Distinct cognitive components and their neural substrates underlying praxis and language deficits following left hemisphere stroke

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Declaration of interest:

The authors declare no competing interests.

Abstract

Apraxia is characterised by multiple deficits of higher motor functions, primarily caused by left hemisphere (LH) lesions to parietal-frontal praxis networks. While previous neuropsychological and lesion studies tried to relate the various apraxic deficits to specific lesion sites, a comprehensive analysis of the different apraxia profiles and the related (impaired) motor-cognitive processes as well as their differential neural substrates in LH stroke is lacking.

To reveal the cognitive mechanisms that underlie the different patterns of praxis and (related) language deficits, we applied principal component analysis (PCA) to the scores of sub-acute LH stroke patients (n = 91) in several tests of apraxia and aphasia. Voxel-based lesion-symptom mapping (VLSM) analyses were then used to investigate the neural substrates of the identified components.

The PCA yielded a first component related to language functions and three components related to praxis functions, with each component associated with specific lesion patterns. Regarding praxis functions, performance in imitating arm/hand gestures was accounted for by a second component related to the left precentral gyrus and the inferior parietal lobule. Imitating finger configurations, pantomiming the use of objects related to the face, and actually using objects loaded on component 3, related to the left anterior intraparietal sulcus and angular gyrus. The last component represented the imitation of bucco-facial gestures and was linked to the basal ganglia and LH white matter tracts. The results further revealed that pantomime of (limb-related) object use depended on both the component 2 and 3, which were shared with gesture imitation and actual object use.

Data support and extend the notion that apraxia represents a multi-componential syndrome comprising different (impaired) motor-cognitive processes, which dissociate – at least partly – from language processes. The distinct components might be disturbed to a varying degree following LH stroke since they are associated with specific lesion patterns within the LH.

Keywords

Apraxia, imitation, pantomime, principal component analysis (PCA), voxel-wise statistical lesion-behaviour mapping

1 Introduction

Apraxia refers to disorders of higher-order (cognitive) motor functions primarily caused by lesions to parietal-frontal praxis networks within the motor-dominant left hemisphere (LH), for example, due to stroke. Notably, apraxic deficits cannot solely be explained by elementary sensory or motor impairments (e.g., paresis), disturbances in language comprehension, or general cognitive decline. Instead, apraxia is due to impaired performance of specific, skilled, or learned actions (Cubelli, 2017). Apraxia emerges as the inability to (i) imitate gestures, (ii) produce symbolic movements on command, including pantomime of object use, or (iii) actually use objects/tools (Osiurak & Rossetti, 2017). Apraxia can affect different effectors, e.g., the upper limbs (i.e., the arm, hand, and fingers) or the face and mouth (Cubelli, 2017).

Noteworthy, "apraxia is not a unitary disorder with a unique neuropsychological basis" (Cubelli, 2017, p. 227). Instead, apraxia constitutes a heterogeneous syndrome of more or less independently impaired cognitive (and neural) mechanisms. Consistently, several clinical dissociations between various apraxic deficits have been described and accounted for by a wide range of (disturbed) motor-cognitive processes (Bartolo & Ham, 2016). For example, recent findings in apraxic stroke patients showed selective impairments when imitating novel gestures but preserved imitation of familiar gestures (Achilles et al., 2019; Tessari et al., 2021). Besides, several studies indicated (behavioural and neural) differences in gesture imitation depending on the body part/effector performing a gesture (e.g., hand vs. finger; (Goldenberg & Karnath, 2006; Tessari et al., 2021)), whereas other studies did not support body part-specific mechanisms in gesture imitation (Achilles et al., 2017; Hoeren et al., 2014). Further distinctions have been described between the production of transitive (i.e., tool-related) versus intransitive (i.e., non-tool related) gestures (Dressing et al., 2018) and diverse aspects of tool use (i.e., grasp versus use actions; (Lesourd et al., 2020; Randerath et al., 2010)). On the other hand, several apraxic deficits have been shown to be associated rather than dissociated (Buxbaum et al., 2014; Goldenberg, 2017), implying a set of potentially common cognitive (and neural) mechanisms that might be disrupted to a varying degree following LH stroke.

Another cognitive deficit that frequently occurs after LH stroke and thus commonly accompanies apraxia is aphasia, a disturbance in language comprehension or production (Mengotti et al., 2013; Weiss et al., 2016). Aphasia modulates praxis abilities in LH stroke patients (Achilles et al., 2016), putatively by a disturbed semantic processing underlying deficits in language and (meaningful) action (Weiss et al., 2016). Consistent with this notion, previous research reported that impaired pantomiming of object use co-occurred with deficits in various linguistic abilities. In contrast, defective imitation of hand postures specifically coincided with deficient written language, suggesting that the association between apraxia and aphasia varies across the different praxis and language domains (Goldenberg & Randerath, 2015). However, there is also evidence that aphasic and apraxic deficits can dissociate after LH stroke, implying – at least in part – independent cognitive processes underlying both disorders (Mengotti et al., 2013).

In line with the reported associations and dissociations of different apraxic (and aphasic) manifestations, multiple LH lesion sites have been implicated in apraxia, including parietal, frontal, temporal, and subcortical regions (Sperber et al., 2019). More precisely, lesions of the left inferior parietal lobule (IPL), including the angular gyrus (AG) and supramarginal gyrus (SMG), commonly cause poor gesture imitation (Buxbaum et al., 2014; Goldenberg, 2009). Instead, deficient pantomime of object use is associated with (additional) lesions of the inferior frontal gyrus (IFG; (Goldenberg et al., 2007; Weiss et al., 2016)). Further, lesions affecting the left parietal and frontal regions affect actual object/tool use (Goldenberg & Spatt, 2009; Martin et al., 2016). Besides, areas within the left temporal lobe, involving the (posterior) middle and superior temporal gyri and the underlying white matter, are significant contributors to apraxic deficits in pantomiming and actual tool use (Garcea et al., 2020;

Martin et al., 2016; Salazar-López et al., 2016; Vry et al., 2015). Thus, the pattern of distinct yet (partly) overlapping brain structures within the praxis networks in the LH that mediate the different praxis domains reflects the differential dissociations and associations between the diverse manifestations of apraxia. Still, comprehensive analyses that investigate the different sub-components of apraxic deficits, as well as the associated neural substrates, are sparse (but see (Buxbaum et al., 2014; Rounis et al., 2021)).

As diverse deficit associations and dissociations also occur in spatial neglect and aphasia, principal component analysis (PCA) has been employed to elucidate their main functional components (Alyahya et al., 2020; Kümmerer et al., 2013; Lacey et al., 2017; Verdon et al., 2010). Furthermore, combined behavioural (PCA) and lesion analyses have been previously adopted to investigate dissociations and associations between apraxic and visuospatial deficits in patients with LH stroke (Timpert et al., 2015) and right hemisphere (RH) stroke (Ubben et al., 2020).

The present study aimed to elucidate potential common or differential motor-cognitive components underlying the diverse manifestations of apraxia and their relation to language deficits as well as the associated neural correlates following LH stroke. To this end, we utilised principal component analysis (PCA) and voxel-based lesion-symptom mapping (VLSM) to comprehensively analyse neuropsychological and lesion data of 91 patients with LH stroke. We included apraxia tests evaluating three essential action domains in which apraxic symptoms regularly manifest (i.e., imitation of gestures, pantomime of object use, and actual object/tool use; (Dovern et al., 2012; Vanbellingen & Bohlhalter, 2011)). Some of these apraxia tests involved different body parts (i.e., arm/hand, finger, and face). The neuropsychological testing further included a language assessment with the short version of the Aphasia Check List (ACL-K; (Kalbe et al., 2005)). Behavioural and lesion data of the current stroke patients (n = 82) were aggregated from four previously published studies (Ant et al., 2019; Dovern et al., 2016; Kusch, Gillessen, et al., 2018; Kusch, Schmidt, et al., 2018) and one unpublished project (n = 9), and re-analysed according to new hypotheses.

Based on previous reports about dissociable impairments in gesture imitation depending on the body parts involved (Tessari et al., 2021), we assumed distinct (effector-specific) motor-cognitive mechanisms underlying gesture production in the imitation tests. Among the different action domains, the PCA could similarly identify differential components relating to the domain-specific praxis deficits, for example, deficits in gesture imitation versus actual object use. Alternatively, we hypothesised that some apraxia tests might depend on common motor-cognitive processes involved in, for example, the imitation of gestures and production of object use pantomimes. Given the diverse associations and dissociations described between the various aphasic and apraxic deficits (Goldenberg & Randerath, 2015; Mengotti et al., 2013; Weiss et al., 2016), the PCA could reveal common components underlying shared aspects of language and praxis as well as separate language and motor-cognitive components underlying the dissociable aspects of aphasia and apraxia.

2 Material and methods

2.1 Patient sample

The neuropsychological and lesion data of 91 patients (31 female; age [mean ± standard deviation (SD)] = 63.3 ± 13.3 years) who had suffered a single (first-ever) unilateral ischaemic stroke in the left hemisphere (LH) were retrospectively analysed. All patients were examined during the (early) sub-acute phase (> 24 h post-stroke and ≤ 3 months post-stroke; (Bernhardt et al., 2017); time post-stroke [mean ± SD] = 21.3 ± 17.5 days, range 1 – 69 days). The patients were from the Department of Neurology, University Hospital Cologne (n = 35) or the Neurological Rehabilitation Centre Godeshöhe, Bonn (n = 56). All patients were right-handed and had no other neurological or psychiatric diseases.

Patients had provided written informed consent to participate in the original studies on motor cognition/apraxia (Ant et al., 2019; Dovern et al., 2016; Kusch, Gillessen, et al., 2018; Kusch, Schmidt, et al., 2018) from which the current sample was aggregated. All patients had additionally given consent for using their clinical imaging data for lesion mapping. The local ethics committee of the Medical Faculty of the University of Cologne had approved each of the original studies conducted following the ethical principles of the World Medical Association (Declaration of Helsinki). Besides, all patients consented to the re-analyses of their neuropsychological and lesion data, which the ethics committee of the Medical Faculty of the University of Cologne further approved.

2.2 Neuropsychological assessments

Three standard neuropsychological tests evaluating distinct praxis domains (i.e., imitation of gestures, pantomime of object use, and actual object/tool use) that may affect different body parts (i.e., arm/hand, finger, and face) were applied (Dovern et al., 2012) to comprehensively assess putative apraxic deficits following LH stroke. For the apraxia assessments, patients always used their ipsilesional, i.e., left (non-paretic) hand. Besides, all 91 LH stroke patients underwent a language assessment with the short version of the Aphasia Check List (ACL-K; (Kalbe et al., 2005)). In the following, the administered tests are described in detail.

Cologne Apraxia Screening

Using pantomime and imitation tasks, bucco-facial and arm/hand gestures were evaluated by the Cologne Apraxia Screening (Kölner Apraxie Screening; KAS; (Weiss et al., 2013)). More precisely, the KAS consists of the following four subtests: (1) pantomiming the use of objects related to the face/involving (transitive) bucco-facial gestures [pantomime bucco-facial], (2) pantomiming the use of objects related to the limbs/involving (transitive) arm/hand gestures [pantomime arm/hand], (3) imitation of (intransitive) bucco-facial gestures [imitation bucco-facial], and (4) imitation of (intransitive) arm/hand gestures [imitation arm/hand]. As described previously (Ant et al., 2019), the pantomime tasks consist of photos depicting various objects related to the face (e.g., toothbrush, cup with handle, comb) or the limbs (e.g., whisk, dice, pair of scissors) whose handling the patient is asked to pantomime. Depending on the complexity of the movements, one or two points are given for the presence of certain predefined features of the pantomime (with the number of movement features varying between two and four). Accordingly, there are pantomime items for which two movement features can be scored with two points each (e.g., pantomiming the use of a pair of scissors) or pantomime items for which four movement features can be scored with one point each (e.g., pantomiming the use of a cup). For example, for the item ‘pantomiming the use of a cup (with handle)’, the following features are scored with one point each: (i) lifting the cup by the handle with thumb and index finger, (ii) bringing the cup to the mouth, (iii) opening the mouth, and (iv) slightly tilting the cup by hand rotation. Otherwise, no point is given when movement features are absent. In the imitation tasks, the test material comprises photos of a woman who demonstrates different bucco-facial (e.g., pulling in cheeks, sticking out the tongue, raising eyebrows) or arm/hand gestures (e.g., putting the thumb on the forehead, wiping the mouth, stop sign) that the patient should mimic. In the subtest imitation of arm/hand gestures, the woman in the photos demonstrates the gestures to be imitated with her right hand. For each gesture, four points are given for correct imitation on the first trial. If the imitation is incorrect, the photo is shown again, and two points are given for correct imitation on the second trial or no point for an erroneous second attempt.

Each of the four subtests comprises five items, and the maximum score of each item is four points, resulting in a maximum score of 20 points in each subtest (and a total maximum test score of 80 points). The KAS total score was used to classify patients as apraxic based on the published cut-off criterion of scoring below 77 points (out of 80 points; (Weiss et al., 2013)). For the neuropsychological profiling, different combinations of the four subtests of the KAS were used. To this end, for the pantomime and imitation task scores, the bucco-facial and arm/hand gestures were pooled (maximum score of 40 points). Conversely, the pantomime and imitation tasks were pooled for the bucco-facial and arm/hand effector scores (maximum score of 40 points). Based on the cut-off criterion of the KAS total score (i.e., ≤ 76 points), a separate cut-off score for apraxic deficits for the impaired praxis domain (i.e., pantomime and imitation deficits) and the body part affected (i.e., bucco-facial and limb apraxia) was defined. Patients scoring less than 39 points in a given domain were considered to have pantomime or imitation deficits or bucco-facial or limb apraxia (for a similar procedure, see (Kusch, Schmidt, et al., 2018)).

Imitation tests by Goldenberg

The imitation of hand positions and finger configurations was further evaluated with two apraxia tests devised by Goldenberg (Goldenberg, 1996). For both imitation subtests, the patient is asked to reproduce the (hand and finger) gestures demonstrated by the examiner in a mirror-like fashion (after the first demonstration of each gesture). The examiner sits opposite the patient and uses the right hand, while the patient uses the ipsilesional left hand. For each gesture, two points are given for correct imitation on the first trial. If the imitation is incorrect, the examiner demonstrates the gesture once more, and one point is allocated for correct imitation on the second trial. Otherwise, no point is given if the patient fails to imitate the gesture at the second attempt correctly. For further details of the testing procedure, please refer to Achilles et al. (2019).

The subtest of imitating hand positions contains ten meaningless hand postures relative to the head with invariant finger position. The finger imitation subtest involves ten finger configurations, of which some (up to eight) might be perceived as familiar/meaningful (Achilles et al., 2016). The maximum score for each imitation subtest is 20 points (two maximum points for each of the ten gestures). Patients were considered to present a hand imitation deficit if they scored less than 18 points in the Goldenberg hand imitation test. The cut-off score for presenting a finger imitation deficit is less than 17 points in the Goldenberg finger imitation test (Goldenberg, 1996).

The KAS subtest for imitating arm/hand gestures and the hand imitation test by Goldenberg overlap concerning the effector/body part involved. Note, however, that both tests also differ regarding the presentation mode of the gestures. While the imitation tests of the KAS comprise photos of a woman who demonstrates the gestures that the patient should mimic, the Goldenberg imitation tests require the patient to reproduce the gestures demonstrated by the examiner. On the one hand, using photographs avoids potential stimulus differences that might occur when different examiners demonstrate gestures. On the other hand, the presentation of gestures on two-dimensional photographs (as in the KAS imitation tests) poses higher demands on visual analysis than the presentation of gestures demonstrated by a person in three-dimensional space (as in the Goldenberg imitation tests). Despite these differences in the test material/presentation mode, we could show that both (sub)tests assessing the imitation of hand gestures similarly loaded on the same component and thus seem to draw upon the same motor-cognitive processes (see Results, section 3.2).

Actual object use test

For assessing actual object/tool use, a modified version of the De Renzi test for actual object use (De Renzi et al., 1968) was performed. The test comprises five single objects (hammer, toothbrush, pair of scissors, toy gun, and pencil eraser) and two tool-object pairs (a key with a padlock, a matchbox with a candle), consecutively placed on the table in front of the patient. The patient is asked to demonstrate the use of each of the seven items with the left hand. The presence of certain predefined features of the object use is scored with one or two points (depending on the movement complexity). For example, for the ‘toothbrush’ one point each is given for the following features: (i) the toothbrush is held in front of the mouth, (ii) the mouth is slightly opened, and the teeth are shown, (iii) circling/pushing movements with the toothbrush at hand, and (iv) the brushes of the toothbrush are directed against the teeth. The absence of a given feature is scored with 0 (zero) points. The maximum score for the single objects and tool-object pairs is four or six points, respectively. Thus, the total maximum score of the test is 32 points, with a cut-off of fewer than 30 points indicating an object use deficit.

Short version of the Aphasia Check List (ACL-K)

In addition to the praxis assessment, putative language impairments were assessed using the short version of the Aphasia Check List (ACL-K; (Kalbe et al., 2005). The ACL-K consists of the following four subtests: (1) a reading aloud task, (2) a colour-figure task (modified Token Test) assessing auditory comprehension, (3) a verbal fluency task (supermarket), and (4) a rating of the patient’s verbal communication abilities by the examiner. The ACL-K’s maximum score is 40 points, with patients classified as aphasic when they score less than 33 points. The pathological range can be further subdivided into intervals for mild (26-32 points), moderate (15-25 points), and severe (0-14 points) language impairments (Kalbe et al., 2002).

2.3 Behavioural data analysis

Statistical analyses of the neuropsychological data were performed using IBM SPSS Statistics (Statistical Package for the Social Sciences, version 25, SPSS Inc., Chicago, Illinois, USA). Independent-samples *t*-tests compared means of demographic, clinical, and neuropsychological data between apraxic and non-apraxic patients. Fisher’s exact test was used to assess associations between cognitive deficits (based on the dichotomised behavioural scores of the respective neuropsychological tests, i.e., presence or absence of a deficit). Note that a significant Fisher's exact test indicates a significant association between two respective cognitive deficits. For all analyses, a significance level of $p < .05$ was applied (Bonferroni-corrected for multiple comparisons if applicable).

To evaluate the correlational pattern between the performance in the administered praxis and language tests, 11 different scores (i.e., the scores of the four KAS subtests [pantomime bucco-facial, pantomime arm/hand, imitation bucco-facial, and imitation arm/hand], the scores of the hand and finger imitation tests by Goldenberg, the score of the actual object use test, and the scores of the four subtests of the ACL-K) were subjected to a principal component analysis (PCA). The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy (Kaiser, 1974) and Bartlett's test of sphericity (Bartlett, 1951) were used to determine the suitability of the data for the PCA. We extracted components with eigenvalues above 0.7 (Jolliffe-criterion; (Jolliffe, 1973)) and used a subsequent varimax rotation to retain independent components (while not assuming unrelated components in theoretical terms; see also (Fridriksson et al., 2018; Harris et al., 2019; Ubben et al., 2020)). Notably, by utilising varimax rotation, we aimed to avoid problems of collinearity in the subsequent lesion-behaviour analyses to reveal (putative) specific brain correlates associated with each component (Alyahya et al., 2020; Halai et al., 2017).

The rotated component matrix was then used to examine the relative contributions (i.e., loadings) of each neuropsychological (sub)test on the extracted components. In general, higher loadings reflect a more substantial contribution of a test to a component. Following practical guidelines (Beavers et al., 2013), a (sub)test was considered meaningful for a given component when its loading is 0.7 or higher, and it does not cross-load on another component greater than 0.4. Otherwise, loadings with an absolute value above 0.4 were considered reliable (as applied in (Chen et al., 2016; Randerath et al., 2011; Verdon et al., 2010)). Based on the contributing loadings of the neuropsychological tests on each principal component, we defined the underlying cognitive mechanisms according to the (assumed) processes required to accomplish the respective tests.

Then, individual weighted component scores on each extracted component were estimated through regression as implemented in SPSS. Specifically, the individual component scores were computed by a linear combination of the component score coefficients from the PCA (used as regression weights) and the individual (standardised) test scores. The individual component scores provide information about the patients' relative position along the principal components (in terms of their weighted performance in the neuropsychological tests that cluster on the respective component (Halai et al., 2017)). The individual weighted component scores were then used as behavioural variables in the voxel-wise statistical lesion-behaviour mapping analyses.

2.4 Lesion delineation and voxel-based lesion-symptom mapping (VLSM)

For lesion mapping, the patients' clinical CT (n = 23) or MRI (n = 68) scans were used. All lesions were manually drawn on axial slices of a T1-weighted template MRI scan (ch2.nii) from the Montreal Neurological Institute (MNI) with a 1 mm x 1 mm in-plane resolution using the freely available software package MRIcron. Lesions were mapped in steps of 5 mm in MNI space onto the axial slices that were identical to or closest matched the slices of each individual's CT or MRI. Two examiners had to jointly agree upon the exact lesion location and extent in each patient. This manual lesion delineation is currently considered the (gold) standard for precise lesion demarcation (de Haan & Karnath, 2018).

The lesion maps were then used for the voxel-based lesion-symptom mapping (VLSM) analyses to associate (lesioned) brain regions with the patient's neuropsychological test performance at the voxel level (Bates et al., 2003). Specifically, voxel-wise lesion-behaviour associations were assessed for the individual weighted component scores derived from the PCA on the neuropsychological test scores (separately for each retained principal component). VLSM was conducted using the non-parametric mapping (NPM) program distributed with MRIcron (Version 30/04/2016, https://www.nitrc.org/projects/mricron). Statistical lesion analyses included only voxels that were damaged in at least 5% of all patients (i.e., in at least five patients; see also (Finkel et al., 2018; Garcea et al., 2020; Martin et al., 2017)). Then, voxel-wise *t*-test statistics on the behavioural scores (here: the individual weighted component scores derived from the PCA) were calculated, with groups defined by the absence or presence of damage in each voxel (Rorden et al., 2007). We performed separate VLSM analyses for the retained PCA components to identify lesioned voxels associated with each cognitive process assumed to be represented by the components. Similar to previous studies in LH stroke patients (Dressing et al., 2018; Finkel et al., 2018; Watson & Buxbaum, 2015), voxels were considered significant when passing a statistical threshold of $p < .05$, with correction for multiple comparisons accomplished by false discovery rate (FDR) thresholding (de Haan & Karnath, 2018). We report significant clusters with a minimum size of 20 voxels (arbitrary cluster threshold), along with a region-specific (maximum) *Z*-value and the corresponding coordinates in MNI space. The anatomical localisations comprising significant voxels were determined using the Johns Hopkins University (JHU) atlas template (Faria et al., 2012) provided by MRIcron (as used in (Achilles et al., 2019)) as well as the Anatomy toolbox (Version 3.0; (Eickhoff et al., 2005)) implemented in the Statistical Parametric Mapping software (SPM12, Wellcome Centre for Human Neuroimaging, London, UK, https://www.fil.ion.ucl.ac.uk).

3 Results

3.1 Sample characteristics and neuropsychological profiles

Based on the overall KAS performance used as a standardised diagnostic criterion for apraxia (Weiss et al., 2013), 38 of the 91 LH stroke patients (42%) were classified as apraxic (i.e., scored less than 77 points). The apraxic and non-apraxic (n = 53) patients were comparable concerning age [$t(89) = -2.45$, $p = .016$], time post-stroke [$t(89) = 1.97$, $p = .052$], and lesion size [$t(89) = -0.67$, $p = .507$]. In contrast, the severity of hand imitation deficits [$t(89) = 6.79$, $p < .001$], finger imitation deficits [$t(89) = 4.63$, $p < .001$], object use deficits [$t(89) = 3.45$, $p = .006$], and aphasic deficits [$t(89) = 5.69$, $p < .001$] significantly differed between the two groups (adjusted significance level of $p < .007$; i.e., $p < .05$, Bonferroni-corrected for the number of tests, n = 7). **Table 1** provides an overview of the demographic, clinical, and neuropsychological characteristics separately for the apraxic and non-apraxic patients.

− Please insert Table 1 about here −

Concerning specific praxis deficits in the current sample, almost all apraxic patients (n = 36, 95%) were impaired in the pantomime and imitation tasks of the KAS, while two patients with apraxia showed an isolated pantomime deficit. Accordingly, all apraxic patients suffered from pantomime deficits. Regarding the affected effectors, 28 patients (74%) suffered from bucco-facial and limb apraxia, nine patients (24%) presented with limb-related praxis deficits only, and one patient had isolated bucco-facial apraxia as assessed with the KAS [$\chi^2(1) = 0.32$, $p = .763$]. Thus, following previous clinical studies (Latarnik et al., 2020), limb-related gestures (in contrast to bucco-facial gestures) were more impaired in apraxic LH stroke patients. Besides, in the 38 apraxic patients, an isolated impairment of imitating hand postures was more frequent (n = 13, 34%) than an isolated impairment of imitating finger configurations (n = 4, 11%), as assessed with the Goldenberg imitation tasks. Ten apraxic patients (26%) showed both hand and finger imitation deficits [$\chi^2(1) = 1.10$, $p = .242$].

In line with previous reports (Randerath et al., 2011; Sperber et al., 2018), impairments in actual object use were seen in only a few of the current apraxic patients (n = 8, 21%). To explore whether the current sample of LH stroke patients had a differential performance in the De Renzi test for actual object use when using single objects or tool-object pairs, we compared the performance in the two conditions with paired samples *t*-tests. To this end, subscores were computed for the 'single object use' condition (items 1 – 5) and the 'use of tool-object pairs' condition (items 6 and 7) and converted into percentages to account for the different score ranges. This analysis revealed no significant differences in the performance between single object use and the use of tool-object pairs in the overall sample of the current LH stroke patients [96.9% vs. 97.3%; $t(90) = -0.40$, $p = .689$] nor in the current stroke patients with apraxia [93.3% vs. 94.3%; $t(37) = -0.46$, $p = .649$].

Further, three patients were not classified as apraxic according to the KAS but were slightly/borderline impaired in imitating hand (n = 2; scores of 16 and 17, cut-off-score = 18) or finger gestures (n = 1; score of 16, cut-off-score = 17).

Regarding language performance, 53 of the 91 LH stroke patients (58%) showed aphasia symptoms indicated by the ACL-K (Kalbe et al., 2002). Of those, 24 patients had mild language impairments, 15 had moderate language impairments, and 14 suffered from severe language impairments. As expected (Goldenberg & Randerath, 2015; Weiss et al., 2016), there was a significant association between aphasic and apraxic deficits [$\chi^2(1) = 14.61$, $p < .001$], with 31 of the 91 LH stroke patients (34%) showing concurrent aphasia and apraxia (as assessed by the KAS). Accordingly, most apraxic patients presented with co-morbid aphasia (31 of 38 patients, 82%). On the other hand, 22 aphasic patients did not suffer from apraxia (24% of all cases), while apraxia without aphasia was less common in the LH stroke patients (n = 7, 8%).

3.2 PCA results

For the PCA on the 11 different neuropsychological scores, the KMO measure verified the sampling adequacy of the data (KMO = .87; 'meritorious'), and all KMO-values for individual subtests were >.83 (acceptable limit: .50; (Kaiser, 1974)). Bartlett's test of sphericity was significant [χ^2 (55) = 641.57, $p < .001$], indicating sufficiently high correlations between the variables.

The PCA yielded four (orthogonal) principal components (eigenvalues before rotation > 0.7) that accounted for 81.5% of the total variance observed. The component loadings for each (sub)test are shown in **Table 2**. After varimax rotation, three (of the four) language subtests (i.e., the colour-figure task, the verbal fluency task, and the verbal communication rating) highly loaded on component 1 that explained 25.1% of the variance. The two (different) tests assessing the imitation of arm/hand gestures (i.e., the KAS subtest arm/hand imitation and the Goldenberg hand imitation test) showed distinct loadings on component 2 that explained 22.6% of the variance. Imitating finger configurations and pantomiming object use related to the face/involving bucco-facial gestures highly loaded on component 3, which explained 20.8% of the total variance. Moreover, performance in actually using objects showed a relevant loading (only) on component 3, albeit to a lesser degree than the other two variables (i.e., > 0.4, but < 0.7). Lastly, component 4 accounted for performance in the bucco-facial gesture imitation test and explained 13.0% of the total variance. Two (sub)tests showed reliable loadings (> 0.4) on more than one component, suggesting that performance in these tasks relies on more than one underlying cognitive process. In particular, pantomiming the use of limb-related objects loaded to a similar degree on the second and third component, while the reading aloud task of the ACL-K was related to both component 1 (as the other language subtests) and component 2.

– Please insert Table 2 about here –

To account for a potential effect of the time interval between stroke onset and neuropsychological testing, we performed correlation analyses between the time post-stroke (in days) and the individual weighted component scores for the four retained PCA components using Pearson correlation. Note that the individual component scores indicate the patients' relative position along the principal components, based on their weighted performance in the neuropsychological tests that cluster on the respective component. These analyses did not reveal any significant correlations (all *p*-values > .235). Accordingly, there appeared to be no relevant confounding effect of the different times post-stroke on the current PCA findings.

3.3 Lesion distribution and VLSM results

Figure 1 shows the lesion distribution of the current patients with LH stroke (n = 91; **A**) and an adjusted lesion overlap (**B**). In the latter, voxels are displayed if damaged in at least 5% of the patients and included in the VLSM analyses. The lesioned brain regions mainly covered the left middle cerebral artery (MCA) territory, most commonly affected by ischaemic stroke (Treadwell & Thanvi, 2010). In the current sample of LH stroke patients, the most frequently lesioned brain regions comprised the insula, the basal ganglia (mainly putamen) and adjacent central white matter tracts, the pre- and postcentral gyri, and the supramarginal gyrus (SMG). The most substantial lesion overlap was observed in 27 of the 91 patients (30%), a proportion comparable to previous lesion studies in LH stroke patients (Binder et al., 2017; Martin et al., 2016). Note that (pre)frontal and occipital regions were affected in only a few patients (n < 5) and were, therefore, not tested in the lesion analysis.

− *Please insert Figure 1 about here* −

Separate voxel-wise statistical lesion-behaviour mapping analyses were performed for the four retained PCA components, using the individual weighted component scores and the binary lesion images of the 91 LH stroke patients. Results of the VLSM analyses are displayed in **Figure 2**.

The individual weighted scores of component 1 (representing performance in the language tests; **Fig. 2 A**) showed large lesion clusters (as indicated by the respective maximum *Z*-values) within the insula (max. *Z*-value = 4.82, corresponding MNI coordinates [*x, y, z*]: -32, -10, +13) encompassing subcortical (grey and white matter) areas, the (posterior) superior temporal gyrus (STG; max. *Z*-value = 4.48, corresponding MNI coordinates [*x, y, z*]: -55, -33, +8) extending into the posterior middle temporal gyrus as well as the middle frontal gyrus (MFG; max. *Z*-value = 3.51, corresponding MNI coordinates [*x, y, z*]: -32, +6, +38) and inferior frontal gyrus (IFG; max. *Z*-value = 3.08, corresponding MNI coordinates [*x, y, z*]: -28, +27, +8). Moreover, lesion correlates of component 1 involved the angular gyrus (AG; max. *Z*-value = 3.42, corresponding MNI coordinates [x, y, z]: -39, -53, +28) and supramarginal gyrus (SMG; max. *Z*-value = 2.98, corresponding MNI coordinates [*x, y, z*]: -33, -25, +38).

Scores for component 2 (representing mainly performance in the KAS subtest arm/hand imitation and the Goldenberg hand imitation test; **Fig. 2 B**) were most strongly associated (as indicated by the respective maximum *Z*-values) with lesions affecting the SMG (max. *Z*-value = 4.82, corresponding MNI coordinates [*x, y, z*]: -65, -38, +33) and AG (max. *Z*-value = 4.72, corresponding MNI coordinates [*x, y, z*]: -44, -49, +38) as well as the precentral gyrus (max. *Z*-value = 3.90, corresponding MNI coordinates [*x, y, z*]: -39, -14, +33). For the weighted component 2 scores, additional significant clusters of lesioned voxels were found in the (posterior) STG (max. *Z*-value = 3.89, corresponding MNI coordinates [*x, y, z*]: -44, -23, +13).

Lesions within the AG (max. *Z*-value = 5.06, corresponding MNI coordinates [*x, y, z*]: -44, -59, +53) extending into the intraparietal sulcus (IPS) were significantly associated with the component scores of component 3 (representing mainly performance in imitating finger configurations and pantomiming object use related to the face as well as to a lesser degree in actually using objects; **Fig. 2 C**).

Finally, clusters of voxels where damage was associated with component 4 (representing performance in the imitation of bucco-facial gestures; **Fig. 2 D**) were predominantly located (as indicated by the respective maximum *Z*-values) in the basal ganglia and white matter tracts, with extensions to the rolandic operculum. In particular, significant subcortical lesion sites included the putamen (max. *Z*-value = 5.29, corresponding MNI coordinates [*x, y, z*]: -24, -3, -2), the corona radiata (max. *Z*-value = 4.73, corresponding MNI coordinates [*x, y, z*]: -22, +5, +23), and the internal capsule (max. *Z*-value = 4.70, corresponding MNI coordinates [*x*, *y*, *z*]: -31, -23, +8). Furthermore, the scores of component 4 were significantly associated with lesions of the (posterior) STG (*Z*-value = 4.37, corresponding MNI coordinates [*x*, *y*, *z*]: -63, -22, +13) and postcentral gyrus (*Z*-value = 2.57, corresponding MNI coordinates [*x*, *y*, *z*]: -55, -11, +28).

− Please insert Figure 2 about here –

4 Discussion

The present study characterises the motor-cognitive processes underlying praxis functions and their relationship with language performance in 91 sub-acute left hemisphere (LH) stroke patients at the behavioural and neural levels. A principal component analysis (PCA) was applied to the patients' scores in different apraxia and aphasia (sub)tests. Note that the praxis assessment involved the different action domains in which apraxic deficits commonly manifest (i.e., imitation of gestures, pantomime of object use, and actual object/tool use) and various body parts (i.e., arm/hand, finger, and face). Voxel-based lesion-symptom mapping (VLSM) analyses were used to unveil the neural substrates associated with the underlying cognitive components of apraxia and (related) language deficits identified by the PCA.

The notion that apraxia represents not a unitary disorder but results from a combination of impaired cognitive and neural mechanisms (Cubelli, 2017) was supported by the current PCA-VLSM analyses, which revealed four (orthogonal) principal components that were associated with specific lesion patterns. In particular, a first component accounted for variance in the language (sub)tests. It was related to large clusters in the superior/middle temporal gyri and underlying insula, the inferior and middle frontal gyri, and the inferior parietal cortex. Performance in imitating arm/hand gestures (and to a lesser degree in pantomiming the use of limb-related objects and reading aloud) was represented by a second component that was significantly associated with the inferior parietal lobule (IPL; supramarginal and angular gyri) as well as the precentral and superior temporal gyri. Imitating finger configurations, pantomiming the use of (bucco-facial- and limb-related) objects, and (to a lesser degree) actually using objects loaded on a third component, which was associated with the angular gyrus (AG), extending into the anterior intraparietal sulcus (IPS). A fourth component was representative of performance in imitating bucco-facial gestures and linked to white matter tracts and the basal ganglia (particularly the putamen), extending into the posterior temporal cortex.

On a first note, PCA is a data-driven approach that takes into account the shared (and differential) variance within a dataset of individuals' test scores and extracts the underlying latent (cognitive) components that best represent the associations (and dissociations) between the test performances (Santos et al., 2015). Accordingly, for the apraxia and aphasia tests included (and the group of 91 LH stroke patients studied), the present PCA appeared to decompose the language- and praxis-related components first. The language component explained the largest proportion of the total variance, likely reflecting the clinical predominance of aphasic deficits following LH stroke. Notably, 58% (53 of 91) of the current LH stroke patients suffered from aphasia, and 42% (38 of 91) of the LH stroke patients were apraxic. While aphasia without apraxia was present in 24% of the LH stroke patients, apraxia without aphasia was less common (8%) in the current LH stroke sample. This pattern of apraxic and aphasic deficits in LH stroke is consistent with previous neuropsychological studies (Goldenberg & Randerath, 2015; Papagno et al., 1993; Weiss et al., 2016). In line with the PCA results and the prevalence of aphasic deficits in the current patient sample, the most extensive lesion associations were found for the language component (component 1). Please note that the proportion of explained variance is more evenly distributed after varimax rotation of the components (see also **Table 2**). Due to the statistical independence (orthogonality) of the (rotated) PCA components, we were able to identify rather specific neural substrates associated with the three praxis-related motor-cognitive components.

In the following, we will discuss the distinct components and their represented cognitive processes, the associated lesion patterns after LH stroke, and the dissociations and associations between aspects of the praxis and language deficits.

Component 1 separates language and praxis

The present PCA in LH stroke patients showed that the language (sub)tests (auditory comprehension, verbal fluency, rating of verbal communication abilities, and to a lesser degree reading aloud) loaded on one component, which was rather not associated with praxis functions. Converging with the PCA results, the lesion correlates of component 1 within the left insular, superior temporal, inferior frontal, and inferior parietal cortices represent a network of brain regions commonly associated with (impaired) language processing (Landrigan et al., 2021; Weiss et al., 2016). These findings imply separable cognitive (and neural) mechanisms underlying aphasic and apraxic deficits following LH damage, which adds to previous studies suggesting – at least in part – (functional) independence of language and praxis abilities (Mengotti et al., 2013; Papeo & Rumiati, 2013).

In contrast, other studies have identified cognitive (sub-)processes and neural substrates underlying both aphasia *and* apraxia in LH stroke patients (Goldenberg & Randerath, 2015; Weiss et al., 2016). Notably, these studies compared the results of separate VLSM analyses based on diverse language and praxis tests (in patients with LH stroke). This approach rather emphasises lesion sites common to both domains, whereas the present PCA-based VLSM approach instead highlights distinct lesion correlates of aphasia and apraxia.

Furthermore, the partly diverging findings between previous studies and the current results might presumably be due to methodological aspects or clinical characteristics of the examined LH stroke patients. For example, in the study of Weiss and colleagues (2016), half of the patients (50%) suffered from co-morbid aphasia and apraxia. By contrast, in the current study (only) about one-third of the LH stroke patients (34%) presented with combined aphasic and apraxic deficits, which might have resulted in a less pronounced association between language and praxis functions. Moreover, the investigation of common (or differential) processes of apraxia and aphasia in the study by Goldenberg and Randerath (2015) was based on a broader language assessment (i.e., the Aachen Aphasia Test; (Huber et al., 1983)) than used for the present study (here: the four subtests of the ACL-K; (Kalbe et al., 2002)). Accordingly, more comprehensive coverage of language functions might be necessary to capture the diverse association and dissociation patterns between the differential manifestations of aphasia and apraxia. Note, however, that the reading aloud task also loaded on component 2 (in addition to showing a reliable loading on component 1), suggesting that performance in this task shared cognitive processes with the imitation of arm/hand postures (and to a lesser degree pantomime of limb-related object use; see below).

Component 2 and the IPL

The current PCA finding that the two (different) arm/hand gesture imitation tests (and to a lesser degree the pantomime test with arm/hand items and the reading aloud task) loaded on component 2 suggests that this component could represent processing of spatial relationships between body parts or (external) objects and the body. This interpretation was corroborated by the VLSM results showing a significant association of lesions in the angular gyrus (AG) and supramarginal gyrus (SMG) of the left inferior parietal lobule (IPL) with the component scores of component 2. Notably, the cognitive and neural mechanisms of component 2 support the seminal work of Goldenberg on parietal lobe function in apraxia (Goldenberg, 1996, 2009; Goldenberg & Hagmann, 1997).

The current PCA and VLSM results add to prior research on apraxia in stroke patients that commonly implicated left parietal regions in imitating (arm/hand) gestures (Achilles et al., 2017; Buxbaum et al., 2014; Goldenberg, 2009) and pantomiming object use (Garcea et al., 2020; Niessen et al., 2014; Sperber et al., 2019). Also, the VLSM results revealing an association of lesions in the left precentral and superior temporal gyri with the individual weighted component scores of the PCA component 2 are in line with several functional imaging studies in healthy subjects that assigned the precentral gyrus and (superior) temporal regions to the gesture imitation network (Caspers et al., 2010; Lesourd et al., 2018). Moreover, precentral and temporal areas have been increasingly implicated in object use pantomimes (Garcea et al., 2020; Sperber et al., 2019).

The current cognitive interpretation and lesion associations of component 2 bear similarities with a previous finding by Buxbaum and colleagues (2014). By applying a componential analysis approach to various imitation and pantomime tasks, these authors identified a ‘kinematic component’ representing spatial and body-related aspects of imitative (intransitive and transitive) actions associated with the left IPL and precentral regions. These authors also found that a ‘posture component’ reflecting arm/hand positioning of tool-related actions (i.e., the pantomime of tool use on command and imitation) was critically associated with the left posterior temporal gyrus. Note that the ‘posture component’ proposed by Buxbaum et al. (2014) reflects a representational (or semantic) aspect of praxis underlying tool-specific gestures. Given these findings, both components contain aspects of the here identified principal component 2 that represents spatial processing of arm/hand positions in relation to the body or other (pretended) objects, contributing to both imitating arm/hand gestures and pantomiming the use of (limb-related) objects/tools.

Furthermore, the current finding that the reading aloud task also loaded on component 2 might be interpreted in light of a similarly reported association between impairments in imitation of hand postures and written language related to lesions in the left IPL (Goldenberg & Randerath, 2015). In that former study, the subtest ‘written language’ comprised reading aloud simple and compound nouns and sentences, combining words from anagram letters, and writing to dictation. Per the proposal by Goldenberg and Randerath (2015), reading aloud (here: simple and compound nouns, sentences as well as pseudo-words) might involve the processing of relationships between items, with the unique feature that, in this case, these relationships may include serial properties that are not spatial in a strict sense (e.g., the serial features of letters or words).

Component 3 and the AG/IPS

Lesions of the anterior intraparietal sulcus (IPS) and the AG were significantly associated with the individual weighted component scores of the PCA component 3, underlying the imitation of finger configurations, the pantomime of object use, and actual object use. These findings suggest that component 3 could represent processing of structural features of (parts of) the body or objects/tools, which serves appropriate distinction of the finger configurations in the finger imitation test and (functional) grasping movements/grip formation in pantomimed and actual object use.

In line with this notion, previous VLSM studies showed that finger gesture imitation depended (among others) on regions around the left IPS and AG supporting the structural analysis of perceptually similar finger configurations as well as finger (movement) control (Achilles et al., 2019; Hoeren et al., 2014). Moreover, our results converge with a critical role of the IPS in tactile shape-processing and coordination of finger movements for object manipulation, as implicated by several lines of previous research comprising electrophysiological studies in non-human primates (for review, see (Grefkes & Fink, 2005)), functional imaging studies in healthy subjects (Culham & Valyear, 2006; Grefkes et al., 2002), and lesion studies in stroke patients (Binkofski et al., 1998). Besides, previous lesion studies in stroke patients with apraxia associated grasping errors (incorporating inaccurate finger grip) during actual object/tool use also with lesions to the left AG and anterior IPS (Martin et al., 2016; Randerath et al., 2010).

Finally, the observation that the current PCA component 3 was also associated with pantomiming object/tool use (as assessed by the KAS subtests of bucco-facial and (to a lesser degree) arm/hand pantomimes) is consistent with a recent VLSM study in apraxic LH stroke patients showing that the AG is critical for the motor-cognitive aspects of object use pantomimes, and in particular for the proper use of grip that “include forming fingers as if the object would be held in hand” (Finkel et al., 2018, p. 1011). Interestingly, a region-of-interest analysis of functional imaging data revealed a differential activation of the left IPS for pantomiming object use when contrasted with actual object use (Hermsdörfer et al., 2007).

Component 4 and subcortical structures

Component 4 specifically reflected the imitation of bucco-facial gestures and was mainly linked to the basal ganglia (particularly the putamen) and LH white matter tracts. This finding suggests that component 4 represents a rather general processing of bucco-facial features, which might be associated with increased visuoperceptual demands or visuospatial working memory. This notion is compatible with clinical findings that bucco-facial apraxia occurs predominantly in patients who have suffered a stroke in the right hemisphere (when compared to patients with LH stroke; (Bizzozero et al., 2000; Latarnik et al., 2020)), presumably due to disturbances in visuospatial processing (Ubben et al., 2020). The lesion correlates (and cognitive interpretation) of component 4 further add to a neuropsychological study in patients with Parkinson's disease (PD) that implicated a functional role of the basal ganglia in action imitation and visuospatial memory functions (Bonivento et al., 2013).

Concerning the neural correlates underlying bucco-facial apraxia in LH stroke patients, a previous study using qualitative lesion analyses related deficits in imitating (bucco-)facial gestures also to lesions of the basal ganglia as well as to peri-sylvian and central areas, the insula, and the inferior frontal gyrus (Raade et al., 1991).

Generally, that basal ganglia and white matter lesions were significantly associated with the component scores of component 4 supports recent reports of a relevant contribution of subcortical structures to apraxia in LH stroke patients (Lesourd et al., 2018; Sperber et al., 2019). However, only a few neuropsychological (case) studies documented apraxic (imitation and pantomime) deficits in patients with circumscribed subcortical lesions (Agostoni et al., 1983; De Renzi et al., 1986; Tabaki et al., 2010). Note that apraxic deficits have also been described in Parkinson's disease (PD), a neurodegenerative disorder affecting basal ganglia–cortex loops (Heilman, 2020). Since stroke-induced lesions of the basal ganglia often encompass adjacent central white matter tracts, it remains a matter of debate whether *isolated* basal ganglia lesions cause apraxic deficits (Pramstaller & Marsden, 1996). Notably, the neural correlates of component 4 encompassed the basal ganglia and subcortical white matter tracts, including the internal capsule and corona radiata.

Distinct and shared contributions of the motor-cognitive components to apraxic deficits

The current PCA showed distinct (effector-specific) motor-cognitive components (associated with differential neural correlates) underlying the imitation of arm/hand (component 2), finger (component 3), and bucco-facial gestures (component 4). This finding is consistent with previous neuropsychological studies in apraxic patients with LH stroke that have reported behavioural and neuroanatomical dissociations in imitation performance between arm/hand *and* facial gestures (Raade et al., 1991; Scandola et al., 2021) as well as between hand *and* finger postures (Dovern et al., 2011; Goldenberg & Karnath, 2006; Tessari et al., 2021).

The current pattern of results suggests that the PCA component 2 represents the processing of spatial relationships between different body parts (i.e., the arm/hand in relation to the head/face). In contrast, the PCA component 3 represents the processing of structural features of body parts (e.g., for the appropriate distinction of finger configurations). In line with this interpretation, a behavioural distinction in imitation performance between hand and finger gestures was initially accounted for by differing demands on body part coding (i.e., the determination of the spatial relationship between the hand and several parts of the head/face) and on perceptual discrimination between relatively uniform elements of the body (i.e., fingers), respectively (Goldenberg & Karnath, 2006). Similarly, it has been proposed that the imitation of arm/hand versus finger gestures may rely on distinct types of representations of the human body (Rumiati et al., 2010; Schwoebel & Coslett, 2005). That is, the imitation of arm/hand postures might primarily depend on (online sensorimotor) representations that code the spatial position of different body parts relative to each other (Schwoebel et al., 2004). In contrast, the imitation of finger configurations might be more sustained by representations of structural properties of the body/body parts (Tamè et al., 2017).

Furthermore, the current PCA indicating a distinct (fourth) component specific for the *imitation* of bucco-facial gestures (in contrast to the imitation of arm/hand and finger gestures) supports the notion that bucco-facial and limb apraxia rely on (at least partially) separable motor-cognitive functions, and may thus be considered different forms of praxis disorders (Cubelli, 2017; Raade et al., 1991). However, performance in pantomiming the use of objects related to the face and head (bucco-facial *pantomime* subtest of the KAS) loaded on component 3 – together with finger imitation, actual object use, and (to a lesser degree) arm/hand pantomimes. Taken together, the current PCA results suggest that it is not (only) the effector that determines the underlying components. Instead, separable and shared motor-cognitive processes reflected by the distinct PCA components contribute to the performance in the different apraxia tests and thus to the different apraxia types.

Besides, the current PCA revealed that pantomiming object use shared motor-cognitive components (and associated brain regions) with gesture imitation and actual object use. This result of common components across diverse action domains is consistent with previous studies in LH stroke patients that indicated at least partly joint cognitive processes (and neural substrates) underlying pantomime of object use *and* imitation (Buxbaum et al., 2014; Hoeren et al., 2014) as well as pantomime *and* actual object use (Hermsdörfer et al., 2013; Randerath et al., 2011).

In addition, pantomiming the use of limb-related objects drew on more than one motor-cognitive component, which aligns with the notion that several cognitive processes are required to produce object use pantomimes (Bartolo & Ham, 2016; Goldenberg, 2017). Previously, an impaired pantomime of object/tool use has been associated with deficits in (action-related) working memory (Bartolo et al., 2003), semantic processing (Goldenberg & Randerath, 2015; Weiss et al., 2016), or communicative skills (Finkel et al., 2018). The current PCA results further point to the relevance of processing spatial relationships between the acting hand in relation to the (pretended) object and the processing of structural object representations, including the body, in pantomiming object use.

Notably, the KAS subtest bucco-facial pantomime depended on (only) one motor-cognitive component (here: component 3). This finding suggests that processing structural features/representations of body parts (or external objects) specifically contributes to object use pantomimes related to the face/body, putatively because they demand (enhanced) processing of structural body representations.

To explore a potential influence of reflexive versus non-reflexive gestures on the performance in the apraxia tests (and therefore in the PCA), we considered the component loadings of the imitation and pantomime tests on the respective components. While the imitation of hand postures is directed towards the body (i.e., reflexive), the imitation of finger configurations is produced away from the body (i.e., non-reflexive; cf. (Bartolo et al., 2019)). Conversely, in the pantomime tasks, the bucco-facial items involve gestures performed towards the body (i.e., reflexive; e.g., pantomiming the use of a comb), whereas the arm/hand items involve gestures performed away from the body (i.e., non-reflexive; e.g., pantomiming the use of a dice; cf. (Bartolo et al., 2019)). The PCA revealed that the finger imitation test and the pantomime task with bucco-facial items highly loaded on component 3, even though the tasks involve gestures performed away from (non-reflexive) and toward the body (reflexive), respectively. Moreover, the pantomime task with arm/hand items involving non-reflexive gestures loaded to a similar extent on component 2 and component 3 and thus shared common variance with tasks that involve reflexive gestures (i.e., imitation of hand postures [component 2] and bucco-facial pantomime [component 3]). The pantomime task with arm/hand items also shared variance with the finger imitation test, both involving non-reflexive gestures. However, the (overall) pattern of results does not suggest a relevant influence of the reflexive nature of the gesture on the cognitive components identified by the current PCA.

Limitations

The adopted VLSM method assesses statistical associations between brain damage and behavioural performance on a voxel-by-voxel basis and thus provides a spatial resolution comparable to functional neuroimaging (Bates et al., 2003; Rorden et al., 2007). Notably, the spatial resolution of the current lesion maps was lower between (5 mm) than within the mapped slices (1 mm). Moreover, the current lesion analyses were based on clinical imaging aggregated from several studies. Thus, differences between imaging methods (CT and MRI) and various scanning procedures might also have affected spatial resolution (de Haan & Karnath, 2018). However, similar procedures have been applied in previous VLSM studies in LH stroke patients (Achilles et al., 2019; Sperber et al., 2019).

Regarding the behavioural data that were derived from several previous studies and used for the current PCA, in all patients, the neuropsychological testing was conducted at the 'baseline' assessment, before any (experimental) tasks (Dovern et al., 2016; Kusch, Gillessen, et al., 2018) or therapeutic procedures (Ant et al., 2019; Kusch, Schmidt, et al., 2018). Accordingly, the neuropsychological data should not have been biased by sequence effects in any relevant way.

Finally, the tests included in the PCA do not capture all aspects that could be relevant for characterising the principal (motor-cognitive) components underlying apraxic deficits, for example, the meaning of a gesture (i.e., a distinction between abstract/meaningless and symbolic/meaningful gestures). Indeed, several neuropsychological studies in LH stroke patients with apraxia showed an influence of the gesture meaning on imitation performance (Achilles et al., 2016; Goldenberg & Hagmann, 1997). Recently, the meaning of a gesture was further found to modulate a differential effect of the body part/effector (i.e., hand vs. finger) on imitation performance; that is, the imitation of gestures was affected by the effector only when the gesture was meaningless (but not when the gesture was meaningful; (Tessari et al., 2021)). Therefore, future studies should investigate whether the meaning of a gesture further subdivides the different motor-cognitive (and language) components.

Conclusion

Using combined PCA and VLSM analyses in a large cohort of sub-acute LH stroke patients, we identified three motor-cognitive components underlying praxis deficits associated with specific lesion patterns in fronto-parietal, anterior intra-parietal, and subcortical brain regions. Besides, a separable language component, associated with lesions of peri-sylvian areas, strongly suggests that praxis- and language-related processes rely – at least in part – on separate cognitive mechanisms, implemented by distinct (albeit partly overlapping) neural substrates within the LH. Thus, our data support the notion that apraxia is a multi-componential syndrome associated with different impaired cognitive motor processes, dissociating from language processes.

Moreover, our results strongly suggest that the neuropsychological praxis examination of LH stroke patients should include multiple tests (assessing different action domains and effectors) to comprehensively assess the motor-cognitive processes underlying the various clinically relevant manifestations of apraxia.

TOP statements

The ethics approval does not permit public archiving of anonymised patient data since public data sharing was not contemplated in ethical consensus and in the patient informed consent. Readers seeking access to the data should contact the senior author (Peter H. Weiss) or the local ethics committee at the Medical Faculty of the University of Cologne. Access to the data may be granted to named individuals per ethical procedures governing the reuse/sharing of clinical data, including completion of a formal data sharing agreement and approval of the local ethics committee. Legal copyright restrictions prevent public archiving of the various tests and assessment batteries used in this study, which can be obtained from the copyright holders in the cited references.

No part of the study procedures or analyses was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

We report how we determined our sample size, all data exclusions (if any), all inclusion/ exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

Acknowledgments / Funding

GRF and PHW are funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project-ID 431549029 – SFB 1451.

CRediT authorship contribution statement

Claudia C. Schmidt: Conceptualisation, Data Curation, Formal analysis, Writing - Original Draft, Visualisation, Writing - Review & Editing; **Elisabeth I. S. Achilles:** Data Curation, Writing - Review & Editing; **Gereon R. Fink:** Writing - Review & Editing, Resources, Project administration, Supervision, Funding acquisition; **Peter H. Weiss:** Conceptualisation, Visualisation, Writing - Review & Editing, Resources, Project administration, Supervision

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Tables

Table 1. Demographic, clinical, and neuropsychological characteristics of the LH stroke patients with (n = 38) and without apraxia (n = 53).

	Apraxic patients (n = 38)	Non-apraxic patients (n = 53)
KAS total#	62.8 (13.6)	79.2 (1.2)
KAS subtests pantomime	31.2 (7.8)	39.3 (1.0)
KAS subtests imitation	31.6 (7.5)	39.9 (0.5)
KAS subtests bucco-facial	32.9 (7.4)	39.5 (0.9)
KAS subtests arm/hand	29.9 (8.2)	39.7 (0.8)
Goldenberg hand imitation test	14.3 (5.2)	19.3 (1.0)*
Goldenberg finger imitation test	17.0 (3.1)	19.1 (1.1)*
Actual object use test (De Renzi)	30.0 (3.8)	31.8 (0.5)*
ACL-K total	21.4 (11.1)	31.9 (6.5)*
Age (years)	67.2 (12.7)	60.5 (13.2)
Time post-stroke (days)	17.1 (16.0)	24.3 (18.0)
Lesion size (voxels)	5486.9 (10489.9)	4283.2 (6719.9)

Means and standard deviations (SD; in parentheses) are given.

Note that the apraxia classification was based on the KAS cut-off score of ≤ 76 points. Therefore, group differences for the KAS scores were not evaluated statistically.

* Significant group effects between apraxic and non-apraxic patients at the level of $p < .007$ (i.e., $p < .05$, Bonferroni-corrected for 7 comparisons) using independent-samples *t*-tests.

KAS = Kölner (Cologne) Apraxia Screening (total maximum score: 80 points; cut-off for apraxia ≤ 76 points). KAS scores for the pantomime and imitation subtests and the subtests of bucco-facial and arm/hand gestures (maximum score: 40 points each; cut-off for impairment ≤ 38 points).

Goldenberg hand imitation test (maximum score: 20 points; cut-off for impairment ≤ 17 points).
Goldenberg finger imitation test (maximum score: 20 points; cut-off for impairment ≤ 16 points).
De Renzi test for actual object use (maximum score: 32 points; cut-off for impairment < 30 points).
ACL-K = Aphasia Check List-short version (maximum score: 40 points; cut-off for aphasia < 33 points).
For detailed information on the neuropsychological tests, see Material and methods (section 2.2.).

Table 2. Results of the principal component analysis (PCA; rotated component matrix) revealing the relationship between the performances of the 91 patients with sub-acute LH stroke in the praxis (n = 7) and language (n = 4) (sub)tests.

	Component 1	Component 2	Component 3	Component 4
Pantomime bucco-facial (KAS)	0.39	0.19	**0.72**	0.34
Pantomime arm/hand (KAS)	0.33	***0.51***	***0.50***	0.39
Imitation bucco-facial (KAS)	0.15	0.20	0.21	**0.91**
Imitation arm/hand (KAS)	0.14	**0.86**	0.30	0.19
Imitation hand (Goldenberg test)	0.23	**0.84**	0.35	0.04
Imitation finger (Goldenberg test)	0.00	0.25	**0.87**	-0.02
Actual object use (De Renzi test)	0.18	0.35	***0.67***	0.36
Reading aloud (ACL-K)	***0.47***	***0.65***	0.09	0.36
Colour-figure task/token test (ACL-K)	**0.79**	0.26	0.17	0.17
Verbal fluency (ACL-K)	**0.87**	0.13	0.13	0.09
Verbal communication rating (ACL-K)	**0.88**	0.16	0.09	0.07
Explained variance (after rotation) in %	53.7 (25.1)	13.8 (22.6)	7.3 (20.8)	6.7 (13.0)
Eigenvalues (after rotation)	5.91 (2.76)	1.52 (2.49)	0.80 (2.29)	0.74 (1.43)

The four components accounted together for 81.5% of the total variance.
Component loadings (after varimax rotation) above 0.7 are printed in bold, with the corresponding (sub)tests considered relevant for that component. Component loadings above 0.4 are marked in bold and italics, indicating (sub)tests that contributed to more than one component. Please note that the De Renzi test for actual object use was assigned to component 3.

ACL-K = Aphasia Check List-short version; KAS = Kölner (Cologne) Apraxia Screening

Figure legends

Figure 1. Lesion overlay plots.
A. Lesion distribution in the current LH stroke patients sample (n = 91).
B. Adjusted lesion overlap of the LH stroke patients: voxels are displayed if damaged in at least 5% of the patients and included in the VLSM analyses.
Colour shades represent the increasing number of overlapping lesions. Axial slices with MNI z-coordinates from -7 to +63 are shown.

Figure 2. Results of the voxel-wise statistical lesion-behaviour mapping analyses with the individual weighted component scores derived from the PCA.
Results of the separate VLSM analyses showing lesions associated with component 1 (**A**), component 2 (**B**), component 3 (**C**), and component 4 (**D**).
A. Lesions affecting the insula as well as temporal and frontal cortices were associated with the weighted scores of component 1, representing performance in several language tasks.
B. Lesions affecting the left inferior parietal lobule (IPL) and the precentral gyrus were associated with the weighted scores of component 2, representing performance in imitating arm/hand gestures (and to a lesser degree in pantomiming the use of limb-related objects and reading aloud).
C. Lesions affecting the left anterior intraparietal sulcus (IPS) and angular gyrus (AG) were related to the weighted scores of component 3, reflecting performance in imitating finger configurations, pantomiming the use of objects related to the face, and actually using objects (and to a lesser degree in pantomiming the use of limb-related objects).
D. Lesions affecting the basal ganglia and white matter tracts were linked to the weighted scores of component 4, reflecting performance in imitating bucco-facial gestures.

Please, refer to the text for further significantly associated lesion sites, region-specific (maximum) Z-values of the significant peak voxels, and the corresponding MNI coordinates.

Note that only voxels lesioned in at least 5% of the patients were included in the VLSM analyses.
Colours indicate the Z-values of the corresponding voxels. Displayed results are thresholded at $p < .05$, FDR corrected; the Z-values corresponding to this statistical threshold (component 1: $Z > 1.75$; component 2: $Z > 2.64$; component 3: $Z > 3.20$; component 4: $Z > 2.48$) are indicated by the white bars.

Axial slices with MNI z-coordinates from -7 to +63 are shown.

Figures

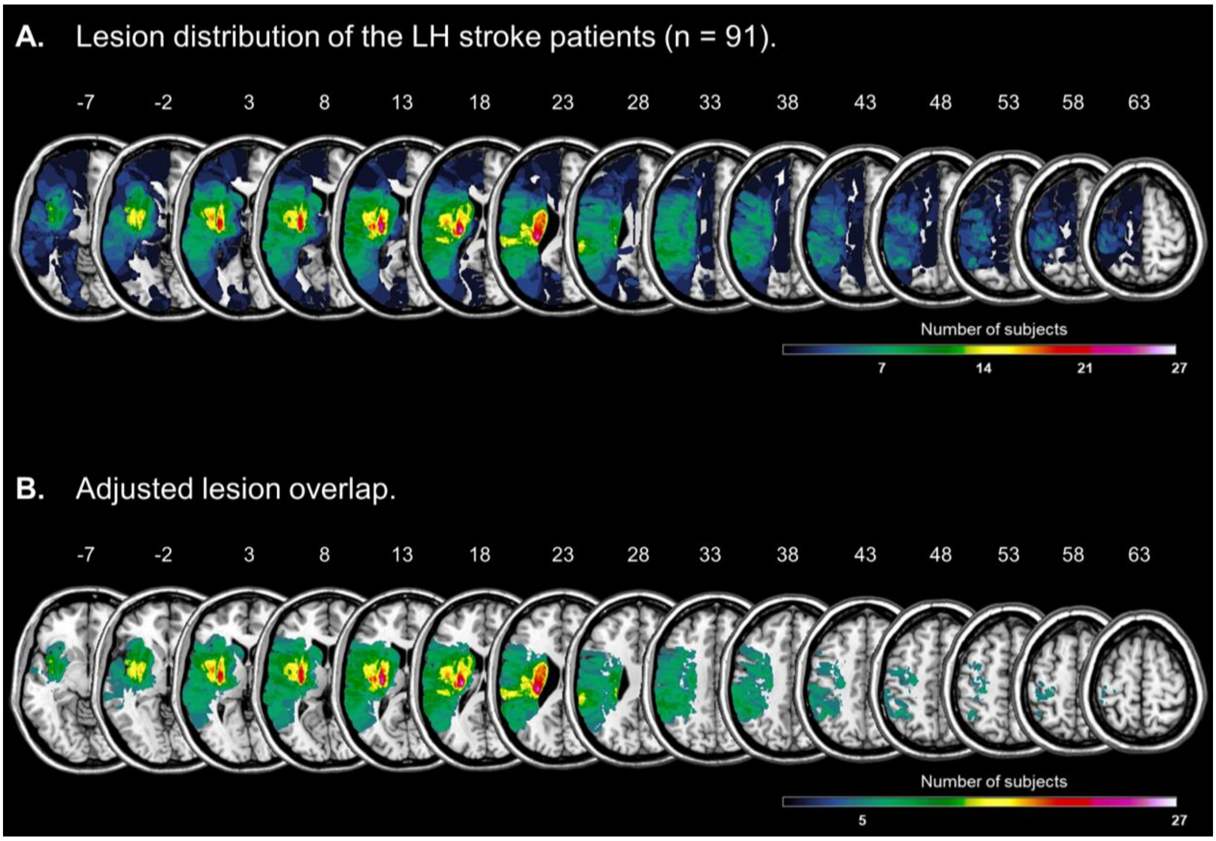

Figure 1.

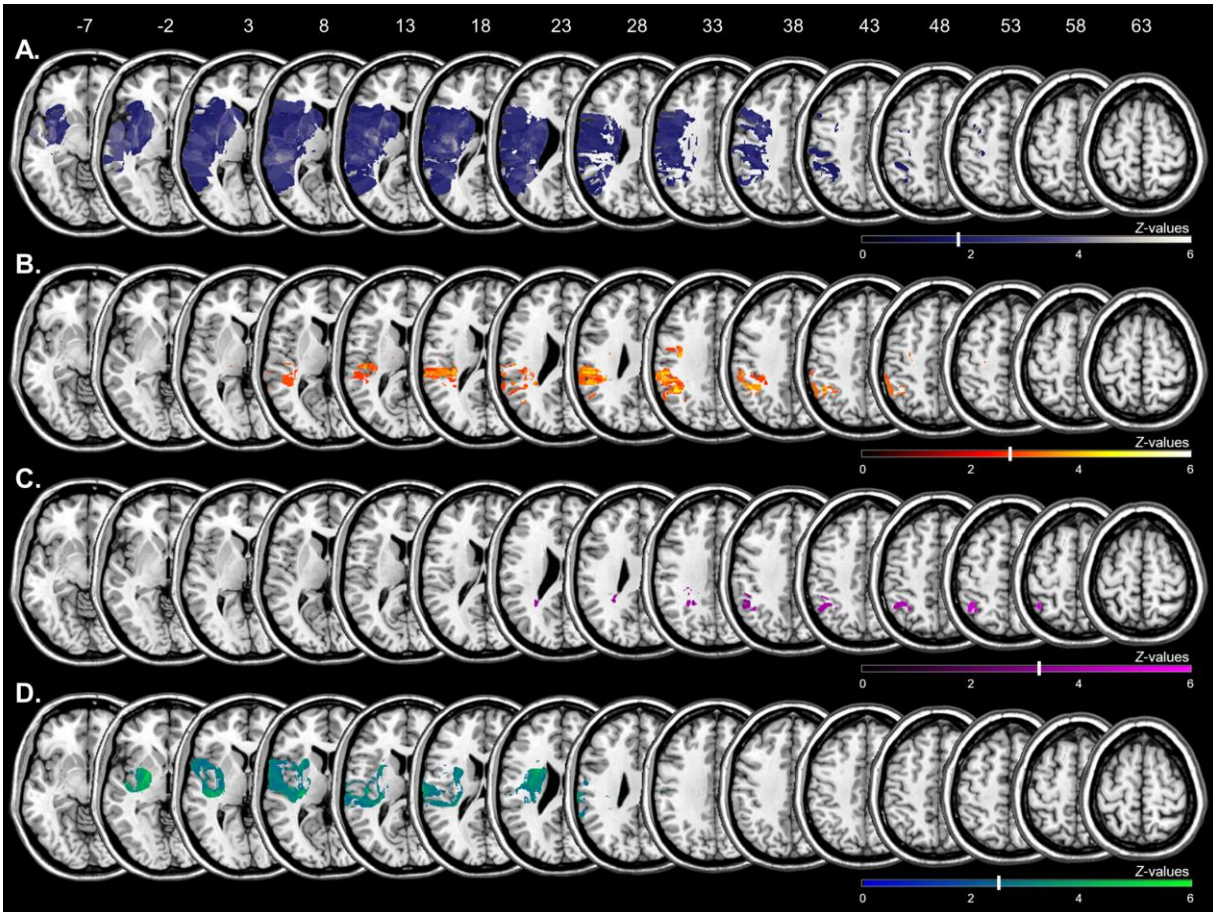

Figure 2.