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Gesture meaning modulates the neural correlates of effector-specific imitation deficits in left hemisphere stroke

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ABSTRACT

Background: Previous studies on left hemisphere (LH) stroke patients reported effector-specific (hand, fingers, bucco-facial) differences in imitation performance. Furthermore, imitation performance differed between meaningless (ML) and meaningful (MF) gestures. Recent work suggests that a gesture's meaning impacts the body-part specificity of gesture imitation.
Methods: We tested the hypothesis that the gesture's meaning (ML vs MF) affects the lesion correlates of effector-specific imitation deficits (here: bucco-facial vs arm/hand gestures) using behavioural data and support vector regression-based lesion-symptom mapping (SVR-LSM) in a large sample of 194 sub-acute LH stroke patients.
Results: Behavioural data revealed a significant interaction between the effector used for imitation and the meaning of the imitated gesture. SVR-LSM analyses revealed shared lesion correlates for impaired imitation independent of effector or gesture meaning in the left supramarginal (SMG) and superior temporal gyri (STG). Besides, within the territory of the left middle cerebral artery, impaired imitation of bucco-facial gestures was associated with more anterior lesions, while arm/hand imitation deficits were associated with more posterior lesions. MF gestures were specifically associated with lesions in the left inferior frontal gyrus and the left insular region. Notably, an interaction of effector-specificity and gesture meaning was also present at the lesion level: A more pronounced difference in imitation performance between the effectors for ML (versus MF) gestures was associated with left-hemispheric lesions in the STG, SMG, putamen, precentral gyrus and white matter tracts.
Conclusion: The current behavioural data show that ML gestures are particularly sensitive in assessing effector-specific imitation deficits in LH stroke patients. Moreover, a gesture's meaning modulated the effector-specific lesion correlates of bucco-facial and arm/hand gesture imitation. Hence, it is crucial to consider gesture meaning in apraxia assessments.

1. Introduction

Besides deficits in actual and pantomimed object use, impaired gesture imitation is a core symptom in patients suffering from apraxia, a (motor-)cognitive disorder that occurs predominantly after lesions to the left-lateralised praxis networks often caused by stroke (Schmidt & Weiss, 2022). Notably, apraxic imitation deficits can impact different effectors, i.e., body parts performing a gesture, such as the arm/hand and fingers (limb apraxia; Goldenberg, 1996) or the mouth and face (bucco-facial apraxia; Scandola et al., 2021).

For limb apraxia, previous lesion studies have reported distinct neural substrates for imitating hand versus finger gestures (Dovern et al., 2011; Goldenberg, 2001; Goldenberg & Karnath, 2006; Goldenberg & Randerath, 2015), suggesting effector-specific neural correlates of imitation deficits. Deficient imitation of hand gestures was associated with posterior lesions, including the left inferior parietal lobule (IPL) and temporo-parieto-occipital junction, whereas impaired finger posture imitation was associated with anterior lesions, including the inferior frontal gyrus (IFG; Goldenberg & Karnath, 2006).

So far, studies on bucco-facial apraxia in left hemisphere (LH) stroke

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patients remain scarce. Using qualitative lesion analyses, Raade and colleagues investigated the neuroanatomical relationship between bucco-facial and limb apraxia. They identified an association between deficits in performing (bucco-) facial gestures and lesions of the striatum, the IFG, and perisylvian central and insular regions. In contrast, that study found no specific lesion correlates for limb apraxia (Raade et al., 1991). Recently, partial neuroanatomical distinctions have been reported for bucco-facial and limb apraxia (Scandola et al., 2021). Furthermore, principal component analysis of behavioural and lesion data of 91 LH stroke patients revealed differential lesion correlates for the imitation of bucco-facial gestures versus arm/hand and finger gestures (Schmidt et al., 2022). In this study, lesions affecting the left basal ganglia and white matter tracts were linked to imitating bucco-facial gestures, while lesions affecting the left IPL and the precentral gyrus were associated with imitating arm/hand gestures. Taken together, these studies support the notion of (at least partly) separable motor-cognitive (and neural) mechanisms underlying the imitation of bucco-facial and limb gestures (Cubelli, 2017; Raade et al., 1991).

Besides, the meaning of a gesture modulates imitation performance. Consistent with the two-route model of imitation (Tessari et al., 2007), behavioural dissociations were found between LH stroke patients' imitation of meaningless (ML) versus meaningful (MF) gestures (Achilles et al., 2016; Achilles et al., 2019). Lesion data suggest that the imitation of ML gestures draws upon the dorso-dorsal stream, while MF gesture imitation relies on the ventro-dorsal stream (Achilles et al., 2019; Hoeren et al., 2014). Deficits in MF gesture imitation were further associated with lesions in the left IFG (Weiss et al., 2016).

Notably, recent work indicates that the meaning of a gesture influences the effector-specificity of gesture imitation in LH stroke patients. While performance differences have been found for the imitation of ML hand versus finger gestures (Goldenberg & Karnath, 2006; Tessari et al., 2021), the imitation of MF gestures did not reveal effector-specific dissociations (Tessari et al., 2021).

However, whether a gesture's meaning modulates effector-specific differences in the imitation of bucco-facial versus limb gestures remains unclear. Therefore, we analysed behavioural and lesion data in a large cohort of LH stroke patients (n = 194). In particular, support vector regression-based lesion-symptom mapping (SVR-LSM) was used to characterise the neural correlates of effector-specific imitation deficits (bucco-facial versus limb gestures) and their putative modulation by gesture meaning (ML versus MF gestures).

2. Material and methods

2.1. Patient sample

Bucco-facial and arm/hand gesture imitation scores and lesion data were retrospectively analysed in 194 patients who had suffered a unilateral left hemispheric (LH) ischaemic stroke. Only right-handed patients with a neuropsychological assessment within three months after stroke, i.e., in the sub-acute phase (Bernhardt et al., 2017), were included. Recruitment sites were the Department of Neurology of the University Hospital Cologne and three neurological rehabilitation centres nearby.

Patients had provided written informed consent to participate in the original studies on motor cognition/apraxia (Ant et al., 2019; Binder et al., 2017; Dafsari et al., 2019; Dovern et al., 2016; Kusch, Gillessen, et al., 2018; Kusch, Schmidt, et al., 2018). These studies contributed 156 stroke patients to the current sample. The remaining 38 stroke patients were derived from a running clinical trial (Kleineberg et al., 2020). The studies were conducted under the Declaration of Helsinki and approved by the local ethics committee of the Medical Faculty of the University of Cologne. All patients had additionally given consent to use their neuropsychological and clinical imaging data. The ethics committee of the Medical Faculty of the University of Cologne approved retrospective data analyses.

2.2. Neuropsychological testing procedure

Apraxia testing was conducted using the Cologne Apraxia Screening (KAS), a standardised, validated diagnostic tool for apraxia (Weiss et al., 2013). The KAS is divided into four subtests assessing (bucco-facial and arm/hand) object-use pantomime and (bucco-facial and arm/hand) imitation performance. Performance of the left, ipsilesional hand is tested with photographs of objects (pantomime tasks) and a woman performing gestures (imitation tasks). The maximum score of the KAS is 80 points (20 points per subtest). Patients scoring 76 points or less are considered apraxic. Besides the published manual (Weiss et al., 2013), please see Dovern et al. (2012) and Schmidt et al. (2022) for further details on the KAS, including its quality criteria and testing procedure.

In the current study, we focused on the imitation performance of bucco-facial and arm/hand gestures assessed with the imitation subtests of the KAS. Here, the patient is asked to reproduce bucco-facial gestures (e.g., pulling in cheeks, sticking out the tongue) or arm/hand gestures (e.g., putting the thumb on the forehead, wiping the mouth), which are presented on photographs showing a female subject performing the gestures (see Fig. 1A for example stimuli of the KAS). For the assessment of the arm/hand gestures, the stroke patients were instructed to use their ipsilesional left hand. For each gesture, the maximum score is four points, achieved by the correct imitation on the first try. If the imitation is incorrect, the photo is shown again, and the patient is asked to repeat the task. Two points are given for correct imitation on this second attempt and no point for an erroneous second try. The bucco-facial and arm/hand imitation subtests comprise five items each: two items are meaningless (ML), and three are meaningful (MF). Given that the maximum score of each imitation item is four points and each of the subtests of the KAS consists of five items, the maximum score for each subtest is 20 points.

Additionally, language function was assessed using the short version of the aphasia check list (ACL-K), which consists of the following four parts: a reading-aloud task, a colour-figure test addressing auditory comprehension, a supermarket task probing semantic verbal fluency, and a rating of the patient's verbal communication skills by the examiner. The maximum score of the ACL-K is 40 points; patients scoring less than 33 points are classified as aphasic with the categories mild (26–43 points), moderate (15–25 points) or severe (14 or fewer points) aphasia (Kalbe et al., 2002; Kalbe et al., 2005).

The neuropsychological testing was conducted by specifically trained neuropsychologists or physicians from the University Hospital Cologne; 11 examiners were involved in assessing the patient cohort. Note that the KAS has a high interrater reliability (rho = 0.907 for the KAS total score; rho = 0.847 for the KAS subtest imitation of gestures, Weiss et al., 2013).

2.3. Behavioural data analysis

Statistical analyses of clinical and neuropsychological data were performed using IBM SPSS Statistics (Statistical Package for the Social Sciences, version 25, SPSS Inc., Chicago, Illinois, USA), and the linear mixed-effects model analysis was conducted in JASP (Jeffreys's Amazing Statistics Program, version 0.14.1).

In order to test for differential modulation of effector-specific imitation deficits by gesture meaning, each of the mean scores of the two ML bucco-facial and arm/hand gestures and the three MF bucco-facial and arm/hand gestures was analysed by a linear mixed-effects model approach with SUBJECT considered as a random factor and EFFECTOR and MEANING as fixed factors. Besides random intercepts, we added random slopes for effector and meaning to the model to better control for type I error. As our model fit was singular, we removed random slopes of the factor meaning to reduce the model's random effect structure.

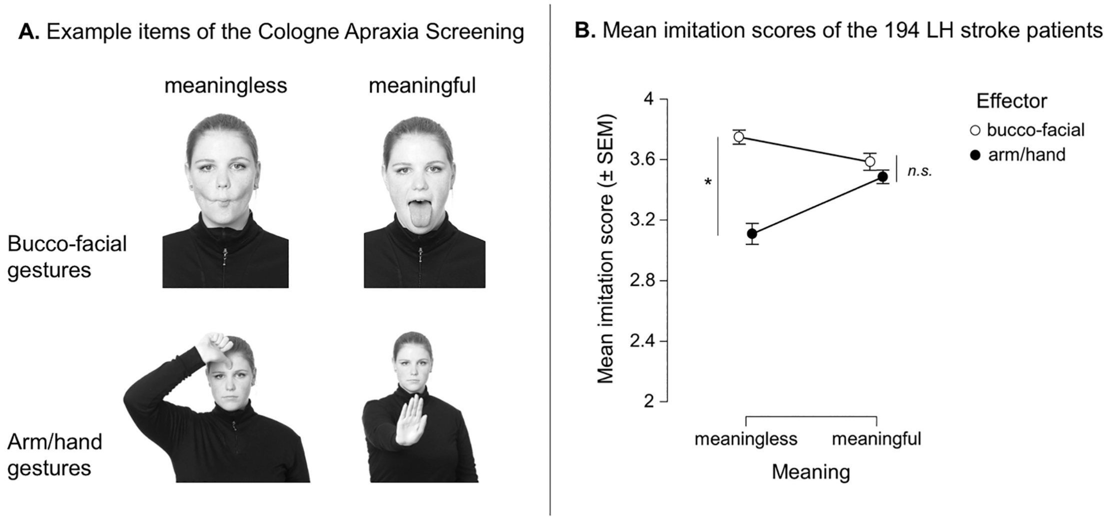

Fig. 1. Stimuli of the imitation subtests of the Cologne Apraxia Screening (KAS) and behavioural results. **A.** Shown is one example of the meaningless and meaningful bucco-facial and arm/hand gesture imitation tasks. **B.** Mean imitation scores as a function of the effectors (bucco-facial and arm/hand) and the gesture's meaning (meaningless and meaningful) in the 194 left hemisphere stroke patients. Error bars indicate the standard error of the mean (SEM). LH = left hemisphere, * = $p <$ 0.001, n.s. = non-significant.

2.4. *Lesion delineation and support vector regression-based lesion-symptom mapping (SVR-LSM)*

The patients' clinical MRI (n = 140) or CT (n = 54) scans were used for lesion mapping. Lesions were manually delineated (de Haan & Karnath, 2018) on axial slices of a T1-weighted template MRI scan (ch2.nii) from the Montreal Neurological Institute (MNI) with a 1 mm × 1 mm in-plane resolution using the software package MRIcron (https://www.nitrc.org/projects/mricron). Lesions were mapped in steps of 5 mm in MNI space onto the axial slices of the ch2-template that were identical or best matched the axial slices of each patient's MRI or CT. Two experienced examiners had to jointly agree upon each individual's exact lesion location and extent.

The lesion maps then entered support vector regression-based lesion-symptom mapping (SVR-LSM) analyses to identify brain regions statistically associated with the specific imitation deficits of the LH stroke patients. SVR-LSM was performed in Matlab 9.8 (2020a) using the SVR-LSM toolbox (v0.15, version 2019–06-16) developed by DeMarco and Turkeltaub (2018) based on the approach of Zhang et al. (2014). SVR-LSM is a multivariate analysis technique that uses a machine learning-based multiple regression method to determine the association between lesioned voxels and behavioural deficits while considering the lesion status of all voxels simultaneously. Only voxels that were lesioned in at least 19 patients, i.e., in ≥ 10 % of the 194 patients (see Fig. 2), were considered in the statistical lesion analyses to ensure that results were generalisable and not biased by voxels affected in only a few patients (Sperber & Karnath, 2017). Lesion size was controlled for by regressing it out of both the behavioural scores and lesion data (DeMarco & Turkeltaub, 2018). SVR-beta maps were generated using fivefold cross-validation, in which for each fold a unique subset of the lesion and behavioural data from 80 % of the patients was used to train the SVR model and the remaining 20 % of patients' lesions and behavioural data were used to test the model. The resulting five maps of beta values were averaged to obtain a final average map of voxelwise beta values. Voxelwise statistical significance was determined by permutation testing in which the behavioural data were randomly assigned to a lesion map using 10,000 iterations. Voxel-wise *Z*-scores were then computed for the actual data (beta values) in relation to the mean and standard deviation of the permutation-based null distributions of beta values; the resulting SVR map was set to a critical threshold of $p < 0.05$. We applied a minimum cluster extent threshold of 100 contiguous voxels to further restrict the permutation-thresholded SVR maps.

2.5. *Analysis of lesion data*

We assessed the lesion-deficit associations for bucco-facial and arm/hand gesture imitation (independent of gesture meaning) by subjecting the mean scores of the KAS subtests "imitation bucco-facial" and

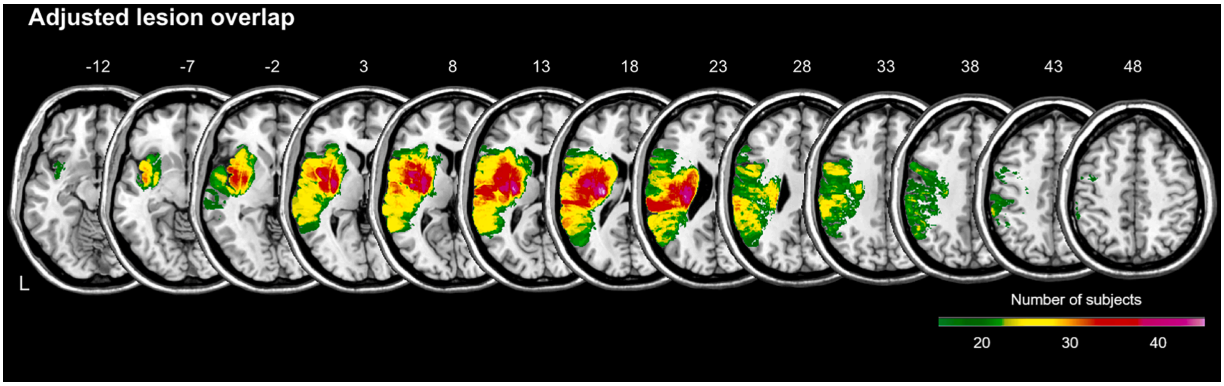

Fig. 2. Adjusted lesion overlap of the 194 left hemisphere stroke patients. Only voxels lesioned in at least 10 % of the patients and tested in the statistical SVR-LSM analyses are displayed. Colour shades represent the increasing number of overlapping lesions. Axial slices with MNI z-coordinates from −12 to +48 are shown.

"imitation arm/hand" to separate SVR-LSM analyses. The difference scores between bucco-facial and arm/hand gesture imitation were used in further SVR-LSM analyses to test for lesions associated with effector-specific imitation deficits.

To reveal the lesion correlates of deficits in imitating ML and MF gestures (independent of effector), we performed separate SVR-LSM analyses with the mean scores of the four ML bucco-facial and arm/hand gestures and the mean scores of the six MF bucco-facial and arm/hand gestures as well as with the difference scores between the ML and MF gestures. The difference scores were used to test for lesions specific to ML versus MF gesture imitation (and vice versa).

Finally, we computed a difference score representing the interaction term to explore the lesion correlates of the interaction between effector-specificity and gesture meaning. Since the patient cohort achieved higher scores when imitating (ML and MF) bucco-facial gestures (compared to arm/hand gestures, see Results section 3.2 and Fig. 1B, *cf.* also Kusch, Schmidt, et al., 2018; Raade et al., 1991), the interaction term was calculated as the difference of the difference between the mean imitation scores for ML bucco-facial vs ML arm/hand gestures and the difference of the mean imitation scores for MF bucco-facial vs MF arm/hand gestures: Interaction term = (ML bucco-facial gestures $_{\text{mean score}}$ − ML arm/hand gestures $_{\text{mean score}}$) − (MF bucco-facial gestures $_{\text{mean score}}$ − MF arm/hand gestures $_{\text{mean score}}$). The resulting interaction score was then entered into an SVR-LSM analysis.

The brain regions comprising significant voxels were identified based on the Automated Anatomical Labeling (AAL; Tzourio-Mazoyer et al., 2002) and Johns Hopkins University (JHU; Faria et al., 2012) atlas templates implemented in MRIcron. We report the *Z*-value of a significant peak voxel and the corresponding coordinates in MNI space for each lesioned cluster.

3. Results

3.1. Patient cohort

Of the 194 patients investigated, 65 were female (33.5 %). The mean age ± standard deviation (SD) was 63.4 ± 13.0 years. All patients were right-handed and suffered from a unilateral ischaemic LH stroke. Neuropsychological testing was performed within three months after the stroke, i.e., in the sub-acute phase (Bernhardt et al., 2017), with a mean time post-stroke ±SD of 21.9 ± 17.7 days.

Based on the overall KAS performance (see section 2.2), 102 of the 194 LH stroke patients (52.6 %) were apraxic. Aphasia assessment was conducted in 191 of the 194 patients, of whom 123 patients (64.4 %) were aphasic according to the ACL-K. Of these, 50 patients had mild aphasia, 32 had moderate aphasia, and 41 had severe aphasia. As expected (Weiss et al., 2016), apraxia was significantly associated with aphasia (χ^2 (1) = 40.26, $p < 0.001$). Concurrent aphasia and apraxia were present in 45 % (86/191) of the patients. Thus, 85 % of the apraxic patients suffered from co-morbid aphasia (86/101 apraxic patients). In total, 37 patients were aphasic but non-apraxic (19 %), while apraxia without aphasia was found in 15 patients (8 %).

3.2. Imitation performance as a function of the effector and gesture meaning

The linear mixed-effects model revealed a significant main effect of EFFECTOR (bucco-facial vs arm/hand; [$F_{(1,193)} = 27.42, p < 0.001$]) and MEANING (ML vs MF; [$F(_{1,386}) = 5.38$, $p = 0.021$]). Overall, the LH stroke patients imitated bucco-facial gestures better than arm/hand gestures, and MF gestures were imitated better than ML gestures. Crucially, the interaction of EFFECTOR × MEANING was also significant [$F(_{1,386}) = 34.41$, $p < 0.001$]. Post-hoc t-tests revealed that the difference in imitation performance between the effectors was significant for ML gestures, with ML bucco-facial gestures imitated better than ML arm/hand gestures [$t_{(193)} = 6.88, p < 0.001$]. In contrast, there was no significant difference in imitation performance between the effectors for MF gestures [$t_{(193)} = 1.33$, $p = 0.185$; Fig. 1B].

3.3. Lesion overlap

The adjusted lesion overlap comprising only those voxels that were lesioned in at least 10 % of the LH stroke patient sample (n ≥ 19/194) and thus entered the multivariate statistical SVR-LSM analyses (see section 2.4) is shown in Fig. 2. The lesioned brain regions were within the left middle cerebral artery (MCA) territory, with the most substantial lesion overlap observed in the putamen and adjacent white matter tracts. Note that anterior (inferior frontal) and posterior (superior temporal, inferior parietal) brain regions were affected in a similar number of patients.

3.4. Lesion correlates of imitation deficits for the effectors (independent of gesture meaning)

The results of the SVR-LSM analyses with the overall (mean) scores of the bucco-facial and arm/hand gesture imitation subtests and the difference scores between bucco-facial and arm/hand gesture imitation are shown in Fig. 3. Please see Table 1 for the MNI coordinates of the peak voxel and the respective (maximum) *Z*-values according to the statistical lesion-deficit association strength, shown in descending order. Note that more negative *Z*-values indicate a more robust lesion-symptom association and that all reported lesion correlates are located in the LH.

Lesion sites associated with impaired bucco-facial *and* arm/hand gesture imitation largely overlapped in the left supramarginal gyrus (SMG) and superior temporal gyrus (STG; Fig. 3A, yellow). Besides the shared lesion sites in SMG and STG, bucco-facial imitation deficits were associated with anterior lesions affecting the left insular region, the post- and precentral gyrus, the inferior frontal gyrus (IFG) and subcortical (grey and white matter) structures (Table 1A and Fig. 3A, red). Similar lesion patterns were identified in the SVR-LSM analysis of the specific lesion-deficit associations for bucco-facial gesture imitation *relative* to arm/hand gesture imitation (Table 1B and Fig. 3B).

In addition to the common lesion sites in SMG and STG, lesioned voxels associated with arm/hand gesture imitation deficits were located in the left angular gyrus (AG) and posterior middle temporal gyrus (pMTG; Table 1C and Fig. 3A, green), lesion sites that were further corroborated by the SVR-LSM analysis of specific deficits in arm/hand gesture imitation *relative* to bucco-facial imitation (Table 1D and Fig. 3C).

3.5. Lesion correlates of imitation deficits for gesture meaning (independent of effectors)

The results of the SVR-LSM analyses with the overall (mean) scores of the ML and MF gestures and the difference scores between the ML and MF gesture imitation are shown in Fig. 4 and Table 2.

For ML as well as for MF gesture imitation deficits (independent of effector), the left STG and SMG were again identified as (shared) lesion correlates (Fig. 4A, magenta, Table 2A and 2B). Also, poor ML gesture imitation was associated with lesions in the left AG (Table 2A and Fig. 4A, blue). For the differential SVR-LSM analysis of deficits in ML *relative* to MF gesture imitation no significant lesion correlates were found at the predefined threshold.

In contrast, deficits in MF gesture imitation *relative* to ML gesture imitation were specifically associated with lesions in the left IFG and the insular region (Table 2C and Fig. 4B).

3.6. Effect of meaning on the effector-specific lesion correlates

SVR-LSM results revealed significant lesion correlates for the interaction of gesture meaning on the effector used for imitation in the STG (*peak MNI coordinate: −41, −32, +13; Z-value = −3.72*), the SMG (*peak*

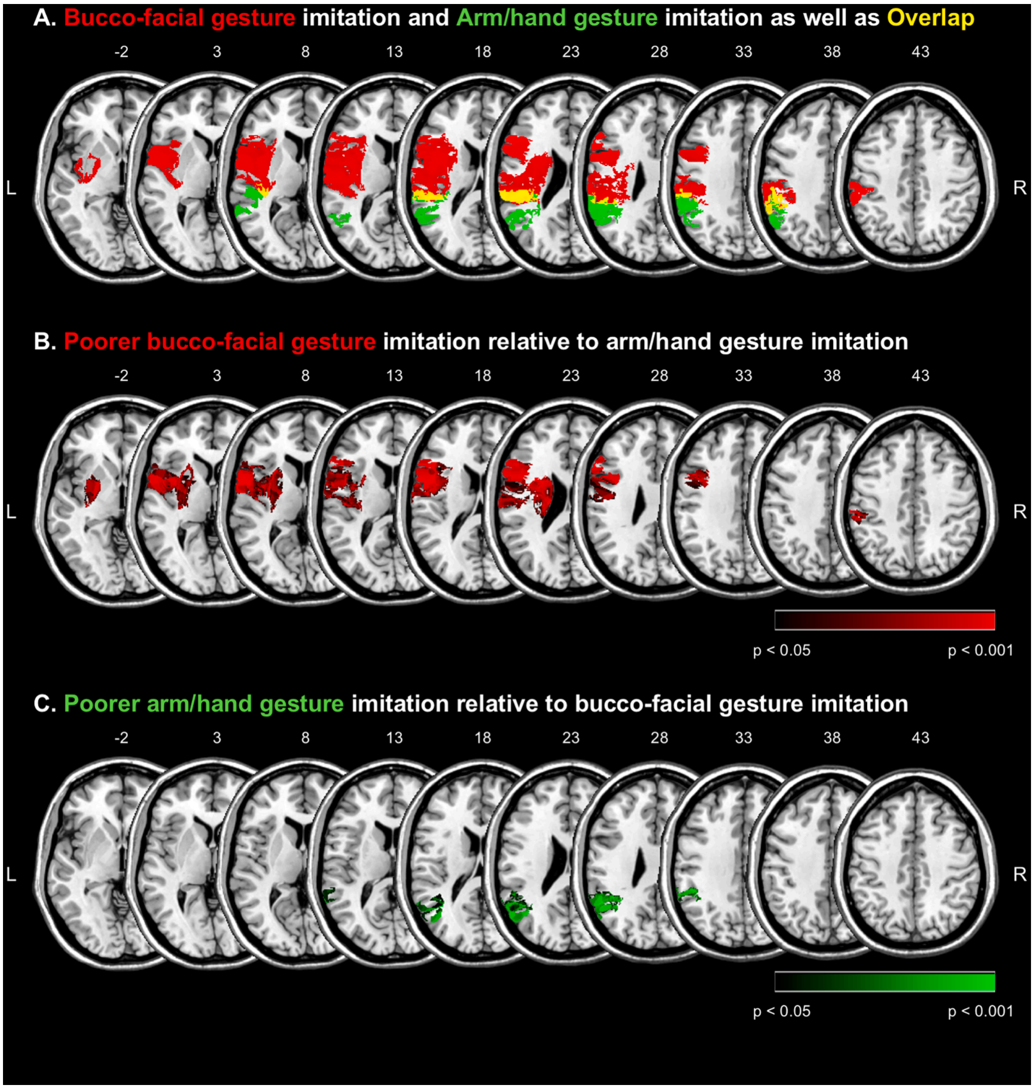

Fig. 3. Results of the SVR-LSM analyses for bucco-facial and arm/hand gesture imitation. **A.** Lesion correlates of bucco-facial gesture imitation deficits (red, *cf.* Table 1*A*) and arm/hand gesture imitation deficits (green, *cf.* Table 1*C*) and their overlap (yellow). **B.** Lesion correlates *specific* to bucco-facial gesture imitation deficits (*cf.* Table 1*B*). **C.** Lesion correlates *specific* to arm/hand gesture imitation deficits (*cf.* Table 1*D*). For B./C.: Colours indicate the *p*-values of the corresponding voxels. For A.-C.: Voxels shown are thresholded at $p < 0.05$ based on 10,000 permutations; the cluster size threshold is 100 voxels. Axial slices with MNI z-coordinates from −2 to +43 are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

MNI coordinate: −64, −32, +23; Z-value = −3.19), and the postcentral gyrus (*peak MNI coordinate: −57, −12, +28; Z-value = −2.42*) in the LH. Moreover, the interaction term was significantly associated with lesions in the subcortical grey and white matter, namely the putamen (*peak MNI coordinate: −31, +6, +8; Z-value = −3.43*), internal capsule (*peak MNI coordinate: −31, −24, +8; Z-value = −3.29*) and corona radiata (*peak MNI coordinate: −25, −8, +23; Z-value = −3.72*; Fig. 5). Thus, these lesion sites were statistically associated with a more pronounced performance difference between the effectors bucco-facial and arm/hand in *ML* gesture imitation compared to the performance difference between these effectors in *MF* gesture imitation.

4. Discussion

In a large sample of 194 sub-acute LH stroke patients, analyses of imitation scores revealed that effector-specific performance differences were modulated by gesture meaning. Therefore, our results confirm and extend previous studies by revealing a differential influence of gesture meaning for imitating bucco-facial gestures and, notably, by delineating specific lesion correlates for the modulation of effector-specific imitation deficits by gesture meaning.

4.1. Behavioural results

On a behavioural level, a significant interaction between the effector used for imitation and the meaning of the imitated gesture was revealed. This interaction was driven by a significant difference in the imitation performance of meaningless (ML) gestures. LH stroke patients imitated ML arm/hand gestures worse than ML bucco-facial gestures, while we observed no significant difference for imitating meaningful (MF) gestures.

The described differences in task performance between ML bucco-facial and arm/hand gestures might be explained by differences in subjacent cognitive models of the direct and indirect route. ML gesture imitation solely relies on the direct route, while for MF gesture processing, the direct route can be adopted besides the commonly used indirect route (Achilles et al., 2019; Hoeren et al., 2014; Rumiati & Tessari, 2002; Tessari et al., 2007). Thus, deficits in ML gesture imitation cannot be compensated by stored action knowledge accessible via the indirect route only. In contrast, such action knowledge can support MF gesture imitation, leading to better performance (Achilles et al., 2016; Achilles et al., 2019), and most likely attenuates any difference in imitation performance between effectors (Tessari et al., 2021).

Hence, our behavioural results indicate that ML gestures are particularly sensitive in assessing effector-specific imitation deficits in LH stroke patients.

Table 1

SVR-LSM results for deficits in imitating bucco-facial and arm/hand gestures.

Brain region	Maximum Z-value	Peak MNI coordinates x, y, z
A. *Lesion correlates of **bucco-facial** gesture imitation deficits independent of meaning*		
Insular region	−3.72	−40, −5, +8
Postcentral gyrus	−3.72	−64, −11, +13
IFG	−3.72	−46, +20, +23
SMG	−3.72	−46, −36, +38
STG	−3.54	−48, −33, +18
Precentral gyrus	−3.29	−36, +8, +33
Corona radiata	−3.16	−26, −3, +28
Putamen	−2.78	−22, +1, −2
B. *Lesion correlates of **bucco-facial** gesture imitation deficits relative to arm/hand gesture imitation (independent of meaning)*		
Precentral gyrus	−3.72	−50, +3, +18
IFG	−3.01	−48, +23, +13
SMG	−2.79	−60, −25, +43
Putamen extending into white matter	−2.74	−22, +1, −2
C. *Lesion correlates of **arm/hand** gesture imitation deficits independent of meaning*		
SMG	−3.72	−50, −40, +33
STG	−2.82	−47, −33, +18
AG	−2.75	−47, −48, +23
pMTG	−2.55	−60, −53, +18
D. *Lesion correlates of **arm/hand** gesture imitation deficits relative to bucco-facial gesture imitation (independent of meaning)*		
SMG	−3.12	−46, −41, +33
pMTG	−2.91	−39, −63, +23
AG	−2.88	−52, −52, +28
STG	−2.44	−66, −49, +13

AG = angular gyrus, IFG = inferior frontal gyrus, pMTG = posterior middle temporal gyrus, SMG = supramarginal gyrus, STG = superior temporal gyrus

For each lesion cluster, a maximum *Z*-value and the MNI coordinates of the corresponding voxel are reported. All lesion correlates are significant at a voxelwise threshold of $p < 0.05$ based on 10,000 permutations. Clusters smaller than 100 voxels were excluded.

4.2. Shared neural correlates of imitation deficits

Overall, SVR-LSM analyses revealed the left SMG, as part of the IPL, and the left STG as joint lesion correlates for gesture imitation deficits. This was shown independently for both effectors (bucco-facial and arm/hand) and MF and ML gesture imitation independent of the effector.

Previous studies have also identified the IPL as a common lesion site for imitation deficits (Buxbaum et al., 2014; Lesourd et al., 2018; Schmidt et al., 2022). Additionally, transcranial magnetic stimulation

Table 2

SVR-LSM results for deficits in imitating meaningless and meaningful gestures.

Brain region	Maximum Z-value	Peak MNI coordinates x, y, z
A. *Lesion correlates of **meaningless** gesture imitation deficits independent of the effector*		
STG	−3.72	−47, −33, +18
SMG	−3.72	−59, −42, +43
AG	−3.54	−42, −42, +38
B. *Lesion correlates of **meaningful** gesture imitation deficits independent of the effector*		
STG	−3.72	−39, −36, +18
SMG	−3.72	−46, −36, +38
IFG	−3.43	−55, +24, +28
Corona radiata superior	−2.74	−29, +3, +23
Insular region	−2.70	−32, +7, +18
Precentral gyrus	−2.61	−48, +4, +3
C. *Lesion correlates of **meaningful** gesture imitation deficits relative to meaningless gesture imitation (independent of the effector)**		
IFG	−3.19	−39, +22, +13
Insular region	−2.54	−37, −3, −7

AG = angular gyrus, IFG = inferior frontal gyrus, SMG = supramarginal gyrus, STG = superior temporal gyrus

For each lesion cluster, a maximum *Z*-value and the MNI coordinates of the corresponding voxel are reported. All lesion correlates are significant at a voxelwise threshold of $p < 0.05$ based on 10,000 permutations. Clusters smaller than 100 voxels were excluded.

* Note that for the reverse contrast (meaningless gesture imitation *relative* to meaningful gesture imitation), no specific lesion correlates were found at the predefined threshold.

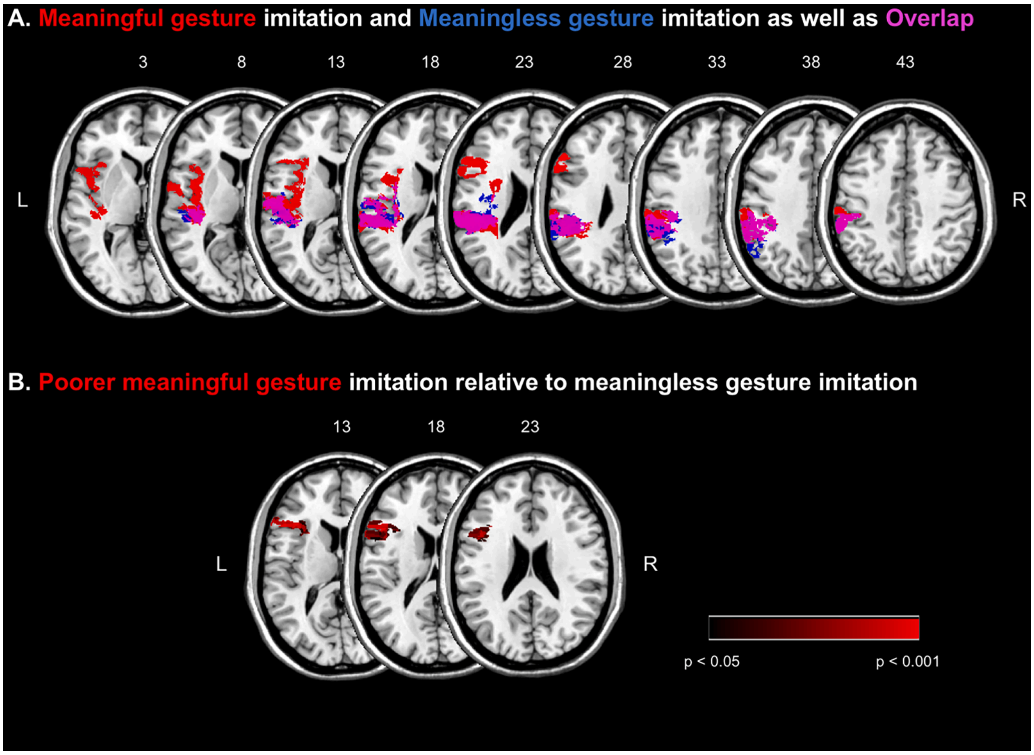

Fig. 4. Results of the SVR-LSM analyses for meaningful (MF) and meaningless (ML) gesture imitation. **A.** Lesion correlates of ML gesture imitation deficits (blue, *cf.* Table 2*A*) and MF gesture imitation deficits (red, *cf.* Table 2*B*) and their overlap (magenta). Axial slices with MNI z-coordinates from +3 to +43 are shown. **B.** Lesion correlates *specific* to MF gesture imitation deficits (*cf.* Table 2*C*). Colours indicate the *p*-values of the corresponding voxels. Axial slices with MNI z-coordinates from +13 to +23 are shown. For A./B.: Voxels shown are thresholded at $p < 0.05$ based on 10,000 permutations; the cluster size threshold is 100 voxels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

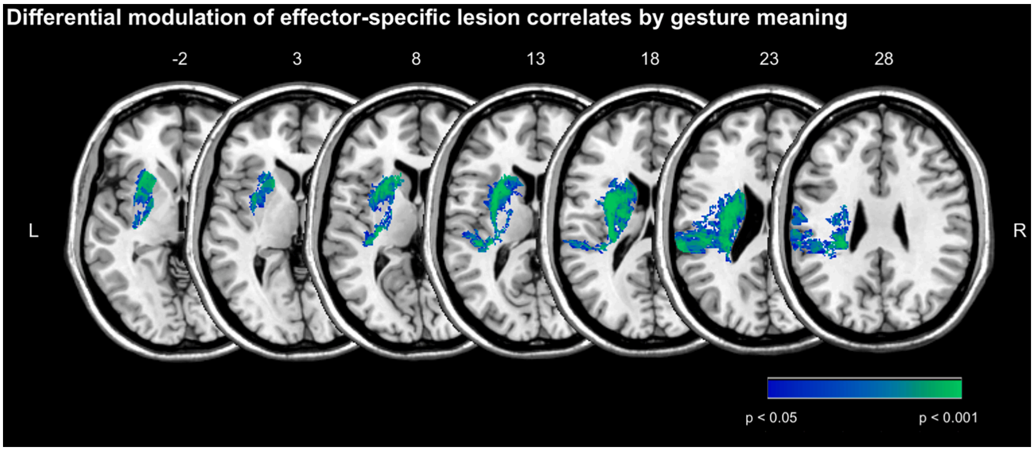

Fig. 5. Differential modulation of effector-specific lesion correlates by gesture meaning. Results of the SVR-LSM analysis for the interaction effect of gesture meaning on the effector used for imitation. The depicted lesion correlates were associated with the interaction term (ML bucco-facial gestures $_{\text{mean score}}$ − ML arm/hand gestures $_{\text{mean score}}$) − (MF bucco-facial gestures $_{\text{mean score}}$ − MF arm/hand gestures $_{\text{mean score}}$). Colours indicate the *p*-values of the corresponding voxels. Voxels shown are thresholded at $p < 0.05$ based on 10,000 permutations; the cluster size threshold is 100 voxels. Axial slices with MNI z-coordinates from −2 to +28 are shown.

showed its involvement in imitating both MF and ML gestures (Vanbellingen et al., 2014). Our data revealed the left SMG as a robust lesion correlate for ML and MF gesture imitation deficits, independent of the effector. The results thus strongly corroborate SMG's role as an integrative hub in the praxis system for controlling intransitive gestures (Lesourd et al., 2018).

Besides, our data revealed the left STG extending into the superior temporal sulcus (STS) as a significant lesion correlate for both effectors (arm/hand, bucco-facial) and ML and MF gesture types. Over and above parietal lesions, damage to the temporal lobe has commonly been associated with apraxic deficits (Buxbaum & Randerath, 2018), including impaired imitation (Dressing et al., 2018; Lingnau & Downing, 2015; Peigneux et al., 2000; Rumiati et al., 2005; Tessari et al., 2007). These clinical observations are supported by functional imaging studies that related activity in the STS and STG to the recognition of transitive and intransitive gestures (Villarreal et al., 2008) as well as to active imitation compared to mere action observation (Decety et al., 2002; Molenberghs et al., 2010). These findings point to the role of superior temporal brain regions (STG/STS) in processing one's actions versus the actions of others. This notion implies that lesions to STG (extending into the STS) impair one's actions, as revealed by their general association with imitation deficits in our patient cohort.

4.3. Distinct neural substrates of deficient imitation with different effectors

Besides, distinct neuroanatomical substrates for imitation deficits with different effectors were identified: within the left middle cerebral artery territory, lesions associated with bucco-facial imitation deficits were located more anterior, and arm/hand gesture imitation deficits were associated with more posterior lesions.

4.3.1. Neural substrates of deficits in bucco-facial gesture imitation

Besides the shared neural substrates SMG and STG for gesture imitation, the left insular region, pre- and postcentral gyri, the IFG, and subcortical regions, including the putamen, were significantly associated with bucco-facial gesture imitation deficits. Furthermore, differential specific lesion-deficit associations for bucco-facial gesture imitation *relative* to arm/hand gesture imitation were revealed in the left precentral gyrus, IFG, and putamen and adjacent white matter.

Consistent with our data, previous studies have revealed that bucco-facial apraxic deficits are associated with lesions in the IFG, the insular region and adjacent subcortical regions (Alexander et al., 1992; Conterno et al., 2022; Maeshima et al., 1997; Raade et al., 1991; Scandola et al., 2021; Tognola & Vignolo, 1980). These results align with the here identified lesion correlates for bucco-facial gesture imitation deficits located more anterior than lesions associated with arm/hand imitation deficits. A recent lesion analysis in 137 LH stroke patients revealed associations of bucco-facial apraxia with large portions of the insula, the precentral gyrus and IFG, the STG, and white matter tracts such as the corona radiata and internal capsule (Conterno et al., 2022). The insula, a region crucial for speech production (Dronkers, 1996), has also been implicated in non-speech oral motor functions (Ackermann & Riecker, 2010) and facial imitation accuracy (Braadbaart et al., 2014). Hence,the insular lesion correlate for bucco-facial imitation deficits corroborates the proposal that this region is a crucial integrator for bucco-facial praxis (Conterno et al., 2022).

Besides temporo-parietal and frontal lesions, bucco-facial apraxia has been associated with striato-capsular lesions (Conterno et al., 2022; Raade et al., 1991; Schmidt et al., 2022), consistent with the here revealed subcortical lesion correlates of bucco-facial gesture imitation deficits (including the basal ganglia).

4.3.2. Neural substrates of deficits in arm/hand gesture imitation

In addition to (shared) lesion sites in the SMG and STG, lesions specifically associated with arm/hand imitation deficits (*relative* to the effector bucco-facial) were found in the left AG and pMTG, and thus extended more posteriorly within the praxis networks of the LH than bucco-facial imitation deficits.

These findings align with previous lesion studies on limb gesture imitation (Goldenberg, 2009; Lesourd et al., 2018; Scandola et al., 2021). Commonly, lesions in the left IPL, including the AG and SMG, have been found to cause limb imitation deficits (Buxbaum et al., 2014; Goldenberg, 2009). Semantic and spatial gesture recognition, crucial in imitating limb gestures, has been ascribed to the pMTG, making this region a central node in processing transitive and intransitive actions (Kalenine et al., 2010; Villarreal et al., 2008). In our study, damage to the pMTG was specifically associated with arm/hand gesture imitation deficits (but not with impaired bucco-facial gesture imitation). This may support the proposal that left posterior temporal regions are also relevant in processing postural components of gestures, i.e., placing the hand relative to other body parts (Buxbaum et al., 2014; Reader & Holmes, 2019). Correct positioning of the hand/arm in relation to other body parts is crucial in the imitation of limb gestures, whereas it is not relevant for bucco-facial gesture imitation.

In summary, the above-described partly distinct lesion patterns (anterior-posterior lesion gradient for bucco-facial versus limb imitation deficits) support the notion that apraxia is not a unitary disorder but that apraxic deficits may dissociate for different effectors. One explanation for such a differential lesion pattern may be that actions with different effectors may rely on – at least partly – dissociable cognitive processes (Schmidt et al., 2022). However, neuroanatomical effector-specific correlates were not entirely independent for bucco-facial and arm/hand gestures, as the SMG and STG were identified as important shared hubs within the praxis networks of the LH.

4.4. Neural substrates of deficits in imitating meaningless and meaningful gestures

Lesions located in the left SMG and STG were jointly associated with ML and MF gesture imitation deficits. ML gesture imitation deficits showed an additional association with lesions in the left AG. Similarly, previous studies have ascribed the processing of ML gestures to the AG (Dressing et al., 2021; Goldenberg, 2009; Goldenberg & Hagmann, 1997; Lesourd et al., 2018; Mengotti et al., 2013; Peigneux et al., 2004). Note that no significant lesion-deficit associations specific to ML (*relative* to MF) gestures were found in the differential SVR-LSM analysis at the predefined threshold.

In contrast, poor MF gesture imitation (*relative* to ML gesture imitation) was specifically associated with lesions in the left IFG and the insular region. The strong association of the left IFG with MF gesture imitation (independent of the effector) fits with previous lesion studies (Weiss et al., 2016). By conveying a meaning, MF gestures incorporate a communicative aspect. Deficits in comprehending MF limb gestures have been associated with damage to the IFG as a language-related region (Pazzaglia et al., 2008). In this regard, fMRI activation patterns in the left IFG were found for the recognition of MF intransitive (limb) gestures (Villarreal et al., 2008) and in processing communicative intentions of gestures during imitation (Mainieri et al., 2013). Furthermore, lesion-deficit associations in the left IFG and insular region were shown for gesture comprehension (Binder et al., 2017), and both regions, together with the STG and SMG, were strongly associated with aphasia severity (Weiss et al., 2016), further supporting the communicative aspect incorporated in MF gestures. While the IFG is a core region within the fronto-temporo-parietal LH praxis networks, the insular region bilaterally supports various, multimodal (cognitive, mnestic, emotional and social) functions (Gogolla, 2017). In this context, higher-level cognitive functions may also be relevant in gesture processing, such as bodily self-awareness (Tsakiris et al., 2007), including the representation and functioning of one's body parts (Corradi-Dell'Acqua et al., 2009; Karnath et al., 2005).

4.5. Differential modulation of effector-specific lesion correlates by gesture meaning

The specific performance difference when imitating ML arm/hand versus ML bucco-facial gestures compared to imitating MF arm/hand versus MF bucco-facial gestures was associated with left-hemispheric lesions in the STG, SMG, postcentral gyrus and subcortical regions. These lesion sites were statistically associated with more pronounced deficits in imitating ML arm/hand gestures when compared to ML bucco-facial gestures than in imitating MF arm/hand gestures compared to MF bucco-facial gestures. Consistent with the significant interaction in the behavioural data, these significant SVR-LSM results for effector-specific performance differences in ML gesture imitation (relative to MF gesture imitation) are likely to constitute the neural correlates of the notion that gesture meaning impacts effector-specific imitation deficits. These findings implicate that clinicians should consider gesture meaning (ML, MF) as a factor when assessing apraxic deficits in (LH) stroke patients, especially when stroke patients suffer from parietal cortex or white matter lesions.

5. Limitations

Besides the retrospective study design, one limitation of the current study relates to the patient sample that, albeit its large size, included left hemisphere stroke patients only. Therefore, the current study cannot reveal whether right-hemispheric regions are differentially involved in modulating effector-specific imitation deficits by gesture meaning. While apraxia is commonly observed in patients with lesions in the left-hemispheric praxis networks, apraxic deficits, including bucco-facial apraxia (Bizzozero et al., 2000), have also been reported after right-sided brain damage (Dressing et al., 2020; Goldenberg, 1996, 1999; Lesourd et al., 2018; Ubben et al., 2020). Thus, future studies are warranted to shed light on the bucco-facial versus arm/hand effector specificity and the effect of gesture meaning in patients with right hemisphere stroke.

Besides the grey matter lesion-deficit associations, we detected statistically significant lesion clusters within white matter tracts, analogous to previous studies (Dressing et al., 2021; Kusch, Schmidt, et al., 2018; Martin et al., 2016; Watson & Buxbaum, 2015). Notably, the association of behavioural performance with cortical structures was more pronounced than the association with white matter tracts, which is consistent with other studies of apraxia (Martin et al., 2016). The observed white matter lesion-deficit associations could indicate connectional diaschisis in the praxis networks resulting in apraxic deficits (Carrera & Tononi, 2014). Future studies applying connectome-based lesion-symptom mapping (Foulon et al., 2018; Fox, 2018; Gleichgerrcht et al., 2017) might enhance the detection of white matter lesion-deficit associations and related network effects in effector-specific gesture imitation deficits modulated by gesture meaning.

6. Conclusion

On a behavioural level, our study revealed that assessing the imitation of ML gestures in LH stroke patients is more sensitive in unravelling effector-specific performance deficits for arm/hand vs bucco-facial gestures than the imitation of MF gestures. This differential effect of gesture meaning on effector-specific imitation performance was mirrored on the neural level by significant lesion correlates of this interaction in the STG, SMG, postcentral gyrus and subcortical structures of the LH. Thus, the current study extends previous work on the modulation of effector-specific imitation deficits by gesture meaning to bucco-facial gestures in revealing for the first time statistically significant lesion correlates for this modulation by adopting SVR-LSM analysis in a large cohort of 194 LH stroke patients.

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CRediT authorship contribution statement

Nina N. Kleineberg: Conceptualization, Investigation, Formal analysis, Visualization, Writing – original draft. **Claudia C. Schmidt:** Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. **Monika K. Richter:** Investigation, Writing – review & editing. **Katharina Bolte:** Investigation, Writing – review & editing. **Natalie Schloss:** Investigation, Writing – review & editing. **Gereon R. Fink:** Resources, Writing – review & editing, Project administration, Funding acquisition. **Peter H. Weiss:** Conceptualization, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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.

References

Achilles, E.I.S., Ballweg, C.S., Niessen, E., Kusch, M., Ant, J.M., Fink, G.R., Weiss, P.H., 2019. Neural correlates of differential finger gesture imitation deficits in left hemisphere stroke. Neuroimage Clin. 23, 101915 https://doi.org/10.1016/j.nicl.2019.101915.

Achilles, E.I., Fink, G.R., Fischer, M.H., Dovern, A., Held, A., Timpert, D.C., Schroeter, C., Schuetz, K., Kloetzsch, C., Weiss, P.H., 2016. Effect of meaning on apraxic finger imitation deficits. Neuropsychologia 82, 74–83. https://doi.org/10.1016/j.neuropsychologia.2015.12.022.

Ackermann, H., Riecker, A., 2010. The contribution(s) of the insula to speech production: a review of the clinical and functional imaging literature. Brain Struct. Funct. 214 (5–6), 419–433. https://doi.org/10.1007/s00429-010-0257-x.

Alexander, M.P., Baker, E., Naeser, M.A., Kaplan, E., Palumbo, C., 1992. Neuropsychological and neuroanatomical dimensions of ideomotor apraxia. Brain 115 (Pt 1), 87–107. https://doi.org/10.1093/brain/115.1.87.

Ant, J.M., Niessen, E., Achilles, E.I.S., Saliger, J., Karbe, H., Weiss, P.H., Fink, G.R., 2019. Anodal tDCS over left parietal cortex expedites recovery from stroke-induced apraxic imitation deficits: a pilot study. Neurol. Res. Pract. 1, 38. https://doi.org/10.1186/s42466-019-0042-0.

Bernhardt, J., Hayward, K.S., Kwakkel, G., Ward, N.S., Wolf, S.L., Borschmann, K., Krakauer, J.W., Boyd, L.A., Carmichael, S.T., Corbett, D., Cramer, S.C., 2017. Agreed definitions and shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. Int. J. Stroke 12 (5), 444–450. https://doi.org/10.1177/1747493017711816.

Binder, E., Dovern, A., Hesse, M.D., Ebke, M., Karbe, H., Saliger, J., Fink, G.R., Weiss, P.H., 2017. Lesion evidence for a human mirror neuron system. Cortex 90, 125–137. https://doi.org/10.1016/j.cortex.2017.02.008.

Bizzozero, I., Costato, D., Sala, S.D., Papagno, C., Spinnler, H., Venneri, A., 2000. Upper and lower face apraxia: role of the right hemisphere. Brain 123 (Pt 11), 2213–2230. https://doi.org/10.1093/brain/123.11.2213.

Braadbaart, L., de Grauw, H., Perrett, D.I., Waiter, G.D., Williams, J.H., 2014. The shared neural basis of empathy and facial imitation accuracy. Neuroimage 84, 367–375. https://doi.org/10.1016/j.neuroimage.2013.08.061.

Buxbaum, L.J., Randerath, J., 2018. Limb apraxia and the left parietal lobe. Handb. Clin. Neurol. 151, 349–363. https://doi.org/10.1016/b978-0-444-63622-5.00017-6.

Buxbaum, L.J., Shapiro, A.D., Coslett, H.B., 2014. Critical brain regions for tool-related and imitative actions: a componential analysis. Brain 137 (Pt 7), 1971–1985. https://doi.org/10.1093/brain/awu111.

Carrera, E., Tononi, G., 2014. Diaschisis: past, present, future. Brain 137 (Pt9), 2408–2422. https://doi.org/10.1093/brain/awu101.

Conterno, M., Kümmerer, D., Dressing, A., Glauche, V., Urbach, H., Weiller, C., Rijntjes, M., 2022. Speech apraxia and oral apraxia: association or dissociation? A multivariate lesion-symptom mapping study in acute stroke patients. Exp. Brain Res. 240 (1), 39–51. https://doi.org/10.1007/s00221-021-06224-3.

Corradi-Dell'Acqua, C., Tomasino, B., Fink, G.R., 2009. What is the position of an arm relative to the body? Neural correlates of body schema and body structural description. J. Neurosci. 29 (13), 4162–4171. https://doi.org/10.1523/jneurosci.4861-08.2009.

Cubelli, R., 2017. Definition: Apraxia. Cortex 93, 227. https://doi.org/10.1016/j.cortex.2017.03.012.

Dafsari, H.S., Dovern, A., Fink, G.R., Weiss, P.H., 2019. Deficient body structural description contributes to apraxic end-position errors in imitation. Neuropsychologia 133, 107150. https://doi.org/10.1016/j.neuropsychologia.2019.107150.

de Haan, B., Karnath, H.O., 2018. A hitchhiker's guide to lesion-behaviour mapping. Neuropsychologia 115, 5–16. https://doi.org/10.1016/j.neuropsychologia.2017.10.021.

Decety, J., Chaminade, T., Grèzes, J., Meltzoff, A.N., 2002. A PET exploration of the neural mechanisms involved in reciprocal imitation. Neuroimage 15 (1), 265–272. https://doi.org/10.1006/nimg.2001.0938.

DeMarco, A.T., Turkeltaub, P.E., 2018. A multivariate lesion symptom mapping toolbox and examination of lesion-volume biases and correction methods in lesion-symptom mapping. Hum. Brain Mapp. 39 (11), 4169–4182. https://doi.org/10.1002/hbm.24289.

Dovern, A., Fink, G.R., Saliger, J., Karbe, H., Koch, I., Weiss, P.H., 2011. Apraxia impairs intentional retrieval of incidentally acquired motor knowledge. J. Neurosci. 31 (22), 8102–8108. https://doi.org/10.1523/jneurosci.6585-10.2011.

Dovern, A., Fink, G.R., Weiss, P.H., 2012. Diagnosis and treatment of upper limb apraxia. J. Neurol. 259 (7), 1269–1283. https://doi.org/10.1007/s00415-011-6336-y.

Dovern, A., Fink, G.R., Timpert, D.C., Saliger, J., Karbe, H., Weiss, P.H., Koch, I., 2016. Timing Matters? Learning of Complex Spatiotemporal Sequences in Left-hemisphere Stroke Patients. J. Cogn. Neurosci. 28 (2), 223–236. https://doi.org/10.1162/jocn_a_00890.

Dressing, A., Nitschke, K., Kümmerer, D., Bormann, T., Beume, L., Schmidt, C.S.M., Ludwig, V.M., Mader, I., Willmes, K., Rijntjes, M., Kaller, C.P., Weiller, C., Martin, M., 2018. Distinct contributions of dorsal and ventral streams to imitation of tool-use and communicative gestures. Cereb. Cortex 28 (2), 474–492. https://doi.org/10.1093/cercor/bhw383.

Dressing, A., Martin, M., Beume, L.-A., Kümmerer, D., Urbach, H., Kaller, C.P., Weiller, C., Rijntjes, M., 2020. The correlation between apraxia and neglect in the right hemisphere: a voxel-based lesion-symptom mapping study in 138 acute stroke patients. Cortex 132, 166–179. https://doi.org/10.1016/j.cortex.2020.07.017.

Dressing, A., Kaller, C.P., Martin, M., Nitschke, K., Kuemmerer, D., Beume, L.A., Schmidt, C.S.M., Musso, M., Urbach, H., Rijntjes, M., Weiller, C., 2021. Anatomical correlates of recovery in apraxia: a longitudinal lesion-mapping study in stroke patients. Cortex 142, 104–121. https://doi.org/10.1016/j.cortex.2021.06.001.

Dronkers, N.F., 1996. A new brain region for coordinating speech articulation. Nature 384 (6605), 159–161. https://doi.org/10.1038/384159a0.

Faria, A.V., Joel, S.E., Zhang, Y., Oishi, K., van Zjil, P.C.M., Miller, M.I., Pekar, J.J., Mori, S., 2012. Atlas-based analysis of resting-state functional connectivity: evaluation for reproducibility and multi-modal anatomy-function correlation studies. Neuroimage 61 (3), 613–621. https://doi.org/10.1016/j.neuroimage.2012.03.078.

Foulon, C., Cerliani, L., Kinkingnéhun, S., Levy, R., Rosso, C., Urbanski, M., Volle, E., Thiebaut de Schotten, M., 2018. Advanced lesion symptom mapping analyses and implementation as BCBtoolkit. GigaScience 7 (3), 1–17. https://doi.org/10.1093/gigascience/giy004.

Fox, M.D., 2018. Mapping Symptoms to Brain Networks with the Human Connectome. N. Engl. J. Med. 379 (23), 2237–2245. https://doi.org/10.1056/NEJMra1706158.

Gleichgerrcht, E., Fridriksson, J., Rorden, C., Bonilha, L., 2017. Connectome-based lesion-symptom mapping (CLSM): A novel approach to map neurological function. Neuroimage Clin 16, 461–467. https://doi.org/10.1016/j.nicl.2017.08.018.

Gogolla, N., 2017. The insular cortex. Curr. Biol. 27 (12), R580–R586. https://doi.org/10.1016/j.cub.2017.05.010.

Goldenberg, G., 1996. Defective imitation of gestures in patients with damage in the left or right hemispheres. J. Neurol. Neurosurg. Psychiatry 61 (2), 176–180.

Goldenberg, G., 1999. Matching and imitation of hand and finger postures in patients with damage in the left or right hemispheres. Neuropsychologia 37 (5), 559–566.

Goldenberg, G., 2001. Imitation and matching of hand and finger postures. Neuroimage 14 (1 Pt 2), S132–S136. https://doi.org/10.1006/nimg.2001.0820.

Goldenberg, G., 2009. Apraxia and the parietal lobes. Neuropsychologia 47 (6), 1449–1459. https://doi.org/10.1016/j.neuropsychologia.2008.07.014.

Goldenberg, G., Hagmann, S., 1997. The meaning of meaningless gestures: a study of visuo-imitative apraxia. Neuropsychologia 35 (3), 333–341. https://doi.org/10.1016/s0028-3932(96)00085-1.

Goldenberg, G., Karnath, H.O., 2006. The neural basis of imitation is body part specific. J. Neurosci. 26 (23), 6282–6287. https://doi.org/10.1523/jneurosci.0638-06.2006.

Goldenberg, G., Randerath, J., 2015. Shared neural substrates of apraxia and aphasia. Neuropsychologia 75, 40–49. https://doi.org/10.1016/j.neuropsychologia.2015.05.017.

Hoeren, M., Kummerer, D., Bormann, T., Beume, L., Ludwig, V.M., Vry, M.S., Mader, I., Rijntjes, M., Kaller, C.P., Weiller, C., 2014. Neural bases of imitation and pantomime in acute stroke patients: distinct streams for praxis. Brain 137 (Pt 10), 2796–2810. https://doi.org/10.1093/brain/awu203.

Kalbe, E., Reinhold, N., Brand, M., Kessler, J., 2002. The short aphasia-check-list: an economical screening for detecting aphasia. Eur. J. Neurol. 9, 209–210.

Kalbe, E., Reinhold, N., Brand, M., Markowitsch, H.J., Kessler, J., 2005. A new test battery to assess aphasic disturbances and associated cognitive dysfunctions—German normative data on the aphasia check list. J. Clin. Exp. Neuropsychol. 27 (7), 779–794.

Kalenine, S., Buxbaum, L.J., Coslett, H.B., 2010. Critical brain regions for action recognition: lesion symptom mapping in left hemisphere stroke. Brain 133 (11), 3269–3280. https://doi.org/10.1093/brain/awq210.

Karnath, H.O., Baier, B., Nagele, T., 2005. Awareness of the functioning of one's own limbs mediated by the insular cortex? J. Neurosci. 25 (31), 7134–7138. https://doi.org/10.1523/JNEUROSCI.1590-05.2005.

Kleineberg, N.N., Richter, M.K., Becker, I., Weiss, P.H., Fink, G.R., 2020. Verum versus sham tDCS in the treatment of stroke-induced apraxia: study protocol of the randomized controlled trial RAdiCS -"Rehabilitating (stroke-induced) Apraxia with direct Current Stimulation". Neurol. Res. Pract. 2, 7. https://doi.org/10.1186/s42466-020-0052-y.

Kusch, M., Gillessen, S., Saliger, J., Karbe, H., Binder, E., Fink, G.R., Vossel, S., Weiss, P.H., 2018. Reduced awareness for apraxic deficits in left hemisphere stroke. Neuropsychology 32 (4), 509–515. https://doi.org/10.1037/neu0000451.

Kusch, M., Schmidt, C.C., Goden, L., Tscherpel, C., Stahl, J., Saliger, J., Karbe, H., Fink, G.R., Weiss, P.H., 2018. Recovery from apraxic deficits and its neural correlate. Restor. Neurol. Neurosci. 36 (6), 669–678. https://doi.org/10.3233/rnn-180815.

Lesourd, M., Osiurak, F., Baumard, J., Bartolo, A., Vanbellingen, T., Reynaud, E., 2018. Cerebral correlates of imitation of intransitive gestures: An integrative review of neuroimaging data and brain lesion studies. Neurosci. Biobehav. Rev. 95, 44–60. https://doi.org/10.1016/j.neubiorev.2018.07.019.

Lingnau, A., Downing, P.E., 2015. The lateral occipitotemporal cortex in action. Trends Cogn. Sci. 19 (5), 268–277. https://doi.org/10.1016/j.tics.2015.03.006.

Maeshima, S., Truman, G., Smith, D.S., Dohi, N., Itakura, T., Komai, N., 1997. Buccofacial apraxia and left cerebral haemorrhage. Brain Inj. 11 (11), 777–782. https://doi.org/10.1080/026990597122981.

Mainieri, A.G., Heim, S., Straube, B., Binkofski, F., Kircher, T., 2013. Differential role of the Mentalizing and the Mirror Neuron system in the imitation of communicative gestures. Neuroimage 81, 294–305. https://doi.org/10.1016/j.neuroimage.2013.05.021.

Martin, M., Dressing, A., Bormann, T., Schmidt, C.S., Kummerer, D., Beume, L., Saur, D., Mader, I., Rijntjes, M., Kaller, C.P., Weiller, C., 2016. Componential network for the recognition of tool-associated actions: evidence from voxel-based lesion-symptom mapping in acute stroke patients. Cereb. Cortex. https://doi.org/10.1093/cercor/bhw226.

Mengotti, P., Corradi-Dell'Acqua, C., Negri, G.A., Ukmar, M., Pesavento, V., Rumiati, R. I., 2013. Selective imitation impairments differentially interact with language processing. Brain 136 (Pt 8), 2602–2618. https://doi.org/10.1093/brain/awt194.

Molenberghs, P., Brander, C., Mattingley, J.B., Cunnington, R., 2010. The role of the superior temporal sulcus and the mirror neuron system in imitation. Hum. Brain Mapp. 31 (9), 1316–1326. https://doi.org/10.1002/hbm.20938.

Pazzaglia, M., Smania, N., Corato, E., Aglioti, S.M., 2008. Neural underpinnings of gesture discrimination in patients with limb apraxia. J. Neurosci. 28 (12), 3030–3041. https://doi.org/10.1523/jneurosci.5748-07.2008.

Peigneux, P., Salmon, E., van der Linden, M., Garraux, G., Aerts, J., Delfiore, G., Degueldre, C., Luxen, A., Orban, G., Franck, G., 2000. The role of lateral occipitotemporal junction and area MT/V5 in the visual analysis of upper-limb postures. Neuroimage 11 (6 Pt 1), 644–655. https://doi.org/10.1006/nimg.2000.0578.

Peigneux, P., Van der Linden, M., Garraux, G., Laureys, S., Degueldre, C., Aerts, J., Del Fiore, G., Moonen, G., Luxen, A., Salmon, E., 2004. Imaging a cognitive model of apraxia: the neural substrate of gesture-specific cognitive processes. Hum. Brain Mapp. 21 (3), 119–142. https://doi.org/10.1002/hbm.10161.

Raade, A.S., Rothi, L.J., Heilman, K.M., 1991. The relationship between buccofacial and limb apraxia. Brain Cogn. 16 (2), 130–146. https://doi.org/10.1016/0278-2626(91)90002-p.

Reader, A.T., Holmes, N.P., 2019. Repetitive transcranial magnetic stimulation over the left posterior middle temporal gyrus reduces wrist velocity during emblematic hand gesture imitation. Brain Topogr. 32 (2), 332–341. https://doi.org/10.1007/s10548-018-0684-1.

Rumiati, R.I., Tessari, A., 2002. Imitation of novel and well-known actions: the role of short-term memory. Exp. Brain Res. 142 (3), 425–433. https://doi.org/10.1007/s00221-001-0956-x.

Rumiati, R.I., Weiss, P.H., Tessari, A., Assmus, A., Zilles, K., Herzog, H., Fink, G.R., 2005. Common and differential neural mechanisms supporting imitation of meaningful and meaningless actions. J. Cogn. Neurosci. 17 (9), 1420–1431. https://doi.org/10.1162/0898929054985374.

Scandola, M., Canzano, L., Avesani, R., Leder, M., Bertagnoli, S., Gobbetto, V., Aglioti, S. M., Moro, V., 2021. Anosognosia for limb and bucco-facial apraxia as inferred from the recognition of gestural errors. J. Neuropsychol. 15 (1), 20–45. https://doi.org/10.1111/jnp.12203.

Schmidt, C.C., Achilles, E.I.S., Fink, G.R., Weiss, P.H., 2022. Distinct cognitive components and their neural substrates underlying praxis and language deficits following left hemisphere stroke. Cortex 146, 200–215. https://doi.org/10.1016/j.cortex.2021.11.004.

Schmidt, C. C., Weiss, P. H., 2022. The cognitive neuroscience of apraxia. In S. Della Sala (Ed.), Encyclopedia of Behavioral Neuroscience (2 ed., Vol. 2, pp. 668-677). Elsevier.

Sperber, C., Karnath, H.O., 2017. Impact of correction factors in human brain-lesion behavior inference. Hum Brain Mapp 38 (3), 1692–1701. https://doi.org/10.1002/hbm.23490.

Tessari, A., Canessa, N., Ukmar, M., Rumiati, R.I., 2007. Neuropsychological evidence for a strategic control of multiple routes in imitation. Brain 130 (Pt 4), 1111–1126. https://doi.org/10.1093/brain/awm003.

Tessari, A., Mengotti, P., Faccioli, L., Tuozzi, G., Boscarato, S., Taricco, M., Rumiati, R.I., 2021. Effect of body-part specificity and meaning in gesture imitation in left hemisphere stroke patients. Neuropsychologia 151, 107720. https://doi.org/10.1016/j.neuropsychologia.2020.107720.

Tognola, G., Vignolo, L.A., 1980. Brain lesions associated with oral apraxia in stroke patients: a clinico-neuroradiological investigation with the CT scan. Neuropsychologia 18 (3), 257–272. https://doi.org/10.1016/0028-3932(80)90122-0.

Tsakiris, M., Hesse, M.D., Boy, C., Haggard, P., Fink, G.R., 2007. Neural signatures of body ownership: a sensory network for bodily self-consciousness. Cereb. Cortex 17 (10), 2235–2244. https://doi.org/10.1093/cercor/bhl131.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15 (1), 273–289. https://doi.org/10.1006/nimg.2001.0978.

Ubben, S.D., Fink, G.R., Kaesberg, S., Kalbe, E., Kessler, J., Vossel, S., Weiss, P.H., 2020. Deficient allo-centric visuospatial processing contributes to apraxic deficits in sub-acute right hemisphere stroke. J. Neuropsychol. 14 (2), 242–259. https://doi.org/10.1111/jnp.12191.

Vanbellingen, T., Bertschi, M., Nyffeler, T., Cazzoli, D., Wiest, R., Bassetti, C., Kaelin-Lang, A., Muri, R., Bohlhalter, S., 2014. Left posterior parietal theta burst stimulation affects gestural imitation regardless of semantic content. Clin. Neurophysiol. 125 (3), 457–462. https://doi.org/10.1016/j.clinph.2013.07.024.

Villarreal, M., Fridman, E.A., Amengual, A., Falasco, G., Gerschcovich, E.R., Ulloa, E.R., Leiguarda, R.C., 2008. The neural substrate of gesture recognition. Neuropsychologia 46 (9), 2371–2382. https://doi.org/10.1016/j.neuropsychologia.2008.03.004.

Watson, C.E., Buxbaum, L.J., 2015. A distributed network critical for selecting among tool-directed actions. Cortex 65, 65–82. https://doi.org/10.1016/j.cortex.2015.01.007.

Weiss, P.H., Kalbe, E., Kessler, J., Fink, G.R., 2013. Kölner Apraxie Screening. Hogrefe.

Weiss, P.H., Ubben, S.D., Kaesberg, S., Kalbe, E., Kessler, J., Liebig, T., Fink, G.R., 2016. Where language meets meaningful action: a combined behavior and lesion analysis of aphasia and apraxia. Brain Struct. Funct. 221 (1), 563–576. https://doi.org/10.1007/s00429-014-0925-3.

Zhang, Y., Kimberg, D.Y., Coslett, H.B., Schwartz, M.F., Wang, Z., 2014. Multivariate lesion-symptom mapping using support vector regression. Hum. Brain Mapp. 35 (12), 5861–5876. https://doi.org/10.1002/hbm.22590.