Deficient allo-centric visuospatial processing contributes to apraxic deficits in sub-acute right hemisphere stroke

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Authors contributions

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Analysis or interpretation of data:	SDU, GRF, SK, EK, SV, PHW
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Abstract

While visuospatial deficits are well characterized cognitive sequelae of right hemisphere (RH) stroke, apraxic deficits in RH stroke remain poorly understood. Likewise, very little is known about the association between apraxic and visuospatial deficits in RH stroke or about the putative common or differential pathophysiology underlying these deficits.

Therefore, we examined the behavioral and lesion patterns of apraxic deficits (pantomime of object use and bucco-facial imitation) and visuospatial deficits (line bisection and letter cancellation tasks) in 50 sub-acute RH stroke patients. Using principal component analysis (PCA), we characterized the relationship between the two deficits. We hypothesized that any interaction of these neuropsychological measures may be influenced by the demands of ego-centric / space-based and / or allo-centric / object-based processing.

Contralesional visuospatial deficits were common in our clinically representative patient sample, affecting more than half of RH stroke patients. Furthermore, about one third of all patients demonstrated apraxic deficits.

PCA revealed that pantomiming and the imitation of bucco-facial gestures loaded clearly on a first component (PCA1), while letter cancellation loaded heavily on a second component (PCA2). For line bisection, overall mean deviation loaded on PCA1, while the difference between the mean deviations in contra- versus ipsilesional space loaded on PCA2.

These results suggest that PCA1 represents allo-centric / object-based processing and PCA2 2 ego-centric / space-based processing. This interpretation was corroborated by the statistical lesion analyses with the component scores.

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Introduction

Apraxia is a cognitive motor disorder impairing imitation and (pantomiming) the use of objects. Since apraxia is i) most often observed after lesions to the left hemisphere ((LH; (Dovern, Fink, & Weiss, 2012)), and ii) considered to be the classical cognitive disorder along with aphasia in LH stroke patients (P.H. Weiss et al., 2016), apraxia research traditionally focuses on apraxic deficits and their neural underpinnings after LH damage.

In contrast, most studies examining cognitive sequelae of right hemisphere (RH) stroke investigated contralesional visuospatial deficits (i.e., neglect) that are common in RH stroke survivors (L.J. Buxbaum et al., 2004).

However, apraxic deficits also occur after lesions to the RH (Hanna-Pladdy et al., 2001). The reported frequency of apraxia in RH stroke varies considerably. This variability is likely due to the different tasks used to assess higher motor cognition and the fact that patients at different stages of their stroke (i.e., sub-acute and chronic) were studied. In an inpatient rehabilitation setting, a recent study reported a prevalence rate of 38% for (bucco-facial and limb) apraxia in 21 sub-acute and chronic RH stroke patients 7 [5-14] weeks post onset (Civelek, Atalay, & Turhan, 2015). With respect to the characteristics of apraxic deficits, a relative predominance of facial apraxia (incidence of 67%) was found after (sub-acute) RH stroke (12.6 [6-30] days post onset; (Bizzozero et al., 2000)). This study pointed to an important role of the RH in imitating (bucco-)facial (meaningful and meaningless) gestures. Furthermore, RH lesions seem to particularly impair the imitation of finger configurations (compared to the imitation of hand gestures; (Goldenberg, Münsinger, & Karnath, 2009)), possibly due to disturbed enhanced visuospatial processing demands.

Likewise, behavioral data is scarce regarding the relationship between apraxic and contralesional visuospatial deficits, i.e., neglect, in RH stroke. In a study focusing on chronic elderly stroke patients (on average 19.9 months after stroke), 90% of neglect patients with predominantly RH strokes (71%) exhibited apraxic deficits (Linden, Samuelsson, Skoog, & Blomstrand, 2005). Note that non-lateralized and lateralized visuospatial deficits were pooled in this study. A significant association of lateralized visuospatial deficits and (ideomotor) apraxia was reported for mostly chronic RH stroke patients in an inpatient rehabilitation clinic (Civelek et al., 2015). Moreover, Goldenberg and colleagues described a strong association between the severity of contralesional visuospatial neglect and the degree of deficit when imitating finger configurations in a sample of sub-acute and chronic RH stroke patients 12.3 [3-44] weeks post onset (Goldenberg et al., 2009).

To date, the lesion correlates of apraxic deficits after RH stroke remain to be elucidated. Descriptive (qualitative) lesion analysis suggests that in both LH and RH stroke patients facial apraxia is associated with lesions to sub-cortical or anterior brain regions (Bizzozero et al., 2000). Furthermore, to the best of our knowledge, only one study exists that employed statistical lesion mapping methods (e.g., voxel-based lesion-symptom mapping, VLSM) to apraxic deficits after RH lesions (Manuel et al., 2013). In that study of 150 left and right brain-damaged patients due to tumors or stroke, the sub-group of 81 stroke patients confirmed that there were more apraxic patients in the group “left hemispheric with aphasia” than in the group “left hemispheric without aphasia” and in the group “right-hemispheric.” With regard to the research question of interest in the current study, impaired pantomiming was observed in 8% of the right brain damaged patients, but no further conclusions regarding the associated lesions within the right hemisphere were drawn.

To advance our understanding of the pathophysiology of apraxic deficits after RH stroke and to further explore their relation to visuospatial deficits, we performed comprehensive behavioral and statistical lesion analyses in a clinically representative sample of sub-acute RH stroke patients (n=50). For the assessment of praxis deficits, we chose centrally presented stimuli to minimize the confounding effects of a lateralized spatial bias in RH stroke patients (e.g. when stimuli are located on the contralesional [here: left] side). Therefore, the stimuli for the pantomime task, a sensitive task to detect apraxic deficits (Niessen, Fink, & Weiss, 2014), were presented centrally. In the same vein, we focused on the imitation of bucco-facial gestures. This task also uses centrally presented stimuli and has been linked to RH functioning in a previous landmark study on apraxia (Bizzozero et al., 2000). Since the term "neglect" describes a rather heterogeneous disorder of spatial cognition that can present with various, partly dissociable clinical sub-types (L.J. Buxbaum et al., 2004; Halligan, Fink, Marshall, & Vallar, 2003), we here focused on lateralized visuospatial deficits that can be further subdivided in allo-centric / object-based or ego-centric / space-based deficits. Hence, for our neglect assessment, we employed line bisection and letter cancellation tasks to evaluate both the allo-centric (object-based) and the ego-centric (space-based) components of visuospatial processing.

As the diverse clinical manifestations of both apraxia and neglect are likely to be caused at least in part by differential dysfunctional cognitive mechanisms, it is essential to approach their potential association at a sub-syndromal level. If apraxia and visuospatial deficits are caused by a disruption of distinct cognitive mechanisms, then apraxic and neglect-related symptoms should dissociate in RH stroke patients. In contrast, the finding of an association between subsets of apraxic and neglect-related symptoms would suggest a common cognitive mechanism that can be impaired by RH stroke. For instance, it is reasonable to assume that impairments in allo-centric / object-based processing caused by RH stroke may affect the visual analysis of gestures (e.g., facial gestures) required for correct imitation (Tessari, Canessa, Ukmar, & Rumiati, 2007), as well as visuospatial tasks that rather draw upon allo-centric / object-based processing like the line bisection task (Oppenländer et al., 2015). A data-driven approach for revealing such specific inter-correlations of neuropsychological task measures is principal component analysis (PCA) (Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). Moreover, entering the resulting individual PCA component scores into lesion analyses employing VLSM may allow to further characterize the neural mechanisms affecting praxis and / or visuospatial functions in RH stroke patients.

Thus, by characterizing the specific apraxic and visuospatial deficits in a large sample of RH stroke patients (n=50) at both the behavioral and lesion level, the current investigation aimed at elucidating the underlying cognitive processes and their neural correlates that cause common or differential impairments of praxis and visuospatial functions in RH stroke.

Methods

Patients

In total, 70 patients with the tentative diagnosis of a supra-tentorial (ischemic or hemorrhagic) RH stroke were consecutively recruited from January 2009 to May 2011. All patients fulfilled the following inclusion criteria: sufficient knowledge of German, age >18 and <90 years, right-handedness, no other neurological or psychiatric diseases affecting cognitive abilities.

In two patients, stroke diagnosis was not confirmed (discharge diagnosis: epilepsy and subarachnoid hemorrhage, respectively). Twelve of the remaining 68 patients exhibited additional exclusion criteria: Nine patients suffered from bi-hemispheric lesions according to patient history or imaging data ((note that patients with left-hemispheric defects greater than 10mm were considered to suffer from bi-hemispheric lesions, (P.H. Weiss et al., 2016)). In three patients, lesions were not sufficiently demarcated in clinical imaging despite persisting neurological / neuropsychological deficit. Finally, in six further patients behavioral assessment (pantomime of object use or line bisection) was incomplete.

The final patient sample (n=50; 28 males, 56.0%) had a mean age of 65.7 years (SD: 14.3; median: 71.0; range: 27-85). Four of the 50 patients (8.0%) suffered from a hemorrhagic stroke. Ischemic infarcts (n=46) involved the carotid artery territory in 39 cases (84.8% of patients with ischemic infarcts), while five patients (10.9%) presented with an ischemic infarction in the territory of the posterior cerebral artery. Two patients (4.4%) showed a hemodynamic ischemic lesion pattern in clinical imaging (posterior border zone or watershed infarction). There were three patients, who presented with *additional* infra-tentorial lesions affecting the pons and / or cerebellum.

Thus, with comparable rates for mean age, proportion of males, hemorrhagic strokes, and proportion of hemodynamic infarcts, the current sample constitutes a clinically representative sample of RH stroke patients according to the Lausanne stroke registry (Bogousslavsky, van Melle, & Regli, 1988).

The mean time interval between stroke onset and neuropsychological assessment was 7.3 days (median: 6.0; range: 1-33; SD: 6.4). All patients were examined during the sub-acute stage of their disease ((i.e., >24h post-stroke (Hillis et al., 2002) and <3 months post-stroke (Bizzozero et al., 2000; Civelek et al., 2015)). The study had been approved by the local ethics committee.

Neuropsychological Assessment

Cognitive tasks were administered by a clinical neuropsychologist and were based on a larger neuropsychological bedside screening tool specifically designed for stroke patients in the early (sub-acute) stage of stroke (Cologne Neuropsychological Screening for Stroke patients, German: Kölner Neuropsychologisches Screening für Schlaganfall-Patienten (KöpSS); (Kaesberg, Fink, & Kalbe, 2013)).

Pantomime of object use and imitation, two common tasks to detect apraxia in stroke patients, were used to assess praxis performance (Dovern et al., 2012). We used centrally presented stimuli to minimize the influence of the contralateral perceptual bias in RH stroke patients. The requirement to move the ipsilesional limb into the contralesional hemispace (as it is the case for some items of Goldenberg's hand imitation test, (Goldenberg & Strauss, 2002)) may cause imitation errors due to neglect-related deficits (e.g., directional hypokinesia, (Coslett, Bowers, Fitzpatrick, Haws, & Heilman, 1990)). Furthermore, a spatial bias resulting in lateralized errors might contribute to a relevant extent to the association between deficient finger imitation and visuospatial neglect (Goldenberg et al., 2009). Therefore, we refrained from including hand or finger imitation tasks in the current apraxia assessment (Goldenberg, 1996). Instead, we adopted an imitation task involving bucco-facial gestures based on previous studies revealing the importance of the right hemisphere for bucco-facial gesture processing (Bizzozero et al., 2000). It is noteworthy that imitation deficits that resulted from basic motor or sensory impairments were not considered in the current praxis assessment, since – by definition (Cubelli, 2017; Osiurak & Rossetti, 2017) – apraxic deficits should be independent of basic sensory-motor impairments. Only unambiguous apraxic deficits were allowed to affect the praxis task scores. Therefore, the scoring procedure prevented that primary motor deficits influenced the performance scores in the bucco-facial imitation task. Note that clinical differentiation was straightforward as bucco-facial apraxic deficits lead to categorically different errors (e.g. not sticking out the tongue at all) than difficulties due to primary motor impairment (e.g., deviation of the tongue to the contralesional side when sticking out the tongue).

- *Imitation of bucco-facial gestures:* Based on three pictures that show a person demonstrating different gestures (blowing cheeks, sticking out the tongue, moving in the lips), the patient was asked to imitate these three bucco-facial gestures.

- *Pantomime of object use:* The patient was shown six pictures illustrating different objects (ball-point pen, dice, drinking glass, razor, toothbrush, and watering pot). In response to each picture, the patient was asked to pantomime the use of the depicted object with the right, i.e., ipsilesional hand.

Each neuropsychological task was explained to the patient using an example item. The score range per praxis task item was 0 to 2. A full score (2 points) was awarded when the respective gesture was produced correctly concerning content and execution. If the gesture was partially correct, a score of one point was given. Patients who showed no response or produced a wrong or amorphous gesture received zero points. Impairment in a given praxis task was defined as scoring less than the maximum score (i.e., failing at one item). Note that patients were allowed to correct their performance in a given trial. Corrected trials were not scored as errors. Patients, who were impaired in at least one of the two praxis tasks (pantomime and / or the imitation of bucco-facial gestures), were classified as apraxic. This approach of defining cognitive impairment has already been used successfully in previous studies (Becker & Karnath, 2007; Ronchi et al., 2014; Vossel et al., 2012; P.H. Weiss et al., 2016).

For neglect examination, two traditional tasks, line bisection and letter cancellation, were employed. This combination of tasks ensured coverage of allo-centric / object-based as well as ego-centric / space-based aspects of neglect (Verdon et al., 2010).

- *Line bisection:* A DIN A4 (orientation portrait) sheet displaying five horizontal lines of the same length (94mm) was presented to the patient: one line for demonstration, four lines for actual testing. Of the four test lines, two were located contralesionally while the other two were positioned ipsilesionally and rather centrally, respectively. The patient was instructed to manually bisect each line in the middle using a pencil as demonstrated by the examiner for the first of the five lines.

Since line bisection assesses both allo-centric and ego-centric visuospatial processing deficits (Verdon et al., 2010), two distinct parameters were computed:

(i) *Mean deviation*: Based on all four horizontal lines the overall mean deviation in mm (i.e., sum of all deviations divided by four; with negative values indicating ipsilesional deviation) reflected allo-centric / object-based processing impairments, since high values should reflect deficits that are rather independent of the line position in ego-centric space. A mean deviation < -6 mm indicated the presence of impairment. Note that more negative values reflected more pronounced ipsilesional deviations.

(ii) *Ego-centric deviation:* The difference between the (mean) deviations in mm of the two contralesionally located lines and the two ipsilesionally and rather centrally located lines reflected ego-centric / space-based processing deficits. A computed deviation < -3 mm indicated deficient performance. Note that more negative values reflected more severe contralesional ego-centric / space-based visuospatial deficits.

Patients who scored below the cut-off in at least one of the parameters derived from the line bisection test (*mean deviation* or *ego-centric deviation*), i.e., who demonstrated allo-centric / object-based or ego-centric / space-based deficits, were classified as being impaired in the line bisection task.

- *Letter cancellation:* The patient was asked to manually mark all the ten **B**'s on a horizontally aligned DIN A4 sheet systematically covered with mixed capital letters (A, B, C and D). The 54 letters were arranged in nine vertical columns with six letters each. The middle vertical column did not contain any B's, while five B's were located among the letters on the left and right sides, respectively. The patients used his / her right, ipsilesional hand to mark the respective letter.

To measure the severity of contralesional visuospatial deficits based on the results of the letter cancellation task, we calculated the laterality index (LI = left-sided hits – right-sided hits / left-sided hits + right-sided hits (Bartholomeo & Chokron, 1999)). Here, a score < 0 was employed to indicate the presence of impairment.

Patients were considered to suffer from neglect if they showed impairment in either one of the two visuospatial tasks (line bisection, letter cancellation).

Lesion mapping

Lesion mapping was performed using either MRI (n=25) or CT (n=25) clinical imaging data. If multiple images were available, the image set closest to the date of neuropsychological testing was selected. In addition to the sub-acute stroke lesion, microangiopathic lesions in both hemispheres were mapped if they were 5 - 10mm in diameter.

As in Weiss et al. (2016), we identified lesion boundaries on a standard Montreal Neurological Institute (MNI) template using the freely available MRIcron software package (RRID: nif-0000-00122; http://www.mccauslandcenter.sc.edu/mricro/mricron/install.html) after reslicing the T1-weighted MNI template brain (ch2.nii) to match the angle of acquisition for each patient's scan. Subsequently, each slice of the patient's scan was matched to a slice in the MNI template. Thereafter, SDU manually drew the lesion contour onto the corresponding axial slices of the template (at 5mm slice distance). As CT scans provide fewer slices than the template, we manually interpolated between CT slices to render the lesion on the respective slices of the template. This manual tracing technique is currently considered to be the gold standard for exact lesion delineation (Wilke, De Haan, Juenger, & Karnath, 2011). Lesion mapping was consecutively checked by PHW, a board-certified neurologist. Both examiners were blind to the individual patient's neuropsychological performance at the time of lesion mapping and had to agree upon the exact lesion extent (P.H. Weiss et al., 2016).

Statistical analyses of neuropsychological data

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM) version 24.

To analyze the correlative patterns between the performance in the two visuospatial and the two praxis tasks, we performed a PCA on five task variables. For line bisection, *mean deviation* and *ego-centric deviation* (each in mm) were used as separate variables. The other three variables used for the PCA were: the laterality index of the letter cancellation (LI), imitation (of bucco-facial gestures) score, and pantomime (of object use) score. Only components with eigenvalues >1 were extracted (Kaiser criterion). Subsequently, the extracted factors underwent a varimax rotation to facilitate the interpretation of factor loadings.

Statistical analyses of lesion data

To characterize the neural underpinnings of the components revealed by the PCA on the neuropsychological performance, VLSM with the individual component scores was performed (Verdon et al., 2010). For all lesion analyses, only voxels damaged in at least 5% of the patients were included. Statistical lesion results are reported at $p<0.05$ (corrected for false discovery rate, FDR).

Results

Behavioral data

Prevalence and severity of apraxia and neglect

Based on our diagnostic criteria, 16 of the 50 patients with sub-acute RH stroke suffered from apraxia (32.0%). Contralesional neglect was present in 26 of the 50 RH stroke patients (52.0%). The association between apraxia and neglect is depicted in **Table 1**. Even though there was no significant association between neglect and apraxia as assessed by the Fisher's exact test (p=0.14), most of the apraxic patients in our sample of RH stroke patients also presented with co-morbid neglect (11 of 16 patients, 68.8%). On the other hand, neglect also occurred without any concomitant apraxic deficits (15 of 26 patients, 57.7%), while apraxia without neglect was rare in the current sample of RH stroke patients (n=5). Our current PCA results suggest that the neglect patients without apraxia (or pantomime deficits) exhibit mainly ego-centric processing deficits. In fact, all patients with neglect, but no apraxia (n=15) suffered from deficits in ego-centric processing (i.e., showed an abnormal ego-centric deviation in the line bisection task and/or deficits in the letter cancellation task).

Regarding specific apraxic deficits, pantomime of object use and bucco-facial imitation were each impaired in 10 of the 50 RH stroke patients (20.0%), respectively. Notably, the imitation of bucco-facial gestures (two of the three tested gestures being meaningless and one meaningful) and pantomiming (a task that is commonly considered meaningful; (Goldenberg & Randerath, 2015; P. H. Weiss et al., 2016)) loaded on the same (allo-centric/ object-based) component in the current RH stroke patients.

For the pantomime task (6 items, score 0-2 per item), the overall mean score for all patients (n=50) was 11.2 (SD 2.1, range 1-12), while the mean score in impaired patients (n=10) was 8.1 (SD 3.3, range 1-11). In impaired patients (task score <12), the mean number of items failed in the pantomime task was 2.3 (SD 1.8, range 1-6).

For bucco-facial imitation (3 items, score 0-2 per item), the overall mean score for all patients (n=50) was 5.6 (SD 0.95, range 2-6) and the mean score in impaired patients (n=10) was 4.0 (SD 1.16, range 2-5). In impaired patients (task score <6), the mean number of items failed in the bucco-facial imitation task was 1.2 (SD 0.4, range 1-2). Thus, for both praxis tasks, the mean score of impaired patients was below the cut-off for impairment.

Line bisection revealed contralesional neglect in 16 (32.0%) of the 50 RH stroke patients, while letter cancellation was impaired in 18 (36.0%) of the 50 RH stroke patients.

Supplementary **Table S1** depicts an additional cross tables for the association between pantomiming and neglect.

The association of apraxic and neglect-related deficits: principal component analysis (PCA)

PCA was employed to look more closely at the inter-correlation between the different apraxia and neglect subtests in order to reveal potential common cognitive processes.

The PCA based on five performance variables (pantomiming, bucco-facial imitation, mean deviation in line bisection, ego-centric deviation in line bisection, and letter cancellation) yielded two components that explained together 68.6% of the total variance (**Table 2,** for the correlation table see supplementary **Table S2**). The Kaiser-Meyer-Olkin measure of sampling adequacy revealed an acceptable value of 0.524. Furthermore, the Bartlett's Test of sphericity was significant (χ^2 (10) = 58.3, p < .001). After varimax rotation, the two praxis tasks (pantomime of object use and bucco-facial imitation) as well as the mean deviation score of line bisection strongly loaded on component 1. By contrast, letter cancellation performance and ego-centric deviation in line bisection loaded heavily on component 2. This pattern of results suggests an association of apraxic and allo-centric visuospatial deficits and a dissociation between apraxia / allo-centric visuospatial and ego-centric visuospatial deficits.

Note that for the line bisection task two variables were entered into the PCA, since this task is affected by both allo-centric and ego-centric visuospatial processing deficits (Verdon et al., 2010) resulting in changes in mean deviation or ego-centric deviation, respectively. Our hypothesis that these two variables will load on different components was supported by the current PCA results (see **Table 2**). That this finding is not simply due to entering two variables for the same task was (indirectly) shown by an additional PCA, in which performance in the pantomime task was entered by two variables depending on the effector (bucco-facial, arm/hand). Both variables (bucco-facial pantomime and arm/hand pantomime) similarly loaded on component 1 (see supplementary **Table S3**) despite the fact that they rather concern reflexive and non-reflexive objects, respectively. Thus, the fact that the mean and the ego-centric deviations in the line bisection task loaded on different components in the main PCA indicated that these different types of deviations result from deficits in separate mechanisms (here: allo- versus ego-centric processing).

To assess the potential influence of non-reflexive versus reflexive objects on the performance in the pantomime task, we conducted an additional PCA entering the scores for the bucco-facial items (involving reflexive objects, i.e., toothbrush, drinking glass and razor) and the arm-hand items (involving non-reflexive objects, i.e., dice, ball-point pen and watering pot) of the pantomime task as separate variables. This additional PCA is now included in the revised manuscript as supplementary material

(**Table S3**). This additional PCA revealed that for both effectors and thus for non-reflexive and reflexive objects alike, the performance in the pantomime task loaded on component 1 (allo-centric / object-based processing). Moreover, the two component values were very similar: 0.84 for bucco-facial pantomime with reflexive objects and 0.83 for arm-hand pantomime with non-reflexive objects. Note that in the initial PCA, in which the pantomime score was entered as only one variable, the component score for pantomiming was 0.85. Thus, the loading of the pantomime task on component 1 does not seem to depend on the effector or the reflexive nature of the object, the use of which should be pantomimed.

To further elucidate the role of visuospatial processing on praxis performance, additional correlation analyses were performed between the PCA components scores and the scores of the naming task of the neuropsychological bedside screening tool (Cologne Neuropsychological Screening for Stroke patients; German: Kölner Neuropsychologisches Screening für Schlaganfall-Patienten (KöpSS); (Kaesberg, Fink, & Kalbe, 2013). In the naming task, participants have to state what they see on three pictures. The three pictures show a noun (“necklace”), a verb (“bathing”), and a sentence / situation (“The man drives a car.”). Correlation analysis between the score in this naming task and the two components derived from the PCA revealed that the PCA component 1 (allo-centric processing) was significantly correlated with the naming score ($r=0.80$, $p<0.001$). No such correlation was observed for the PCA component 2 (ego-centric processing; $r=0.02$, $p=891$). Notably, the naming score was also significantly correlated with the scores of the three tests that loaded on the PCA component 1 (bucco-facial imitation: $r=0.754$, $p<0.001$; pantomiming: $r=0.759$, $p<0.001$; mean deviation in the line bisection task: $r=0.379$, $p=0.007$). Especially, the latter significant correlation between the PCA component 1 and the mean deviation in the line bisection task indicates that the association between PCA component 1 and the naming task cannot solely be explained by the processing of pictures, but by allo-centric processing in a more general sense.

Lesion analysis

General distribution of the lesions

The lesion overlay plot of all patients is shown in **Figure 1**. Consistent with the fact that the current sample constituted a clinically representative sample of sub-acute RH stroke patients, the highest lesion overlap was observed within the territory of the middle cerebral artery (MCA), especially in the insula, putamen, and adjacent sub-cortical areas, i.e., areas constituting core MCA territory. In contrast, (anterior) frontal and particularly (posterior) temporo-parietal regions were affected to a lesser degree.

Lesions analysis based on the individual component scores as revealed by PCA

The VLSM analysis based on the individual component scores of component 1 revealed a lesion pattern including mainly temporo-occipital and parahippocampal regions ($p<0.05$, FDR-corrected, **Figure 2A**). Further lesion correlates were found in the right parieto-occipital junction and in the periventricular white matter (corona radiata) of the right frontal lobe. The highlighted areas (red circles in **Figure 2A**) reflect the most significant voxels that were found for component 1 in the right inferior temporal lobe including the fusiform gyrus.

VLSM analysis based on the individual component scores of component 2 yielded a different lesion pattern encompassing large right temporo-parieto-central regions as well as the inferior frontal gyrus and sub-cortical areas ($p<0.05$, FDR-corrected, **Figure**

2B). Temporal involvement included primarily the middle and superior temporal lobe. Large parts of the right inferior parietal lobe (angular and supramarginal gyri) were also affected. Sub-cortical areas predominantly involved the striatum. Again, the highlighted areas (red circles in **Figure 2B**) represent the most significant voxels, located mainly within the (head of) caudate nucleus, the middle and superior temporal gyri, the inferior parietal lobe (angular and supramarginal gyrus), as well as the adjacent white matter.

Discussion

In a clinically representative sample of RH stroke patients (n=50), we investigated the prevalence and association of apraxic and visuospatial deficits at the behavioral and lesion level. Data revealed that 32% of patients with sub-acute RH stroke were apraxic (i.e., showed deficits in pantomiming and / or imitation of bucco-facial gestures), while about half of the RH stroke patients (52%) exhibited visuospatial deficits.

We hypothesized that some cognitive processes that are impaired in RH stroke might affect both specific praxis and visuospatial functions. This notion was supported by a principal component analysis (PCA) that revealed two main components: Praxis tasks (pantomime, bucco-facial imitation) unambiguously loaded on component 1, while letter cancellation loaded on component 2. The two line bisection parameters for allo-centric and ego-centric deficits loaded on different components: while the parameter mean deviation loaded on component 1 (as the praxis tasks), the parameter ego-centric-deviation loaded on component 2 (as letter cancellation). These PCA results strongly suggest that component 1 represents an object-based / allo-centric aspect of visuospatial processing, while component 2 reflects space-based / ego-centric processing. Therefore, these findings implicate that deficient object-based / allo-centric processing in RH stroke leads to concomitant apraxic and visuospatial deficits.

Consistent with this notion, the cognitive two-route model of apraxia caused by LH damage (Rothi, Ochipa, & Heilman, 1991) postulates that the process of visuomotor transformation is a core component of the direct route and seems to rely heavily on personal and peri-personal space processing (Tessari et al., 2007). While these mechanisms (personal and peri-personal space processing) are assumed to depend on LH functioning, the RH may possess a distinct role in providing extra-personal processing, i.e. allo-centric / object-centered coding (Weiss et al., 2000). Some models of praxis suggest that allo-centric / object-centered processing is also essential for praxis, particularly in the presence of higher visuoperceptual demands including the complex visual features of tools or facial gestures (Bartolo & Ham, 2016; L. J. Buxbaum, 2001).

The VLSM results based on the component scores corroborated this notion, as individual component scores for component 1 were associated with lesions to postero-ventral brain regions such as temporo-occipital areas, while individual performance in component 2 was related to more dorsal lesions to right temporo-parietal regions as well as to damage affecting the caudate nucleus.

Behavioral data

Prevalence of apraxia and neglect

In the current sub-acute RH stroke patients, apraxic deficits (including pantomime of object use and the imitation of bucco-facial gestures) showed a prevalence of 32%. One might argue that our cut-off for diagnosing apraxia (i.e., patients who showed an impairment in one of the two praxis tasks due to deficits in one praxis item were classified as being apraxic) was strict. However, the prevalence rate found in the current study (32%) corresponds well to previous investigations on (bucco-facial and limb) apraxic deficits in the sub-acute and chronic stages of RH stroke, for example 38% (Civelek et al., 2015) and 21-53% (Stamenova, Roy, & Black, 2010). Bizzozero and colleagues (2000) reported an even higher prevalence of facial apraxia of 67% in (sub-acute) RH stroke, which is considerably higher than the current frequency of bucco-facial imitation deficits (20%). This apparent discrepancy can be explained by the fact that these authors found a higher prevalence of apraxic deficits for upper face gestures (44%), while the current imitation assessment focused on lower face gestures. In fact, the frequency for isolated lower face apraxia (20%) in the RH stroke patients (<30 days post-stroke) of Bizzozero and colleagues was identical to the prevalence of bucco-facial apraxia (tested with lower face stimuli) in the current sample of RH stroke patients (time post stroke: 7.3 ± 6.4 days; median: 6.0 days; range: 1-33 days).“

Stamenova and colleagues demonstrated a predominant impairment of performing transitive gestures in RH stroke (Stamenova et al., 2010). These authors attributed their finding to deficient visuospatial processing in RH stroke patients affecting rather the imitation of the more complex transitive gestures than the imitation of intransitive gestures. Our study does not replicate these findings as pantomime of object use (transitive gestures) and bucco-facial imitation (intransitive gestures) showed identical frequency rates (20%, respectively). Whether this discrepancy could possibly be explained by the different mean time intervals post-stroke in the two studies (19 days in the study by Stamenova and colleagues versus 7.3 days in the current study) warrants further investigation.

As pantomimes represent a special category of gestures (Niessen, Fink, & Weiss, 2014), it has been proposed that working memory - mediated integration and manipulation of visuoperceptual input is necessary for the proper execution of pantomimes (Bartolo, Cubelli, Della Sala, & Drei, 2003). Furthermore, Goldenberg suggested that apraxia tasks demand the categorical apprehension of spatial relationships (Goldenberg, 2009). It is well conceivable that RH stroke also leads to praxis deficits (here: deficient pantomiming and bucco-facial imitation) by disturbing the visuospatial workspace or working memory and / or the processing of spatial relationships.

The role of the right hemisphere in praxis and thus apraxia is by and large underestimated. Most studies on praxis / apraxia focus on the left hemisphere. However, there is evidence from functional imaging ((Koski et al., 2002); see also a meta-analysis by (Caspers, Zilles, Laird, & Eickhoff, 2010)) as well as neuromodulation studies (Heiser, Iacoboni, Maeda, Marcus, & Mazziotta, 2003) that right hemisphere regions (e.g., right supramarginal gyrus, right inferior frontal gyrus) are involved in praxis, especially in goal-directed actions. Therefore, the current study adds neuropsychological and lesion evidence to this notion.

For the assessment of visuospatial deficits, the line bisection and letter cancellation tasks showed comparable sensitivities (32.0% and 36.0%, respectively). Importantly, the combination of both cognitive tasks led to a significantly higher sensitivity, so that 52% of patients with sub-acute RH stroke could be diagnosed with contralesional visuospatial neglect. This finding emphasizes the importance of combining complementary tasks when assessing a syndrome that comprises different cognitive processes (L.J. Buxbaum et al., 2004; Halligan et al., 2003; Verdon et al., 2010).

Association of apraxia and neglect

Line bisection is considered to examine *both* ego-centric / space-based and allo-centric / object-based aspects of neglect (Oppenländer et al., 2015; Verdon et al., 2010). Therefore, two parameters of the line bisection performance representing allo-centric / object-based processing (mean deviation) and ego-centric / space-based processing (ego-centric deviation), respectively, were included in the PCA. This PCA revealed that mean deviation in line bisection loaded on component 1 suggesting that this component represented allo-centric / object-based processing. Notably, performance in both praxis tasks also loaded on this first component. In contrast, both letter cancellation performance and ego-centric deviation in line bisection loaded on component 2, thereby reflecting ego-centric / space-based processing.

Previously, Goldenberg and colleagues have specifically investigated the association between the severity of visuospatial neglect (also assessed with the help of line bisection and cancellation tasks) and apraxic imitation deficits for finger configurations and hand positions [Goldenberg, Münsinger, and Karnath2009]. In their chronic RH stroke patients, neglect severity was correlated with disturbed imitation of both types of gestures. Of note, imitating the configuration of the fingers that were located on the contralesional, i.e., left side of the hand, which was presented in the ipsilesional, right hemifield, was differentially impaired. Thus, their findings also point to a causal role of allo-centric / object-based processing deficits for (finger) imitation disturbances in RH stroke patients.

Lesion analysis

Lesions associated with deficient allo-centric / object-based versus ego-centric / space-based processing as revealed by the PCA-based VLSM

As we defined neglect based on impairments in line bisection *or* letter cancellation, neglect patients with deficits in ego-centric as well as allo-centric processing were included in the current analyses. Moreover, the PCA revealed that deficits in the praxis tasks (bucco-facial imitation and pantomime) also loaded on component 1 representing allo-centric/ object-based processing. With the help of VLSM analyses based on the individual PCA component scores, we were able to delineate the differential lesion correlates of these components. While component 1 (representing allo-centric / object-based processing deficits) was associated with lesions to ventrally located parahippocampal and inferior temporal regions, component 2 (representing ego-centric / space-based processing deficits) was related to more dorsally located regions like the superior temporal and supramarginal gyri as well as central regions (Committeri et al., 2004).

The parahippocampal region has already been implicated in visual neglect after right posterior cerebral artery stroke (Mort et al., 2003). Anatomical and imaging studies have revealed extensive connections between the parahippocampal region and the angular gyrus of the inferior parietal lobe (Rushworth, Behrens, & Johansen-Berg, 2006) and deficits in allo-centric visuospatial processing are assumed to result rather from remote dysfunction (diaschisis) of the angular gyrus than from primary parahippocampal damage (Molenberghs, Sale, & Mattingley, 2012; Verdon et al., 2010). The lesion correlates of component 1 also included the right inferior temporal lobe which is consistent with its prominent role in far space processing (Weiss et al., 2000; Weiss, Marshall, Zilles, & Fink, 2003) and allo-centric judgments (Chen, Weidner, Weiss, Marshall, & Fink, 2012). Involvement of the right inferior temporal lobe extended into the right fusiform gyrus also comprising the fusiform face area (FFA). Thus, in addition to deficient allo-centric / object-based processing, disturbed imitation of bucco-facial gestures in the current RH stroke patients might be – at least in part – caused by a dysfunction of face processing areas, predominantly located in the right hemisphere (Lesli, Johnson-Frey, & Grafton, 2004). The fact that deficient performance in the bucco-facial imitation task also loaded on the PCA component 1 supports this notion.

Lesion correlates of the PCA component 2 representing ego-centric / space-based processing deficits were mainly located in right dorsal temporo-parietal regions. The most significant regions in this VLSM analysis were found within right middle and superior temporal gyrus, inferior parietal lobe (angular und supramarginal gyrus), and (head of) caudate nucleus. These results confirm previous lesion studies that described an association of damage to right middle / superior temporal regions as well as to inferior parietal lobe with ego-centric symptoms of neglect (Karnath, Rennig, Johannsen, & Rorden, 2011; Vossel et al., 2011). The involvement of sub-cortical structures (caudate nucleus) could point to an additional relevance of motor / intentional aspects of neglect for the observed deficits in letter cancellation and bisecting contralesionally located horizontal lines. Especially, the head of caudate nucleus has been implied as a specific lesion site in patients with a response bias as revealed by the Landmark task (Vossel, Eschenbeck, Weiss, & Fink, 2010).

Conclusion

In the present study, about a third of sub-acute RH stroke patients demonstrated apraxic deficits (in pantomiming the use of objects / tools and in imitating bucco-facial gestures), even after minimizing the effects of a potential lateralized spatial bias by focusing on centrally presented stimuli. Further analyses revealed the relevance of deficient extra-personal (allo-centric / object-based) visuospatial processing in the pathophysiology of these apraxic deficits. Thus, we hypothesize that a core deficit in the allo-centric / object-based visuospatial processing may lead to both apraxia and (allo-centric) neglect in RH stroke. Consequently, therapeutic strategies aiming at improving allo-centric / object-based processing may not only ameliorate visuospatial deficits, but also apraxic deficits in RH stroke.

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Table 1.

Association of neglect and apraxia at the patient level (n=50)

	apraxia	no apraxia	
(contralateral) neglect	n=11 (22%)	n=15 (30%)	n=26 (52%)
no (contralateral) neglect	n=5 (10%)	n=19 (38%)	n=24 (48%)
	n=16 (32%)	n=34 (68%)	n=50

The Fisher exact test revealed a non-significant p-value of 0.14.

Table 2.

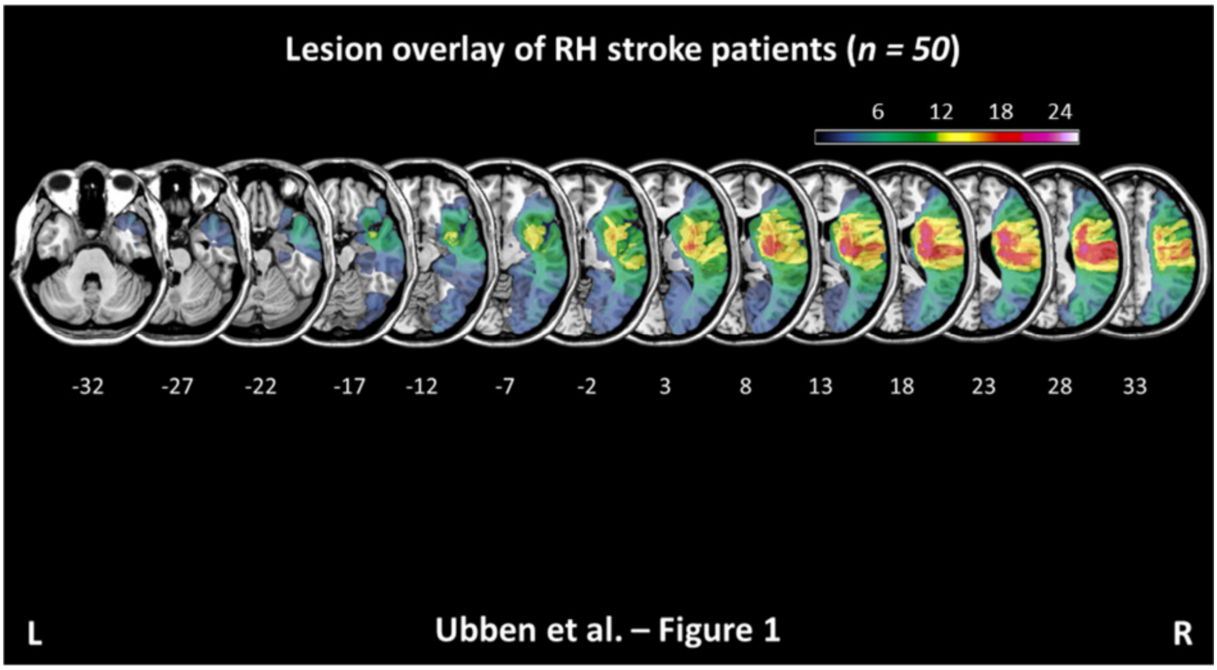
Results of the principal component analysis (PCA) examining the behavioral association between the individual test scores in the praxis and visuospatial tasks (n=50)

	component 1	**component 2**
pantomime score	**0.85**	-0.33
BF imitation score	**0.89**	0.11
line bisection: mean deviation	**0.73**	0.29
line bisection: ego-centric deviation	-0.02	**0.81**
letter cancellation (LI)	0.09	**0.72**
cumulative (*explained*) variance in %	**41.14 (*41.14*)**	**68.61 (*27.47*)**
Eigenvalues	2.06	1.37

The Kaiser-Meyer-Olkin measure of sampling adequacy revealed an acceptable value of 0.524. Furthermore, the Bartlett's Test of sphericity was significant (χ^2 (10) = 58.3, $p < .001$).

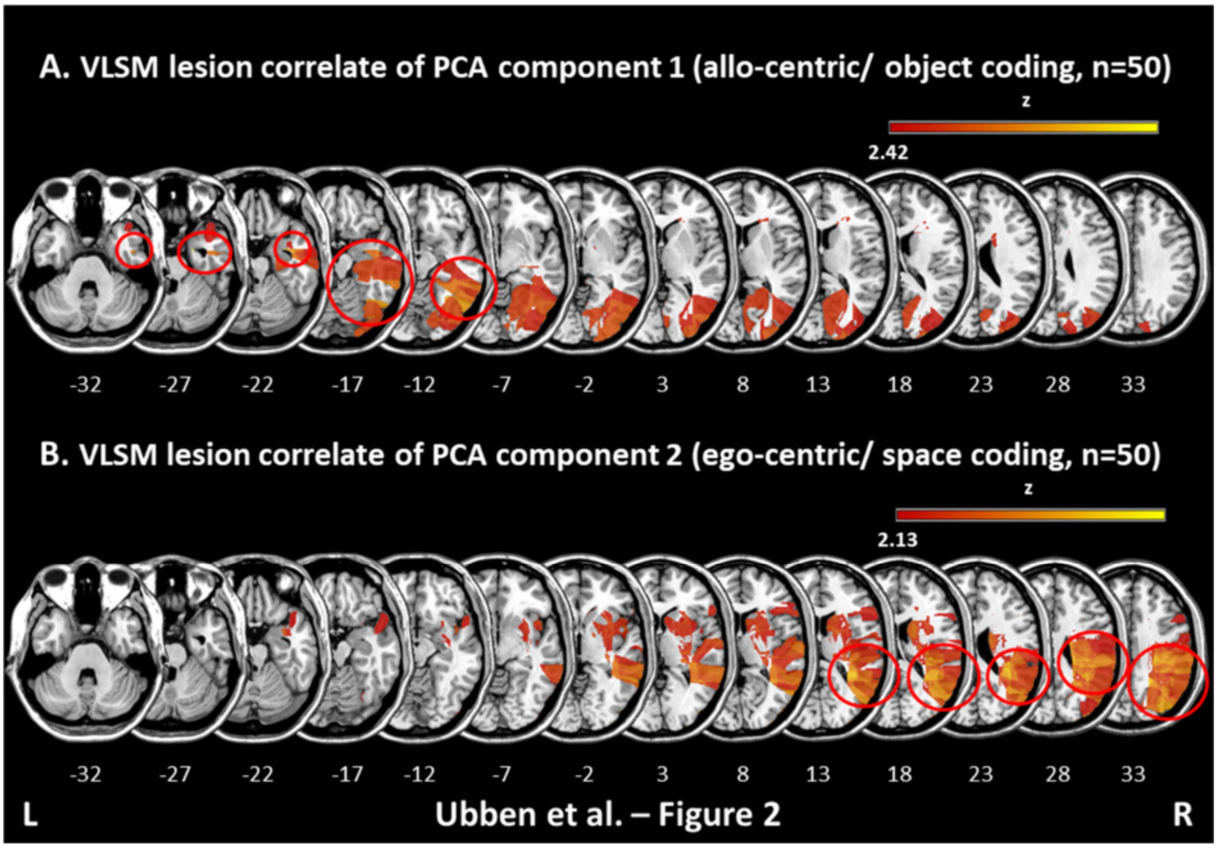
Figures

Figure 1.



Lesion overlay of all sub-acute right hemisphere stroke patients (n = 50). Color shades represent the increasing number of overlapping lesions. Slices with the MNI-z-coordinates from -32 to 33 are shown.

Figure 2.



VLSM of the individual component scores of the PCA based on the praxis (pantomime, bucco-facial imitation) and neglect tasks (line bisection, letter cancellation). Note that line bisection performance was operationalized by two different parameters that differentially drew on allo-centric / object-based processing (mean deviation) and ego-centric / space-based processing (ego-centric deviation).

Results are FDR-corrected, $p<0.05$. Only voxels damaged in at least 5% of the patients were tested, axial MNI-z-coordinates from -32 to 33 are shown. Red circles highlight the most significant areas / voxels of each analysis.

A. Component 1: allo-centric/ object coding. The significant voxels correspond to $z>2.42$.

B. Component 2: ego-centric/ space coding. The significant voxels correspond to $z>2.13$.

Table S1.

Association of neglect and pantomime deficits (n=50 patients)

	pantomime deficit	**no pantomime deficit**	
(contralateral) neglect	n=7 (14%)	n=19 (38%)	n=26 (52%)
no (contralateral) neglect	n=3 (6%)	n=21 (42%)	n=24 (48%)
	n=10 (20%)	n=40 (80%)	n=50

The Fisher's exact test revealed a non-significant p-value of 0.29.

Table S2.

Correlation matrix including all five variables that entered the PCA

	bucco-facial (BF) imitation	***line bisection: mean deviation***	***line bisection: ego-centric deviation***	***letter cancellation (LI**)***
pantomime	**r=0.66** **p<0.001**	**r=0.376** **p<0.01**	r=-0.242 n.s.	r=-0.063 n.s.
bucco-facial (BF) imitation		**r=0.515** **p<0.001**	r=0.155 n.s.	r=0.073 n.s.
line bisection: mean deviation			r=0.127 n.s.	r=0.189 n.s.
line bisection: ego-centric deviation				r=0.244 n.s.*

* There was a non-significant tendency with p=0.088.

** Laterality Index

Table S3.

Results of an additional principal component analysis (PCA, n=50) in which performance in the pantomime task was entered by two variables depending on the effector (bucco-facial, arm/hand)

	component 1	**component 2**
bucco-facial pantomime score	**0.84**	-0.26
arm/hand pantomime score	**0.83**	-0.21
bucco-facial imitation score	**0.85**	0.21
line bisection: mean deviation	**0.65**	0.4
line bisection: ego-centric deviation	-0.09	**0.8**
letter cancellation (LI)	0.04	**0.71**
cumulative (*explained*) variance in %	**42.5 (42.5)**	**66.6 (24.1)**
Eigenvalues	2.55	1.45