective ownership ratings, finding a significant negative correlation by means of a linear mixed model (F = 7.73, $p = 0.017$). However, this correlation does not rule out that lower ownership ratings and reaching errors might be unrelated epiphenomena of visuo-proprioceptive incongruency. Therefore, to demonstrate their relation in a more compelling way, we isolated trial-level fluctuations in BO and reaching errors from the overall effect of VPD by subtracting from ownership ratings and reaching error at each disparity their corresponding average. We found a significant correlation between *residual error* and *residual rating* by means of a linear mixed model (F = 131.2, $p < 0.001$), demonstrating that reaching errors covaried with ownership ratings even at fixed disparity (Figure 2); that is, trials in which the subject relied more on vision for reaching the target were associated with higher subjective ownership ratings for the virtual hand. This result indicates that trial-level fluctuations in subjective ownership are reflected in motor

(D) In the upper plot, proprioceptive judgment (PJ) task to measure proprioceptive precision: a virtual hand is displayed in VR at the left or the right of participants' real hand. The perceived position of the hand is determined using a two-alternative forced-choice converging algorithm. Lower plot: midline judgment task (MJ), to measure visuo-spatial precision, in which participants are asked to report when they feel that a visual cue, moving across their visual field, is at their body midline.

(E) Schematic representation of the causal inference model: the brain infers a common cause (C = 1) or independent causes (C = 2) for the visual and proprioceptive information depending on their level of congruency and the relative precision of the unisensory systems. At low disparities (bottom), the common cause (ownership) probability is high, and signals coming from vision (χ_v, red curve) and proprioception (χ_p, blue curve) are strongly integrated. In this case, the final reached position is a combination of visual and proprioceptive positions with a high reaching bias. At high disparities (top), the common cause (ownership) probability is low, and signals coming from vision and proprioception are less integrated. The final reached position is mostly based on proprioception (low reaching bias).

(F) Predictions of the BCI model on simulated reaching errors at the VPD task in the case of low and high sensory (proprioceptive) precision (yellow and light blue solid lines). A high probability of self-attribution of the virtual hand and associated reaching bias persists at larger disparities (larger σ_{Pcom}) when sensory precision is lower. By contrast, the FF model predicts that the weights of vision and proprioception in determining the final reaching position and ownership ratings do not vary with disparity (straight dashed lines).

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

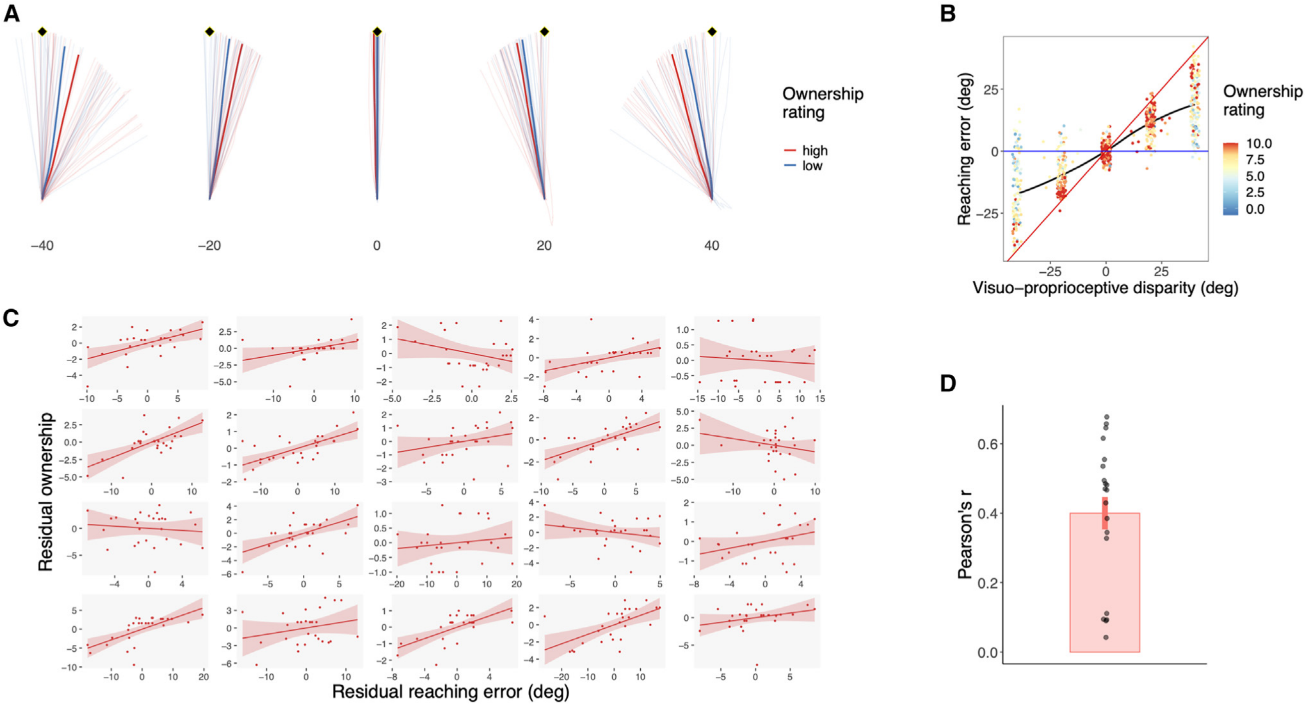


Figure 2. Relation between behavioral (reaching errors) and subjective ownership (ownership ratings) measures at the single-trial level

(A) The participants' reaching trajectories during the third block grouped by disparity (−40, −20, 0, 20, 40) and split by the median of the ownership ratings: trajectories deviate more from the target (black diamond) when participants give high ownership rating (red) compared to trials with low ownership ratings (blue).

(B) The panel illustrates the relationship between reaching errors and ownership ratings. The black solid line indicates the average reaching error for each disparity and dots the individual reaching errors. The expected error in the case of a purely visual or proprioceptive dominance are represented by the red and blue lines, respectively. The color of the dots indicates the ownership rating (1–10) associated with that trial. Higher ownership ratings are associated with more weight attributed to the virtual hand.

(C) The correlation between residual reaching error and residual ownership rating, with each subplot corresponding to one of the 20 stroke patients.

(D) The individual Pearson correlation coefficients between residual reaching errors and ownership ratings. The error bar represents the standard error of the mean.

behavior, and therefore reaching error induced by the virtual hand can be used as a behavioral proxy of ownership.

We then compared both behavioral (Figure 3A, left plot) and subjective (Figure 3A, right plot) ownership measures between the intact and affected limb of patients to assess the effects of stroke on BO. As qualitatively evident from the plots, for the affected limb, the weight of visual cues in reaching movements, as well as ownership ratings, remained high up to larger spatial disparities, as if patients were more tolerant to spatial incongruence on the affected limb. To demonstrate this effect quantitatively, we estimated the spatial windows (σ_{Pcom} and σ_{ratings}) of incongruence yielding a decrease in behavioral and subjective ownership (see STAR Methods). The behavioral and subjective ownership windows for the affected limb were significantly larger compared with both the intact limb (σ_{Pcom}, $T_{19} = 2.93$, $p = 0.008$; σ_{ratings}, $T_{19} = 5.37$, $p < 0.001$; Figure 3B, left plot) and healthy controls (σ_{Pcom}, $T_{53} = 3.82$, $p < 0.001$; σ_{ratings}, $T_{53} = 4.85$, $p < 0.001$; Figure 3B, right plot). No significant difference was found for either measure between the intact limb of patients and healthy controls (σ_{Pcom}, $T_{53} = 0.57$; $p = 0.571$; σ_{ratings}, $T_{53} = 2.00$, $p = 0.052$).

We performed further analyses to assess the potential contribution to our results of attention, which was not explicitly included in our model but may play a role in gauging the integration of visual and proprioceptive cues.[32] First, we compared ownership alterations in right- and left-brain-damaged patients, without finding any significant differences (σ_{Pcom}, $T_{19} = 1.88$ $p = 0.08$; σ_{ratings}, $T_{19} = 0.27$, $p = 0.793$) (Figure S2). Second, the presence of attention deficits was added as a covariate in our analyses without finding any significant effect. To further explore the possible effect of lateralized attention deficits, we also analyzed separately targets in the left and right hemifield without finding any significant difference between ipsilesional and contralesional hemifield (σ_{Pcom}, $T_{19} = -0.67$; $p = 0.508$; σ_{ratings}, $T_{19} = 1.74$, $p = 0.098$) or between the two hemifields for patients with left- (σ_{Pcom}, $T_{19} = -0.81$, $p = 0.448$; σ_{ratings}, $T_{19} = 0.57$, $p = 0.591$) and right-brain (σ_{Pcom}, $T_{19} = 0.48$, $p = 0.64$; σ_{ratings}, $T_{19} = 1.65$, $p = 0.125$) lesions.

Disembodiment of the real limb in stroke patients

We then aimed at testing whether such increased tendency to embody an incongruent virtual hand could be related to the disembodiment of patients' real hands. We reasoned that trials in which the virtual hand was congruent with the real hand reproduce the congruency between visual and proprioceptive inputs determining ownership from one's real hand, approximating

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

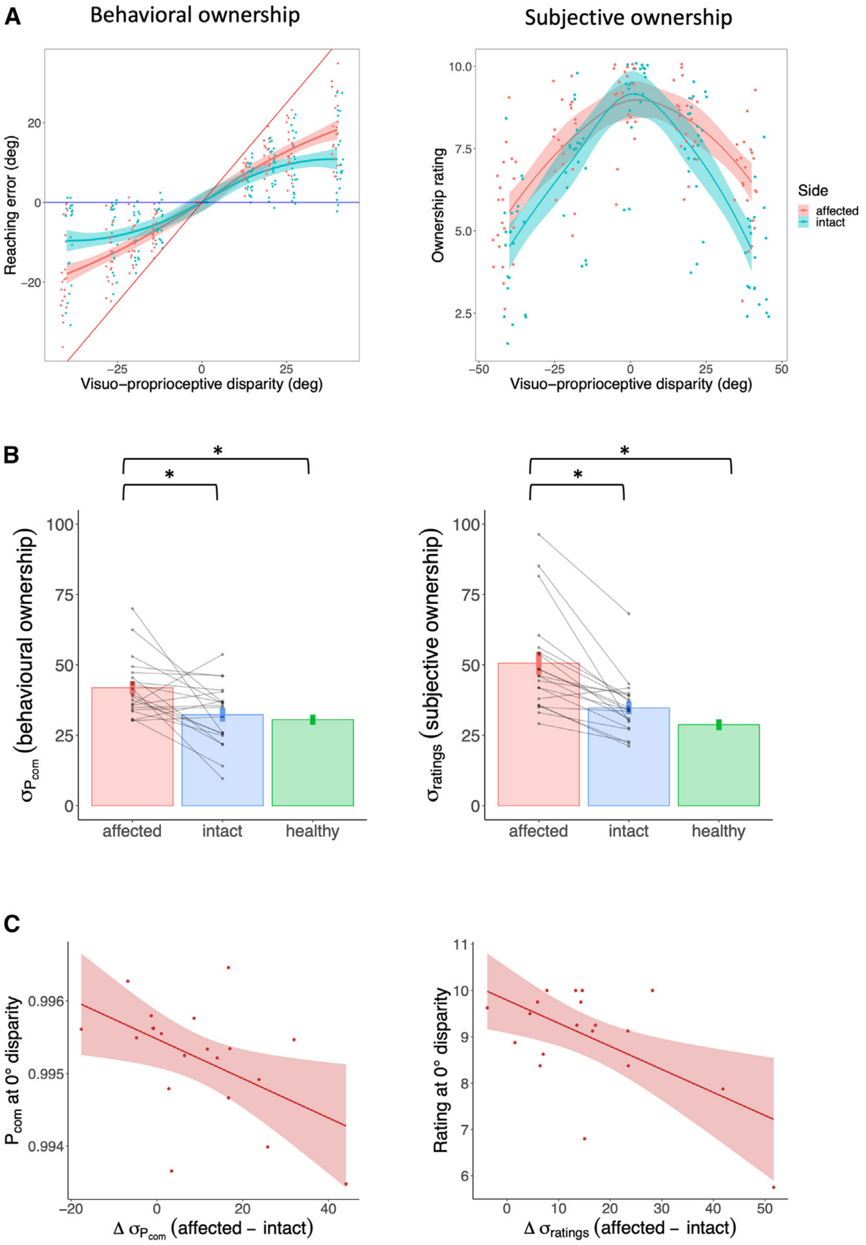


Figure 3. BO alterations in stroke patients

(A) The raw data of the VPD task in stroke patients. In the left plot, the x axis indicates visuo-proprioceptive disparities, while the y axis reports the reaching errors. The expected errors in the case of a purely visual or proprioceptive dominance are represented by the red and blue lines, respectively. Right plot: ownership ratings as a function of the VPD. A comparison between patients with left and right brain lesion can be found in Figure S2.

(B) Fitted σ_{Pcom} (behavioral ownership) and $\sigma_{ratings}$ (subjective ownership) of the affected limb, compared to the intact limb of patients (within-subject comparison) and to healthy controls (between-subject comparison). The error bars represent the standard error of the mean; asterisks indicate $p < 0.05$.

(C) Correlation between indexes of behavioral (P_{com}) and subjective ownership (average ownership rating) at 0° disparity and BO alterations in stroke patients, as measured by the difference in the tolerated window of behavioral and subjective ownership between the affected and intact limb ($\Delta\sigma_{Pcom}$ and $\Delta\sigma_{ratings}$).

patients' hand experience in everyday life. Therefore, we considered both the affected limb's subjective ownership and behavioral ownership (P_{com} model fits from reaching errors) in congruent trials (0° disparity). We correlated them with the observed increased tendency to embody an incongruent virtual hand, measured both subjectively ($\Delta\sigma_{ratings}$ affected, intact) and behaviorally ($\Delta\sigma_{Pcom}$ affected, intact). Correlations for both subjective and behavioral measures were negative and significant ($\Delta\sigma_{ratings}$, Pearson's $r^2 = 0.32$, $p = 0.008$; $\Delta\sigma_{Pcom}$, Pearson's $r^2 = 0.26$, $p = 0.022$). Thus, patients demonstrating an increased ownership for the incongruent virtual hand also showed decreased ownership in case of congruent visuo-proprioceptive information (i.e., for a virtual hand mimicking their own hand in natural situations).

BO alterations are partially explained by impaired proprioception

Consistently with the Bayesian causal inference (BCI) model, the higher tendency to embody an incongruent hand (and the subsequent disembodiment of one's own) could be explained by an impairment of visual and/or proprioceptive sensitivity. Indeed, proprioceptive precision measured through the proprioceptive judgment (PJ) task was lower for the affected limb when compared to the intact side ($T_{19} = 6.48$, $p < 0.001$) and healthy controls ($T_{19} = 2.67$, $p = 0.026$), while no significant difference was found between the intact side and healthy controls ($T_{19} = -0.65$, $p = 0.99$) (Figure 4A). Moreover, a reduction in visuo-spatial precision (σ_v), as measured through the midline judgment (MJ) task, was observed in patients compared to controls ($T_{19} = 3.69$, $p < 0.001$) (Figure 4B). To investigate the relation between such unisensory deficits and ownership alterations, we tested the correlation of σ_{Pcom} and $\sigma_{ratings}$ with the visuo-spatial (σ_v) and proprioceptive (σ_p) precision. Both σ_{Pcom} (Pearson's $r = 0.60$, $p = 0.004$) and $\sigma_{ratings}$ (Pearson's $r = 0.57$, $p = 0.008$) showed a significant correlation with proprioceptive precision σ_p (Figures 4C and 4D), while no significant correlation was found between either of these parameters and the visuo-spatial precision σ_v (σ_{Pcom}, $r^2 = -0.06$, $p = 0.814$; $\sigma_{ratings}$, $r^2 = -0.31$, $p = 0.191$). Thus, in the framework

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

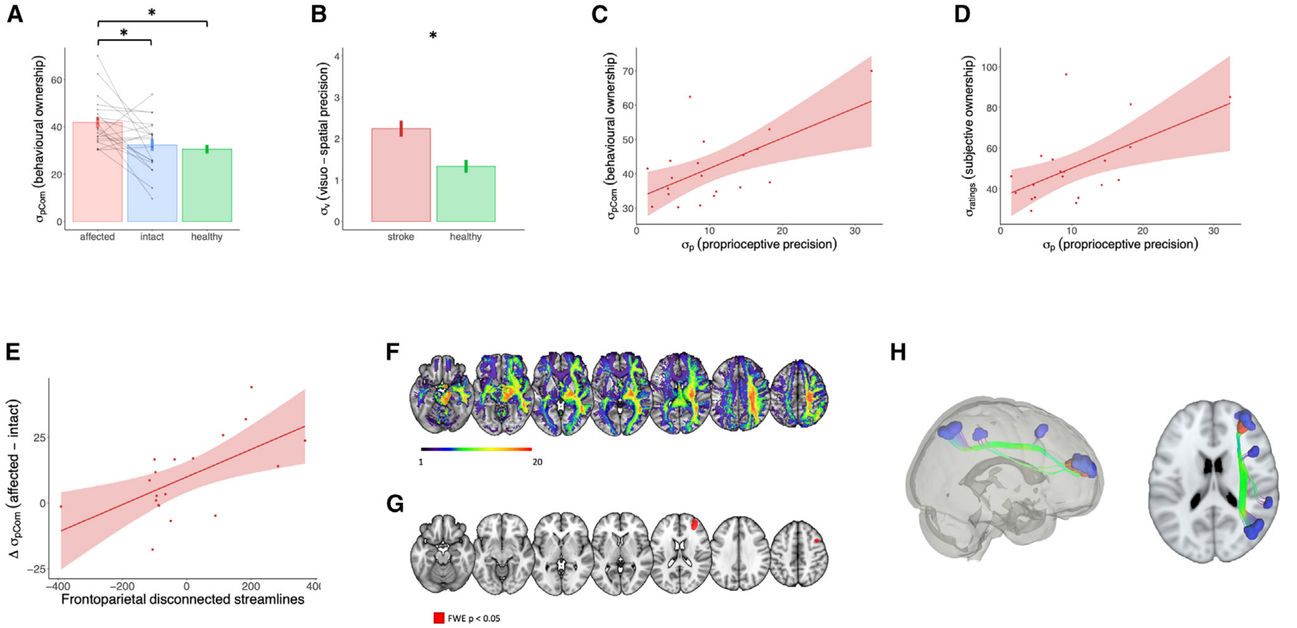


Figure 4. Unisensory and multisensory contributions to BO alterations in stroke patients

(A and B) The bar plots show the visuo-spatial (A) and proprioceptive (B) precision in patients and healthy controls. Error bars represent the standard error of the mean; asterisks indicate $p < 0.05$.

(C and D) Correlation between proprioceptive precision and the behavioral (C) and subjective (D) ownership measures for the affected side of patients.

(E) Using a tractography template (Yeh et al.[33]), we selected the streamlines intersecting the lesion of each patient (step 1). We computed individual region of interest (ROI)-to-ROI disconnectivity matrices based on Yeo's parcellation of brain networks (step 2) and then conducted an ROI-based disconnectivity analysis (step 3). We then performed voxel lesion-symptom mapping on white matter disconnectivity maps (step 4).

(F) Relationship between the difference in the tolerated window of multisensory integration between the affected and intact limb of stroke patients ($\Delta\sigma_{\text{Pcom}}$) and structural damage to the frontoparietal network (orthogonal to lesion volume).

(G) On the upper row, overlap of disconnectivity maps (lesion overlap is shown in Figure S1). All lesions were flipped to the right side. On the bottom row, significative clusters within the frontoparietal network associated with an increased $\Delta\sigma_{\text{Pcom}}$ (affected-intact).

(H) Overlap of the two significative clusters (in red) with the frontoparietal projection fibers connecting the intraparietal sulcus and supramarginal gyrus with the premotor and dorsolateral prefrontal cortex (blue ROIs).

of our causal inference model, the amount of proprioceptive deficit induced by stroke explained part of the alteration of both behavioral and subjective BO emerging in the VPD task.

BO alterations are further explained by a lesion of the frontoparietal network

Our computational model assumes by definition a fully functional integration process and can thus only account for the component of BO alterations that directly derives from unisensory impairment. However, brain lesions might also directly affect the multisensory integration process itself, leading to further variability in BO alterations not explained by unisensory deficits. This effect cannot be accounted for by the model itself, but its source may be found in the location of brain lesions and their impact on brain connectivity. We thus investigated unexplained variability in both behavioral and subjective measures of BO through voxel-based lesion-symptom mapping (VLSM) and disconnectivity analyses. To control for the effects of non-lateralized cognitive factors, we focused on the difference in the ownership window between the affected and intact limb ($\Delta\sigma_{\text{Pcom}}$ and $\Delta\sigma_{\text{ratings}}$). To control for the contribution of somatosensory deficits, we regressed out the effects of unisensory deficits from BO alterations (see STAR Methods). It is worth mentioning that some patients show a negative $\Delta\sigma_{\text{Pcom}}$. This could be due to several reasons, including some form of motor or cognitive compensation. Noise in reaching patterns and in the fitting procedure could also explain some of these cases. We checked the potential origin of this pattern by assessing the correlation between $\Delta\sigma_{\text{Pcom}}$ and the parameters of the clinical assessment without finding any significant result.

The VLSM on brain lesions did not yield any significant result. Since the multisensory integration process leading to BO likely relies on the interaction between multiple brain areas, we analyzed the effect of focal brain lesions on large-scale brain networks connectivity. To this aim, we tested the correlation of $\Delta\sigma_{\text{Pcom}}$ and $\Delta\sigma_{\text{ratings}}$ with the number of disconnected streamlines in each of the brain networks identified by Yeo and colleagues.[34] We found a positive correlation between $\Delta\sigma_{\text{Pcom}}$ and the structural damage to the frontoparietal network (Pearson's r = 0.61, p = 0.005) (Figure 4F). Lesions to other networks showed no significant correlation with $\Delta\sigma_{\text{Pcom}}$. We found a positive correlation between $\Delta\sigma_{\text{Pcom}}$ and the structural damage to the frontoparietal network (Pearson's r = 0.61, p = 0.005) (Figure 4F). Lesions to other networks showed no significant correlation with $\Delta\sigma_{\text{Pcom}}$. This correlation was also significant after

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

removing the subjects with a negative $\Delta\sigma_{Pcom}$ (i.e., with a stronger bias for the ipsilesional than the contralesional hand; Pearson's $r = 0.8$, $p = 0.001$).

We then used VLSM to better characterize the functional-anatomical correlation between BO alteration and damage to the frontoparietal network (all lesions flipped on the same side). A higher $\Delta\sigma_{Pcom}$ was associated with disconnection in two significative clusters within the frontal lobe (Montreal Neurological Institute, MNI, coordinates: $x = 38$, $y = 12$, $z = 42$ and $x = 32$, $y = 47$, $z = 18$) (Figure 4G). These clusters intersected projections of the superior longitudinal fasciculus connecting the intraparietal sulcus ($x = 41$, $y = -63$, $z = 48$) and supramarginal gyrus ($x = 55$, $y = -37$, $z = 44$) with premotor ($x = 41$, $y = 13$, $z = 48$) and dorsolateral prefrontal cortex ($x = 34$, $y = 51$, $z = 19$) (Figure 4H).

DISCUSSION

We investigated the complex relationship between multisensory integration, BO, and sensorimotor deficits in stroke patients by combining computational modeling, psychophysics, and lesion analysis. We modeled BO as emerging from online causal inference based on the perceived congruency between visual and proprioceptive cues about hand position during movement. We measured BO through subjective ratings and behaviorally as the error induced by visuo-proprioceptive incongruency in a reaching task. Compared to their intact limb and to healthy controls, stroke patients showed an increased tendency to experience ownership for an incongruent virtual hand and to rely on its position in motor plans. Importantly, such tendency correlated with lower BO when the virtual hand was aligned with the real one (i.e., reproducing the congruency between visual and proprioceptive inputs that should determine ownership for the real hand in natural situations). The association between the tendency to misattribute an alien hand to the body and a reduced ownership for one's own hand had already been observed qualitatively in previous studies on pathological embodiment.[25] Here, we demonstrate this effect quantitatively in a broader population without clinically overt BO disorders. Furthermore, the observed BO alterations correlated with the severity of the proprioceptive deficit, in line with predictions of our computational model. This suggests that BO alterations partially emerge from a reduced proprioceptive precision, affecting the processing of visuo-proprioceptive incongruence. However, somatosensory deficits are not the only factor involved. Indeed, variability in BO alterations that was not captured by proprioceptive deficits was explained by damage to the frontoparietal network. This result points to impairment in higher-level multisensory integration processes, not directly modeled in our computational framework, as a further cause for BO alterations.

Patients with somatoparaphrenia or other forms of pathological embodiment usually suffer from severe proprioceptive deficits. A typical delusion of BO in stroke patients is characterized by an immediate feeling of ownership for another person's limb, when presented in a plausible anatomical posture.[35] In the probabilistic perspective of the BCI model, this behavior can be explained by the dominance of visual information, becoming comparably more reliable when proprioception is impaired. Accordingly, we found that proprioceptive deficits are linearly related with subtle BO alterations, covertly affecting patient's body experience and behavior. In this perspective, alterations in the relative weighting of sensory information, driven by proprioceptive impairment, may constitute an objective substrate for more severe and manifest disorders (e.g., somatoparaphrenia) lying on a pathological continuum.

In a BCI framework, the presence of a proprioceptive deficit alters the multisensory integration process and associated sense of ownership as the weight of the less reliable modality is reduced, in line with optimal causal inference. However, disorders of BO may further depend on deviations from optimality (i.e., deficits that make the integration process sub-optimal). We used lesion analysis to investigate the origin of potentially sub-optimal integration in stroke patients thus exploring other factors, beyond proprioceptive deficits, that might contribute to BO alterations.

When accounting for proprioceptive deficits (i.e., after linearly regressing the variance explained by proprioceptive precision), part of the variability in BO alterations was explained by lesion of the frontoparietal network[34] and, more specifically, fibers of the superior longitudinal fasciculus connecting the intraparietal sulcus and supramarginal gyrus with the premotor and dorsolateral prefrontal cortex. Studies on monkeys showed that information from different sensory modalities converges at the single-cell level within these regions,[36] which are considered critical for both multisensory integration and BO.[7,37] Moreover, a recent study, using the same reaching task presented here, described single neurons tuned to the relative visual and proprioceptive weights in the macaque premotor cortex.[22] In humans, the frontoparietal network is involved in multisensory integration and cross-modal attention processes, modulating in a top-down fashion the weight of sensory cues for movement control.[32,38–41] Accordingly, recent findings in stroke patients showed the involvement of the frontoparietal network in multisensory integration deficits and clinically overt disownership.[3,5,42] The present results demonstrate that lesions altering the connectivity between these frontal and parietal regions explain a part of BO alterations in stroke patients beyond lower-level impairments in unisensory processing, possibly by making the multisensory integration mechanism sub-optimal.

Neuro-computational models on different forms of multisensory integration converge on a hierarchical principle, whereby integration begins with early segregated representations in primary unisensory cortices, continues with sensory fusion in parietal-temporal regions, and culminates as causal inference in the frontal lobe (see e.g., Mihalik et al.[43] or Cao et al;[44] for audiovisual integration). Our lesion analysis results add important insight to this view, suggesting that damage to the connection between multisensory parietal and frontal regions impacts on later stages (i.e., causal inference) of visuo-proprioceptive integration, thus perturbing BO and sensorimotor loops involved in motor control.

Taken together, our results can be combined into a putative model of BO alterations after stroke. On the one hand, our causal inference model successfully predicted the amount of BO alteration based on the severity of the unisensory, proprioceptive impairment. This is compatible with a partially functional multisensory integration process in our sample of stroke patients, increasing the weight of visual cues and the tolerance to visuo-proprioceptive conflicts to account for proprioceptive impairment.

However, this also leads to a lability in the multisensory representation of the body compared to healthy subjects, favoring the disembodiment of the affected limb. Thus, within our probabilistic framework, increased alien-limb misidentification and reduced own-limb ownership can be seen as two emergent faces of the same unisensory impairment in congruency detection. On the other hand, since brain lesions can also affect the multisensory integration process itself to a variable extent, part of the BO alteration may not be accounted for by our causal inference model, which can only directly link BO alterations to behaviorally measurable unisensory deficits. We identified the frontoparietal network as the putative source of such unexplained variability. This is consistent with the idea that deficits in the multisensory integration of bodily cues might further contribute to BO alterations. We propose that BO deficits following stroke result from the combination, with variable weights, of unisensory degradation and multisensory integration deficits, which can alter BO and the subsequent integration of multisensory information in motor plans. Our results suggest that these factors can be disentangled and measured. This framework may be used to predict the capability of a lesioned brain to process and combine multisensory information underlying BO and motor control, potentially informing about the efficacy of neurorehabilitation strategies aimed at improving sensorimotor processes (e.g., neuromuscular electrical stimulation[6]) or based on the manipulation of multisensory feedback (e.g., prism adaptation,[45] mirror therapy[46])

In conclusion, in this study, we quantified the effect of unisensory and multisensory integration deficits on multisensory-motor processes underlying subjective BO, combining them into a putative pathophysiological model. Our results represent a substantial advancement in our ability to assess BO deficits and in our understanding of the mechanisms linking sensory deficits and multisensory processing with subjective bodily experience in stroke patients. This quantitative framework may also be applied to the study of BO alterations in other neurological or psychiatric conditions and help developing neurorehabilitation strategies tailored to specific profiles of motor, perceptual, and cognitive deficits.

Limitations of the study

An important limitation of our approach is the motor component of the behavioral assessment, which restricted the number and type of patients eligible for the present study. Indeed, clinically overt BO alterations are often associated with severe motor deficits, which preclude the execution of the present task. A static version of our tasks can be devised to assess the validity of our pathophysiological model in patients with more severe deficits. A second limitation is that we restricted our investigations to the parameters of the model empirically validated in our previous study.[29] However, multisensory integration is not entirely independent of top-down cognitive variables, such as attention[47] and reward[48]; future studies may try to extend the present model to include these factors.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Giulio Mastria (giulio.mastria@msn.com).

Materials availability

This study did not generate new unique material or reagent.

Data and code availability

- Data have been deposited in the Open Science Framework and are publicly available as of the date of publication (OSF: https://osf.io/b48z5/).
- The code to run the BCI model is available at OSF: https://osf.io/azh8p/.
- Any additional information required to reanalyze the data reported in this paper is available from the corresponding author upon request.

ACKNOWLEDGMENTS

This work was supported by a Swiss National Science Foundation professorship grant, grant number 163951, http://www.snf.ch. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

G.M. designed the study, collected and analyzed the data with unrestricted access, and wrote the manuscript. T.B. designed the study, collected and analyzed the data with unrestricted access, and wrote the manuscript. H.P. collected the data. N.A. collected the data. G.R. collected the data and reviewed the manuscript. M.A. collected the data. E.G. collected the data. F.M. designed the study. P.H. supervised the analysis. M.B. designed the study and reviewed the manuscript. A.S. designed the study and reviewed and edited the manuscript. All authors read and approved the final article and take responsibility for its content.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
- METHOD DETAILS
    - ○ Clinical assessment of stroke patients
    - ○ Experimental procedure
    - ○ VPD task
    - ○ PJ task
    - ○ MJ task
- QUANTIFICATION AND STATISTICAL ANALYSIS
    - ○ Key features of the BCI model and model predictions
    - ○ Behavioral analyses
    - ○ Lesion analysis

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.medj.2024.10.013.

Received: October 1, 2023
Revised: May 13, 2024
Accepted: October 14, 2024
Published: November 11, 2024

REFERENCES

1. Gerstmann, J. (1942). Problem of imperception of disease and of impaired body territories with organic lesions. Arch. Neurol. Psychiatry *48*, 890.

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

2. Pia, L., Garbarini, F., Fossataro, C., Fornia, L., and Berti, A. (2013). Pain and body awareness: Evidence from brain-damaged patients with delusional body ownership. Front. Hum. Neurosci. *7*, 1–9.
3. Errante, A., Rossi Sebastiano, A., Ziccarelli, S., Bruno, V., Rozzi, S., Pia, L., Fogassi, L., and Garbarini, F. (2022). Structural connectivity associated with the sense of body ownership: a diffusion tensor imaging and disconnection study in patients with bodily awareness disorder. Brain Commun. *4*, 1–15.
4. Antoniello, D., and Gottesman, R. (2017). Limb Misidentification: A Clinical-Anatomical Prospective Study. J. Neuropsychiatry Clin. Neurosci. *29*, 284–288.
5. Bassolino, M., Franza, M., Guanziroli, E., Sorrentino, G., Canzoneri, E., Colombo, M., Crema, A., Bertoni, T., Mastria, G., Vissani, M., et al. (2022). Body and peripersonal space representations in chronic stroke patients with upper limb motor deficits. Brain Commun. *4*.
6. Crema, A., Bassolino, M., Guanziroli, E., Colombo, M., Blanke, O., Serino, A., Micera, S., and Molteni, F. (2022). Neuromuscular electrical stimulation restores upper limb sensory-motor functions and body representations in chronic stroke survivors. Med *3*, 58–74.e10.
7. Blanke, O., Slater, M., and Serino, A. (2015). Behavioral, Neural, and Computational Principles of Bodily Self-Consciousness. Neuron *88*, 145–166.
8. Tsakiris, M. (2010). My body in the brain: A neurocognitive model of body-ownership. Neuropsychologia *48*, 703–712.
9. Körding, K.P., Beierholm, U., Ma, W.J., Quartz, S., Tenenbaum, J.B., and Shams, L. (2007). Causal inference in multisensory perception. PLoS One *2*, e943.
10. Botvinick, M., and Cohen, J. (1998). Rubber hands ‘feel’ touch that eyes see. Nature *391*, 756.
11. Kalckert, A., and Ehrsson, H.H. (2014). The moving rubber hand illusion revisited: Comparing movements and visuotactile stimulation to induce illusory ownership. Conscious. Cogn. *26*, 117–132.
12. Romano, D., and Maravita, A. (2019). The dynamic nature of the sense of ownership after brain injury. Clues from asomatognosia and somatoparaphrenia. Neuropsychologia *132*, 107119.
13. Vallar, G., and Ronchi, R. (2009). Somatoparaphrenia: a body delusion. A review of the neuropsychological literature. Exp. Brain Res. *192*, 533–551.
14. Fotopoulou, A. (2015). The virtual bodily self: Mentalisation of the body as revealed in anosognosia for hemiplegia. Conscious. Cogn. *33*, 500–510.
15. Llorens, R., Borrego, A., Palomo, P., Cebolla, A., Noé, E., i Badia, S.B., and Baños, R. (2017). Body schema plasticity after stroke: Subjective and neurophysiological correlates of the rubber hand illusion. Neuropsychologia *96*, 61–69.
16. Zeller, D., Gross, C., Bartsch, A., Johansen-Berg, H., and Classen, J. (2011). Ventral premotor cortex may be required for dynamic changes in the feeling of limb ownership: A lesion study. J. Neurosci. *31*, 4852–4857.
17. Wawrzyniak, M., Klingbeil, J., Zeller, D., Saur, D., and Classen, J. (2018). The neuronal network involved in self-attribution of an artificial hand: A lesion network-symptom-mapping study. Neuroimage *166*, 317–324.
18. Zopf, R., Truong, S., Finkbeiner, M., Friedman, J., and Williams, M.A. (2011). Viewing and feeling touch modulates hand position for reaching. Neuropsychologia *49*, 1287–1293.
19. Heed, T., Gründler, M., Rinkleib, J., Rudzik, F.H., Collins, T., Cooke, E., and O’Regan, J.K. (2011). Visual information and rubber hand embodiment differentially affect reach-to-grasp actions. Acta Psychol. *138*, 263–271.
20. Newport, R., Pearce, R., and Preston, C. (2010). Fake hands in action: embodiment and control of supernumerary limbs. Exp. Brain Res. *204*, 385–395.
21. Garbarini, F., Pia, L., Piedimonte, A., Rabuffetti, M., Gindri, P., and Berti, A. (2013). Embodiment of an alien hand interferes with intact-hand movements. Curr. Biol. *23*, R57–R58.
22. Fang, W., Li, J., Qi, G., Li, S., Sigman, M., and Wang, L. (2019). Statistical inference of body representation in the macaque brain. Proc Natl Acad Sci USA *116*, 20151–20157.
23. Pyasik, M., Furlanetto, T., and Pia, L. (2019). The Role of Body-Related Afferent Signals in Human Sense of Agency. J. Exp. Neurosci. *13*, 117906951984990.
24. Rossi Sebastiano, A., Poles, K., Miller, L.E., Fossataro, C., Milano, E., Gindri, P., and Garbarini, F. (2022). Reach planning with someone else’s hand. Cortex *153*, 207–219.
25. Garbarini, F., Fornia, L., Fossataro, C., Pia, L., Gindri, P., and Berti, A. (2014). Embodiment of others’ hands elicits arousal responses similar to one’s own hands. Curr. Biol. *24*, R738–R739.
26. Otaki, R., Oouchida, Y., Aizu, N., Sudo, T., Sasahara, H., Saito, Y., Takemura, S., and Izumi, S.-I. (2022). Relationship Between Body-Specific Attention to a Paretic Limb and Real-World Arm Use in Stroke Patients: A Longitudinal Study. Front. Syst. Neurosci. *15*.
27. Zeller, D., Friston, K.J., and Classen, J. (2016). Dynamic causal modeling of touch-evoked potentials in the rubber hand illusion. Neuroimage *138*, 266–273.
28. Newport, R., and Schenk, T. (2012). Prisms and neglect: What have we learned? Neuropsychologia *50*, 1080–1091.
29. Bertoni, T., Mastria, G., Akulenko, N., Perrin, H., Zbinden, B., Bassolino, M., and Serino, A. (2023). The self and the Bayesian brain: testing probabilistic models of body ownership through a self-localization task. Cortex *167*, 247–272.
30. Samad, M., Chung, A.J., and Shams, L. (2015). Perception of body ownership is driven by Bayesian sensory inference. PLoS One *10*, e0117178.
31. Samad, M., Parise, C., Keller, S., and Di Luca, M. (2018). A common cause in the phenomenological and sensorimotor correlates of body ownership. J. Vis. *18*, 1230.
32. Tang, X., Wu, J., and Shen, Y. (2016). The interactions of multisensory integration with endogenous and exogenous attention. Neurosci. Biobehav. Rev. *61*, 208–224.
33. Yeh, F.C., Panesar, S., Fernandes, D., Meola, A., Yoshino, M., Fernandez-Miranda, J.C., Vettel, J.M., and Verstynen, T. (2018). Population-averaged atlas of the macroscale human structural connectome and its network topology. Neuroimage *178*, 57–68.
34. Thomas Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., et al. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. *106*, 1125–1165.
35. Garbarini, F., Fossataro, C., Berti, A., Gindri, P., Romano, D., Pia, L., della Gatta, F., Maravita, A., and Neppi-Modona, M. (2015). When your arm becomes mine: Pathological embodiment of alien limbs using tools modulates own body representation. Neuropsychologia *70*, 402–413.
36. Cléry, J., Guipponi, O., Wardak, C., and Ben Hamed, S. (2015). Neuronal bases of peripersonal and extrapersonal spaces, their plasticity and their dynamics: Knowns and unknowns. Neuropsychologia *70*, 313–326.
37. Grivaz, P., Blanke, O., and Serino, A. (2017). NeuroImage Common and distinct brain regions processing multisensory bodily signals for peripersonal space and body ownership. Neuroimage *147*, 602–618.
38. Limanowski, J. (2022). Precision control for a flexible body representation. Neurosci. Biobehav. Rev. *134*, 104401.
39. Spence, C., Pavani, F., and Driver, J. (2000). Crossmodal links between vision and touch in covert endogenous spatial attention. J. Exp. Psychol. Hum. Percept. Perform. *26*, 1298–1319.
40. Talsma, D., Senkowski, D., Soto-Faraco, S., and Woldorff, M.G. (2010). The multifaceted interplay between attention and multisensory integration. Trends Cogn. Sci. *14*, 400–410.
41. Limanowski, J., and Friston, K. (2020). Attentional Modulation of Vision Versus Proprioception during Action. Cereb. Cortex *30*, 1637–1648.

42. Moro, V., Pacella, V., Scandola, M., Besharati, S., Rossato, E., Jenkinson, P.M., and Fotopoulou, A. (2023). A fronto-insular-parietal network for the sense of body ownership. Cereb. Cortex *33*, 512–522.
43. Mihalik, A., and Noppeney, U. (2020). Causal inference in audiovisual perception. J. Neurosci. *40*, 6600–6612.
44. Cao, Y., Summerfield, C., Park, H., Giordano, B.L., and Kayser, C. (2019). Causal Inference in the Multisensory Brain. Neuron *102*, 1076–1087.e8.
45. Serino, A., Angeli, V., Frassinetti, F., and Làdavas, E. (2006). Mechanisms underlying neglect recovery after prism adaptation. Neuropsychologia *44*, 1068–1078.
46. Altschuler, E.L., Wisdom, S.B., Stone, L., Foster, C., Galasko, D., Llewellyn, D.M.E., and Ramachandran, V. (1999). Rehabilitation of hemiparesis after stroke with a mirror. Lancet *353*, 2035–2036.
47. Talsma, D., and Woldorff, M.G. (2005). Selective Attention and Multisensory Integration: Multiple Phases of Effects on the Evoked Brain Activity. J. Cogn. Neurosci. *17*, 1098–1114.
48. Bruns, P., Maiworm, M., and Röder, B. (2014). Reward expectation influences audiovisual spatial integration. Attention, Perception, Psychophys *76*, 1815–1827.
49. Acerbi, L., and Ma, W.J. (2017). Practical Bayesian Optimization for Model Fitting with Bayesian Adaptive Direct Search. Adv. Neural Inf. Process. Syst. *30*, 1834–1844.
50. Collin, C., and Wade, D. (1990). Assessing motor impairment after stroke: a pilot reliability study. J. Neurol. Neurosurg. Psychiatry *53*, 576–579.
51. Meseguer-Henarejos, A.-B., Sánchez-Meca, J., López-Pina, J.-A., and Carles-Hernández, R. (2018). Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. Eur. J. Phys. Rehabil. Med. *54*, 576–590.
52. Lincoln, N., Jackson, J., and Adams, S. (1998). Reliability and Revision of the Nottingham Sensory Assessment for Stroke Patients. Physiotherapy *84*, 358–365.
53. Douglas, G. (2000). Introduction to Clinical Neurology (Butterworth Heinemann).
54. Azouvi, P., Samuel, C., Louis-Dreyfus, A., Bernati, T., Bartolomeo, P., Beis, J.M., Chokron, S., Leclercq, M., Marchal, F., Martin, Y., et al. (2002). Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. J. Neurol. Neurosurg. Psychiatry *73*, 160–166.

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
VPD task data	This paper	OSF: https://osf.io/b48z5/
Software and algorithms		
MATLAB	Mathworks	R2018a, https://www.mathworks.com/products/matlab.html
Virtual reality assessment	Bertoni et al., 2023[29]	OSF: https://osf.io/azh8p/
Code for model fitting	Bertoni et al., 2023[29]	OSF: https://osf.io/azh8p/
BADS optimization tool	Acerbi et al., 2017[49]	https://github.com/lacerbi/bads
NiiStat	McCausland Center for Brain Imaging	https://www.nitrc.org/projects/niistat
DSI studio	DSI studio	(https://dsi-studio.labsolver.org)

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

A total of 55 participants have been included in the study over 2 years. Written informed consent was obtained from all participants. Following sample-size estimates from our previous study,[29] we recruited 20 right-handed stroke patients matching the following inclusion criteria: age over 18 years, ischemic or haemorrhagic brain lesion identified with magnetic resonance imaging or computed tomography scans, unilateral upper limb somatosensory deficits clinically observed in at least one of the following modalities: pressure, light touch, sharp-dull discrimination, temperature discrimination or joint position sense.

Patients who could not perform planar, gravity supported, reaching movements because of severe motor deficits, spasticity or pain were excluded (no *a priori* cut off was applied). Other exclusions criteria were: presence of hemianopsia, cerebellar ataxia, severe neglect, severe psychiatric condition, severe sensory aphasia, or cognitive deficits precluding the compliance with the tasks demands, spinal infarction, peripheral neuropathy, previous head trauma.

Data of 13 patients were collected in the Neuropsychology and Neurorehabilitation unit of the Lausanne University Hospital. Seven patients were recruited in the neurorehabilitation clinic “Villa Beretta” of the Valduce Institute.

We also recruited 35 right-handed healthy age-matched controls. Subjects with a history of neurological or psychiatric diseases were excluded from the study.

Demographic and clinical data about participants are summarized in Tables 1 and S1.

This study was approved by approved by the Ethical Committee of the Vaud canton, Switzerland (CER-VD, project identifier: 2017-01588), and by the Ethical Committee of the Province of Lecco Como and Sondrio (48/2016), Italy, and was conducted in accordance with the guidelines of the ethical committees and the Declaration of Helsinki.

METHOD DETAILS

Clinical assessment of stroke patients

Motor deficits and spasticity were assessed by using the Motricity index[50] (upper and lower limb) and Ashworth Modified scale[51] (thumb, wrist, elbow, shoulder), respectively. Sensory deficits were assessed using the items related to tactile sensations of the Nottingham sensory assessment[52] (palm). The ability to discriminate the upward or downward position of the finger was used as a screening for the presence of proprioceptive deficits.[53] Lateralized attentional deficits were assessed through the bell cancellation test and tactile extinction.[54]

Overt BO alterations were clinically assessed as follows: the examiner lifted the upper limb and moved the patient’s hand and forearm into the ipsilesional hemispace. The patient was then asked, “Whose hand is this?”. The patient was considered to have a clinically overt body ownership alteration (i.e., somatoparaphrenia, limb misidentification) if the ownership was incorrectly reported.

Experimental procedure

The experiment consisted of three tasks conducted in VR. A visuo-proprioceptive disparity (VPD) reaching task was used to measure visuo-proprioceptive integration and BO. The other two tasks were used to independently assess unisensory functions, which we hypothesize may explain alterations in visuo-proprioceptive integration and BO: a proprioceptive judgment (PJ) task, measuring proprioceptive precision, and a midline judgment (MJ) task, measuring visuo-spatial precision. These tasks are described in the following paragraphs. Patients performed the VPD and PJ tasks with both the intact and affected limb, in randomized order.

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

VPD task

During the VPD task participants were requested to sit in front of a chest-height table, with their arm placed in front of them. Participants wore a head-mounted display (HMD) and held a motion controller in the tested hand. Participants' real hand was hidden, and a realistic hand was displayed in VR using the tracking of the motion controller. Participants were asked to make reaching movements to a target presented in VR (white spheres with 3 cm diameter) from a fixed starting position. The starting position was a sphere of 15 cm diameter, 15 cm away from the participant's sternum. Target positions were arranged on an arc centered on the starting position. The arc radius was set according to each participant's maximum reaching distance. In each trial, the spatial congruency between the position of the real hand of the participant and the virtual hand was manipulated, by randomly introducing one out of 7 possible disparities, i.e.,: 0° (no disparity), ±13.3°, ±26.6° or ±40° (+: clockwise; −: counter-clockwise) (Figures 1A and Video S1). The task consisted of three experimental blocks. In the first two blocks, 7 targets were equally spaced between −45 and 45° from the midline. In each block, one trial was collected for each combination of target and disparity (7 disparities x 7 targets x 2 blocks = 98 trials in total). In the third block, subjective ratings of ownership were collected. To limit the experiment duration, 5 disparities, equally spaced between −40° and 40° were used (35 trials in total). Each block lasted approximately 5 min.

Participants had to place their hand on the starting position to initiate a trial. At the beginning of the trial, the virtual hand was rotated by one of the possible disparity angles during 1 s, and the target appeared. The mismatch between the real and the virtual hand was maintained until the end of the trial. After 1.5 s, the target was turned green as a "go" signal. Movement of the hand outside the resting position at any time before the "go" cue automatically restarted the trial. Participants were instructed to reach the target with their real (proprioceptive) hand and return to the resting position ending the trial. Participants received no feedback about their reaching performance.

In the third block participants were requested to verbally report their subjective feeling of ownership for the virtual hand at the end of each reaching movement, evaluating their agreement with the statement "I felt as if the virtual hand was my hand" on a scale from 1 to 10. Values were manually recorded by the experimenter.

PJ task

The set-up of the PJ task, aiming at evaluating proprioceptive precision, was similar to the VPD (Figure 1D, upper figure). Participants' real hand was not displayed in VR. The experimenter passively moved participants' real hand to one out of 5 randomized target positions arranged at 0°, ±10, ±20, ±40° with respect to participants' sternum on an arc with radius equal to each participant maximum reaching distance. A two forced-choice converging algorithm was used to find the position in which the participants perceived their hand. At the beginning of each trial, a virtual hand was displayed at +30° (right) or −30° (left, randomized) with respect to participants' real hand. Participants then reported whether they felt that the displayed hand was located to the left or right of their real, unseen hand. In the following step, the position of the virtual hand was moved halving the angle and mirroring it in the opposite direction with respect to participants' previous answer. In five steps, the algorithm converged towards the angle at which participants had an equal probability of reporting left or right. The proprioceptive estimation was computed as the intermediate hand position between the last displayed position and the next position that would have been displayed by the algorithm according to the participant's last answer. Each target position was tested 4 times in randomized order, for a total of 28 trials.

MJ task

In the MJ task (Figure 1D, lower figure), aiming at evaluating the visuo-spatial precision, participants were asked to sit on a chair keeping their head and trunk aligned while wearing an HMD. On each trial, a white sphere with 3 cm diameter moved horizontally across participants' field of view at a speed of 10°/s, starting from ±45°, ±40°, ±35°, and ±30° from the body midline, on an arc centered on participants' sternum, with a radius equal to their maximum reaching distance, as in the VPD. Participants were asked to report when they felt that the visual cue was aligned with the midline of their body by pressing a response button, with the possibility to subsequently ask the experimenter to manually adjust the judgment. The starting positions of the visual cue were randomized across trials. 24 trials in total were collected.

The MJ and PJ were always performed after the VPD in randomized order. All tasks were administered via the Oculus Rift S VR system, comprising an Oculus Rift S head-mounted display (HMD) and two Oculus Touch, or motion controllers. A custom-made software programmed in Unity was used for the tasks.

QUANTIFICATION AND STATISTICAL ANALYSIS

Key features of the BCI model and model predictions

In this section we will briefly describe the key features of the BCI model and model predictions and how these apply to the analysis of the behavioral results. More details about the BCI model can be found in the supplemental information (Method S1).

Even in healthy subjects and in everyday conditions, stochastic noise in neural encoding makes inputs in the different sensory channels (e.g.,: visual and proprioceptive hand position estimates) fluctuate randomly. Bayesian probability theory dictates that, in order to use such noisy information in the best possible (optimal) way, the brain should integrate the different unimodal inputs

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

according to their reliability, so that more reliable sensory modalities contribute more to the final estimate (Figure 1E). Mathematically, an optimal brain should estimate hand position based on visual and proprioceptive inputs as follows:

$$x_{FF} = x_v \frac{\frac{1}{\sigma_v^2}}{\frac{1}{\sigma_p^2}+\frac{1}{\sigma_v^2}} + x_p \frac{\frac{1}{\sigma_p^2}}{\frac{1}{\sigma_p^2}+\frac{1}{\sigma_v^2}} \qquad \text{(Equation 1)}$$

Here X_{FF} is the final estimate of hand position (i.e.,: the position used to calibrate reaching movements in the VPD), and x_v and x_p the unimodal (and noisy) position estimates. σ_v and σ_p denote respectively the precision of visual and proprioceptive position estimates (i.e.,: the typical error in unimodal position estimates).

The estimate in Equation 1 is only correct if there is absolute certainty that the visual and the proprioceptive information originate from the same object, i.e., participant's hand. Thus, x_{FF} is named forced fusion estimate. In realistic situations, the brain needs to first determine which object (if any) within the visual field corresponds to one's hand, and should then become x_v in Equation 1 with a given degree of certainty. In Bayesian causal inference (BCI) models, this is also resolved by the brain by statistically inferring the probability (P_{com}) that an object (i.e., the virtual hand) is one's own hand. P_{com} is assumed to be the mathematical counterpart of body ownership. The estimate in Equation 1 is then refined by weighting the visual estimate not only by its precision, but by the effective probability that such estimate corresponds to one's own hand.

$$x_{BCI} = P_{com} x_{FF} + (1 - P_{com}) x_p \qquad \text{(Equation 2)}$$

Where x_{BCI} is the final estimate of hand position according to the probabilistic causal inference model used here. x_{BCI} reduces to the forced fusion estimate x_{FF} when P_{com} is 1 (certainty of ownership) and to the purely proprioceptive estimate x_p when P_{com} is 0 (certainty of no ownership, see Figure 1E).

P_{com} is a function of the spatial disparity between its location and the proprioceptively perceived hand location:

$$P_{com} = f(|x_v - x_p|) \qquad \text{(Equation 3)}$$

Such function is complex, and its derivation is described in detail in Methods S1, but it has three key characteristics. First, it depends only on visuo-proprioceptive disparity ($|x_v\text{-}x_p|$). Second, P_{com} is maximal at zero visuo-proprioceptive disparity and decreases as disparity increases. Third, the less vision and/or proprioception are precise, the larger the disparity will be needed by the brain to detect an incongruence. Hence, if visuo-spatial and/or proprioceptive precision are reduced, P_{com} will decrease less rapidly as disparity increases, leading to embody the virtual hand up to larger levels of discrepancy. Concurrently, such reduced capacity to detect incongruences would also lead to lower values of P_{com} when the discrepancy is low, translating to a reduced ownership experience for one's own hand in real life.

The above-described framework can be readily transposed to the VPD task to obtain quantitative predictions of reaching error and subjective ownership depending on visuo-proprioceptive disparity. When reaching towards a target in the VPD task, subjects combine spatial information from proprioception and from the (incongruent) virtual hand, and the final reached position is a weighted average between pure visual and pure proprioceptive guidance. The relative weight of vision and proprioception depends on the probability computed by the brain that the virtual hand is one's own (P_{com}). Higher values of P_{com} imply more subjective ownership towards the virtual hand, more weight attributed to the virtual hand in guiding the reaching movement, and thus larger reaching bias (error/disparity; pure proprioceptive guidance as "zero bias"). Thus, P_{com} values can be inferred from reaching errors by computing the relative weight of vision and proprioception, which is proportional to the reaching bias. It is important to notice that the parameter P_{com} is not directly calculated from the behavioral data, whereas it is derived from fitting the BCI model to such data. We will call these inferred P_{com} values "behavioral ownership" and refer to explicitly reported ownership ratings as "subjective ownership. P_{com} decreases with increasing incongruence, so that the relative weight attributed to the virtual hand is high at small values of disparity and gradually decreases with incongruence. This yields the typical sinusoidal shape of reaching error (green line in Figure 1B) and a constant decrease of reaching bias as a function of increasing disparity (dashed line in Figure 1B). Furthermore, Equation 3 implies that, if the spatial precision of vision and/or proprioception is reduced (e.g., by stroke), P_{com} values will start decreasing at larger disparities. As a consequence, we expect subjects with greater unisensory impairment to keep feeling ownership for the virtual hand and using it to guide reaching up to higher levels of disparity (Figure 1F).

Behavioral analyses

We first aimed at demonstrating that a higher weight attributed to the virtual hand was associated with a higher subjective ownership in the VPD task. We analyzed this relation within participants, by submitting ownership ratings and the absolute value of reaching errors to a linear mixed model. We then wanted to demonstrate that this relation can be observed, even at a fixed disparity, at the individual trial level. To do so, we computed the "residual" subjective ownership, by subtracting from each rating the average rating at the same disparity. Similarly, residual reaching errors were obtained by subtracting from the reaching error its average value for each disparity. To indicate larger visual weight with positive residual drift and vice versa, residual drift values were multiplied by the sign of the spatial disparity. Zero disparity values were excluded as they yield no meaningful information in this analysis. Then, we tested whether residual error and ownership values were correlated by means of a linear mixed model. We then combined behavioral data with our computational model to assess alterations in multisensory integration and ownership after stroke. In stroke patients, the most important implication of this model, as per Equation 3, is that a high level of P_{com} and subjective ownership (observed as strong visual weight and reaching bias) will persist until larger disparities when proprioception and/or vision are less precise, as consequence of a brain lesion. To quantify this, we first used the probabilistic causal inference model to infer P_{com} from reaching errors as sketched in the previous section (see Methods S1 for details). Then, we fitted a Gaussian function to both P_{com} values and subjective ownership ratings and extracted its standard deviation to quantify the behavioral (σ_{Pcom}) and subjective ($\sigma_{ratings}$) "windows" for ownership. These values correspond to the tolerated spatial disparity before a sharp decrease of reaching errors and ownership ratings. Fits from the causal inference model further provide estimates of the proprioceptive and visual precisions that would be expected based on reaching errors in the VPD tasks, assuming the model is valid. These values were correlated with the values of unisensory precisions measured through unisensory tasks (σ_v, MJ task; σ_p, PJ task), further validating the BCI model (see Supplementary Materials).

To assess alterations in body ownership both at the behavioral and subjective level, we first compared the σ_{Pcom} and $\sigma_{ratings}$ of the affected and intact side using paired t-tests. This allows controlling for a-specific effects (e.g., general cognitive level, fatigue, motivation). Each side was additionally compared with the σ_{Pcom} and $\sigma_{ratings}$ of healthy controls using simple t-tests. We then aimed at investigating the link between these alterations and the feeling of disownership for the affected limb, often spontaneously reported by patients with clinically overt BO alterations. We took the virtual hand aligned with the real one (disparity = 0°) as a proxy of patient's own hand in natural situations. We then correlated the probability of multisensory integration (P_{com}) and ownership (average ownership rating) at 0° disparity with BO alterations, as measured by the difference of σ_{Pcom} and $\sigma_{ratings}$ between the affected and intact arm of each patient ($\Delta\sigma_{Pcom}$ and $\Delta\sigma_{ratings}$).

Finally, we put these results in relation to the values of visuo-spatial and proprioceptive precision, quantified as the standard deviations of errors in the MJ and PJ tasks (see Supplementary Materials for details). To investigate the proprioceptive deficit, we performed a paired t-test to compare the proprioceptive precision σ_p of the intact and affected arm, and then compared each side with the σ_p of healthy controls using simple t-tests. For visuo-spatial precision, we used t-test to compare the measured visuo-spatial precision σ_v in stroke patients and the σ_v of the healthy controls. Then, we performed a Pearson correlation test for the relation between unisensory precisions (σ_v and σ_p), and behavioral (σ_{Pcom}) and subjective ownership ($\sigma_{ratings}$) scores extracted from the multisensory VPD task.

Besides low-level unisensory impairment, multisensory integration and BO alterations may further depend on deficits in the multisensory integration process itself. These higher-level multisensory deficits may be observed as deviations from the optimal behavior predicted by the BCI model. In patients with lateralised neurological deficits, a suboptimality on the affected side may be present when a significant deviation from the behavior of the intact side is observed, which is not otherwise explained by a difference in unisensory precision, i.e., by the unisensory deficit. Such a comparison can allow to isolate a potential sub-optimality from the effects of other not specific deficits (e.g., general cognitive level, fatigue, motivation which would impact equally the results for both limbs). For this reason, in the following analyses we focused on the difference of the σ_{Pcom} and $\sigma_{ratings}$ between the affected and intact arm of each patient, namely: $\Delta\sigma_{Pcom} = \sigma_{Pcom\ (intact)} - \sigma_{Pcom\ (affected)}$ and $\Delta\sigma_{ratings} = \sigma_{ratings\ (intact)} - \sigma_{ratings\ (affected)}$. To remove variability simply explained by unisensory deficits, and thus isolate sub-optimal integration deficits, we further regressed out the effect of the unisensory impairment, calculated as the difference between the proprioceptive precision of the affected and the intact arm, $\Delta\sigma_p$.

Lesion analysis

Neuroimaging data were collected from the database of the Lausanne University Hospital and the neurorehabilitation clinic "Villa Beretta" of the Valduce Institute. Lesions were manually segmented on structural images (T1, T2, Flair, CT). Structural images and lesion masks were normalized to the standard MNI template using SPM.

We used a publicly available diffusion MRI tractography atlas.[33] The tractography atlas was constructed using high-angular resolution diffusion MRI data (b-values: 990, 1985, and 2980 s/mm^2; diffusion sampling directions: 90, 90, and 90; in-plane resolution: 1.25mm) from 1064 Human Connectome Project participants, reconstructed in MNI space using Q-space diffeomorphic reconstruction.[33] The resulting spin distribution functions (SDFs) where averaged to obtain population-level streamline trajectories. A deterministic fiber tracking was then performed to extract 500,000 streamline trajectories. We defined the disconnectivity profile of each subject by extracting from the tractography template all streamlines intersecting the lesion, using DSI studio (https://dsi-studio.labsolver.org).

We conducted a lesion analysis to identify the neural correlates of behavioral and subjective body ownership alterations, as measured by the difference of the σ_{Pcom} and $\sigma_{ratings}$ of the affected and intact arm of each patient ($\Delta\sigma_{Pcom} = \sigma_{Pcom\ (intact)} - \sigma_{Pcom\ (affected)}$ and $\Delta\sigma_{ratings} = \sigma_{ratings\ (intact)} - \sigma_{ratings\ (affected)}$). This analysis allowed us to isolate higher-order multisensory integration deficits (i.e., suboptimality) from the effect of non-specific cognitive factors (see discussion in the previous section). All the analyses were conducted both on the original images and after flipping the lesioned side of all the patient on the same (right) side.

We first performed a voxel-based lesion-symptom mapping (VLSM) on brain lesions using the software NiiStat (https://www.nitrc.org/projects/niistat). We ran the analysis on both $\Delta\sigma_{Pcom}$ and $\Delta\sigma_{rating}$ using a general linear model (least squares' linear regression) with lesion volume as nuisance regressor, applying FDR correction for multiple comparisons with a statistical threshold of $p < 0.05$.

Please cite this article in press as: Mastria et al., Body ownership alterations in stroke emerge from reduced proprioceptive precision and damage to the frontoparietal network, Med (2024), https://doi.org/10.1016/j.medj.2024.10.013

We then moved to investigate the relation between body ownership alterations and disruption of brain connectivity induced by the focal lesion. In a first step, we performed a ROI-based disconnectivity analysis using ROIs of the seven brain networks identified in Yeo et al..[34] We extracted the number of streamlines that bilaterally terminated (i.e., began and ended) within each pair of ROIs. We then correlated the total number of disconnected streamlines in each network to $\Delta\sigma_{Pcom}$ and $\Delta\sigma_{ratings}$, after accounting for the effect of lesion volume. To exclude that the observed correlations were fully explained by unisensory impairments, and confirm they were related to a deficit in multisensory processing, we repeated the same analysis while regressing out the effect of the unisensory impairment calculated as the difference between the proprioceptive precision of the intact and the affected arm ($\Delta\sigma_p = \sigma_{p\ affected} - \sigma_{p\ intact}$).

In a second step, we performed a VLSM focused on the networks whose damage was found to correlate with $\Delta\sigma_{Pcom}$ or $\Delta\sigma_{ratings}$ at the ROI-based disconnectivity analysis. To generate the mask, the streamlines of the tractography atlas connecting ROIs belonging to the selected networks were transformed into binary ROIs. VLSM was performed on disconnectivity maps obtained by transforming into binary ROIs the disconnected streamlines of each patient. We run the analysis on both $\Delta\sigma_{Pcom}$ and $\Delta\sigma_{rating}$ using a general linear model (least squares' linear regression) with lesion volume and $\Delta\sigma_p$ as nuisance regressors, applying FDR correction for multiple comparisons with a statistical threshold of $p < 0.05$. Streamlines of the selected networks intersecting the significant clusters were recognized using an atlas of white matter tracts.[33] Finally, terminative voxels were used to identify brain regions disconnected by the lesion.