



Special Issue "One century after Liepmann's work on apraxia: where are we now?": Research Report

Anatomical correlates of recovery in apraxia: A longitudinal lesion-mapping study in stroke patients



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ABSTRACT

Objective: This study investigates the clinical course of recovery of apraxia after left-hemisphere stroke and the underlying neuroanatomical correlates for persisting or recovering deficits in relation to the major processing streams in the network for motor cognition.

Methods: 90 patients were examined during the acute (4.74 ± 2.73 days) and chronic (14.3 ± 15.39 months) stage after left-hemisphere stroke for deficits in meaningless imitation, as well as production and conceptual errors in tool use pantomime. Lesion correlates for persisting or recovering deficits were analyzed with an extension of the non-parametric Brunner–Munzel rank-order test for multi-factorial designs (two-way repeated-measures ANOVA) using acute images.

Results: Meaningless imitation and tool use production deficits persisted into the chronic stage. Conceptual errors in tool use pantomime showed an almost complete recovery. Imitation errors persisted after occipitotemporal and superior temporal lesions in the dorso-dorsal stream. Chronic pantomime production errors were related to the supra-marginal gyrus, the key structure of the ventro-dorsal stream. More anterior lesions in the ventro-dorsal stream (ventral premotor cortex) were additionally associated with poor recovery of production errors in pantomime. Conceptual errors in pantomime after

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temporal and supramarginal gyrus lesions persisted into the chronic stage. However, they resolved completely when related to angular gyrus or insular lesions.

Conclusion: The diverging courses of recovery in different apraxia tasks can be related to different mechanisms. Critical lesions to key structures of the network or entrance areas of the processing streams lead to persisting deficits in the corresponding tasks. Contrary, lesions located outside the core network but inducing a temporary network dysfunction allow good recovery e.g., of conceptual errors in pantomime. The identification of lesion correlates for different long-term recovery patterns in apraxia might also allow early clinical prediction of the course of recovery.

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1. Introduction

Apraxia, the impairment of skilled and purposeful movements, is a frequent sequel of left-hemisphere stroke. Behavioral studies on recovery from apraxia show that many patients recover rapidly from their deficits after stroke, while others remain impaired; further, apraxic deficits vary in the rate of recovery (Basso et al., 1987, 2000; Bickerton et al., 2012; Kusch et al., 2018; Mimura, Fitzpatrick, & Albert, 2003). It remains unclear which stroke lesions allow for good recovery from apraxia and which stroke lesions lead to persisting apraxic deficits and why different apraxic deficits vary in their recovery course.

Apraxia is widely conceptualized as fronto-temporo-parietal network disorder in the left hemisphere (Binkofski & Buxbaum, 2013). For the current study, apraxia is described as different apraxic error types during meaningless posture imitation and pantomime of tool use and is discussed in the context of the dual stream model in the left hemisphere. The dual stream model comprises a dorsal stream, which is subdivided into a dorso-dorsal and ventro-dorsal part, and a ventral stream, each of which is related to the processing of different aspects in motor cognition. In this model, errors during the imitation of meaningless postures are related to the most dorsal parts of the network (e.g., superior parietal lobe, SPL) as part of the dorso-dorsal stream (Achilles et al., 2019; Hoeren et al., 2014). The dorso-dorsal stream traverses from visual areas (lateral occipito-temporal cortex, LOTC), which provides visual input for actions (Chaminade, Meltzoff, & Decety, 2005; Lingnau & Downing, 2015), intraparietal sulcus, and SPL via superior longitudinal fascicle (SLF) I to the dorsal premotor cortex. It facilitates the online visuomotor guidance of movements as in reaching, which is necessary to imitate meaningless hand- or finger postures, but also to execute meaningful movements (Binkofski & Buxbaum, 2013; Kalénine, Buxbaum, & Coslett, 2010; Rijntjes, Weiller, Bormann, & Musso, 2012; Rizzolatti & Matelli, 2003; Vingerhoets, 2014). Besides dorso-dorsal stream regions meaningless imitation is also related to the inferior parietal lobe (IPL; hand postures) (Chaminade et al., 2005; Goldenberg, 2001; Goldenberg & Karnath, 2006) extending into the LOTC (Goldenberg & Karnath, 2006), and the inferior frontal gyrus (IFG, pars opercularis; finger postures) (Goldenberg & Karnath, 2006), suggesting a potential role of these regions (i.e., for action representation and body part knowledge) in meaningless

imitation. Pantomime of tool use can be impaired in two different ways according to the model of Heilman and Rothi (Rothi, Ochipa, & Heilman, 1997) with different anatomic correlates in the dual stream model. The execution of skilled and tool-related movements can either display production errors (such as movements flawed in terms of hand configuration, orientation, distance, or movement trajectories), or conceptual errors (e.g., semantically wrong movements, perplexity, or an overall unrecognizable response) (Rothi et al., 1997). The production of tool-related or skilled actions mainly relies on the intactness of the IPL, in particular supramarginal gyrus (SMG), where the stable representation of learned (tool-related) actions (“blueprints”) are stored (Binkofski & Buxbaum, 2013; Buxbaum, Shapiro, & Coslett, 2014; Goldenberg, 2009; Goldenberg, Hartmann, & Schlott, 2003; Goldenberg & Randerath, 2015; Hoeren et al., 2014; Kalénine et al., 2010; Króliczak & Frey, 2009; Niessen, Fink, & Weiss, 2014; Sakreida et al., 2016). Impaired pantomime also arises after lesions to posterior parts of the IFG (pars opercularis; Brodmann area (BA) 44) (Goldenberg, Hermsdörfer, Glindemann, Rorden, & Karnath, 2007; Manuel et al., 2013; Weiss et al., 2016), and the ventral premotor cortex (PMv), which facilitates hand shaping during movement execution (Davare, Montague, Olivier, Rothwell, & Lemon, 2009; Reader & Holmes, 2018; Vingerhoets, Nys, Honoré, Vandekerckhove, & Vandemaele, 2013). These regions are connected via SLF II and III (Binkofski & Buxbaum, 2013; Hamzei et al., 2016; Makris et al., 2005; Vry et al., 2012, 2015) and constitute the ventro-dorsal stream. Growing evidence states an additional role of the ventral stream for the performance of skilled actions. The ventral stream connects IPL, superior and middle temporal gyrus (STG, MTG), and anterior temporal lobe (ATL) with inferior frontal lobe (e.g., BA 45 and 47) via tracts traversing through the extreme capsule (EmC): inferior fronto-occipital fasciculus (IFOF); fronto-temporal extreme capsule tracts (ECF); uncinat fasciculus (UF) (Weiller et al., 2021). The ventral stream is related to processing of conceptual information in different domains (Martinez Oeckel et al., 2021; Rijntjes et al., 2012; Saur et al., 2008; Vry et al., 2012, 2015; Weiller, Bormann, Saur, Musso, & Rijntjes, 2011). In motor cognition, it may represent the neural correlate of the conceptual action system (Rothi et al., 1997) and might be particularly relevant for conceptual aspects in pantomiming (Dressing et al., 2018; Finkel, Hogrefe, Frey, Goldenberg, & Randerath, 2018; Hoeren et al., 2014; Martin et al., 2016; Vry et al., 2015). Ventral stream lesions lead to

severe apraxia in the acute stage, with patients showing conceptual errors (i.e., being perplexed, or presenting with semantic/conceptual errors in tool use).

After an acute stroke, the functionality of one stream or the whole network can be impaired; depending on the location of the stroke lesion the behavioral deficits differ as described above for apraxic deficits. Recovery of a function seems to imply the re-coordination of areas within the preexisting network, each of which may be specialized in one or more aspect of the lost or impaired function (Weiller & Rijntjes, 1999), or in more recent words, “recovery might follow from a reweighting of neural connections in order to reoptimize the remaining computational capacity” (Ueno, Saito, Rogers, & Lambon Ralph, 2011). Different mechanisms for recovery have been proposed on a systems-level in network-based functions including the motor system (Guggisberg, Koch, Hummel, & Bueteftisch, 2019; Johansen-Berg, 2003; Lemon, 1993; Siegel et al., 2018; Weiller & Rijntjes, 1999): First, behavioral recovery can be related to a resolution of temporary network dysfunction effects (e.g., diaschisis); the deficits were induced by a temporary loss of function in regions distant to the actual stroke lesion (Carrera & Tononi, 2014; Price, Warburton, Moore, Frackowiak, & Friston, 2001; Sare, 2016; Stockert et al., 2020; Weiller, Vry, Saur, Umarova, & Rijntjes, 2015). Second, perilesional activation including task-dependent within-area shifts have been reported for recovery of motor deficits and aphasia after stroke (Heiss & Thiel, 2006; Liepert et al., 1998; Weiller et al., 1993, 1995). Third, large scale reorganization takes place within the residual parts of the network including activation in the contralesional hemisphere for recovery in language, visuospatial attention, and motor function with a shift from primary to secondary to tertiary cortices (Chollet et al., 1991; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Grefkes et al., 2008; Musso et al., 1999; Nelles, Jentzen, Jueptner, Müller, & Diener, 2001; Saur et al., 2006; Umarova et al., 2016; Ward, Brown, Thompson, & Frackowiak, 2003; Weiller et al., 1992, 1995).

However, a multitude of deficits does not recover after stroke. Here the “concept of critical lesions” comes into play. It assumes the importance of essential brain regions necessary for functional restitution (Weiller et al., 2015). In the domain of motor function, for example, the structural integrity of the primary motor cortex (M1) and the corticospinal tract (CST), the core structures of the motor system (Lemon, 1993), is a valid predictor for recovery of hand dexterity (Byblow, Stinear, Barber, Petoe, & Ackerley, 2015; Puig et al., 2017; Rijntjes & Weiller, 2002; Ward et al., 2003). Similarly, in the domain of language structural intactness or early reperfusion of brain regions critical for language (e.g., Wernicke's area) (Hillis & Heidler, 2002) is related to good recovery. Without the integrity of these regions, recovery might be impossible. If these principles also apply to apraxia is unclear. However, it is reasonable to assume that this is the case since apraxia on the one hand represents a network disorder like aphasia (Binkofski & Buxbaum, 2013). On the other hand, already Liepmann (Liepmann, 1908) considered the intactness of SMG as a *sine qua non* for skilled actions, which would correspond to a critical lesion. To shed light on the underlying anatomic correlates of recovering or persisting deficits in apraxia, studies are necessary which longitudinally examine apraxic

deficits (or error types) and at the same time considers the corresponding anatomical-functional representation of these different error types. So far, however, only Basso and colleagues (Basso et al., 1987, 2000) studied patients at the sub-acute stage (2–4 weeks after stroke) and followed them for months or even years revealing a better recovery in overall apraxia in patients with frontal lesions versus parietal lesions. Kusch and colleagues (Kusch et al., 2018) studied patients with apraxia on a binary basis (apraxia yes or no) on admission and about 11 days thereafter showing an association of insular lesions and good recovery.

The current study aims to examine recovery of three apraxic error types, each of which relates to one of the three processing streams: imitation (related to the dorso-dorsal stream), production of tool-use pantomime (related to the ventro-dorsal stream), and conceptual aspects of tool-use pantomime (related to the ventral stream). Studies addressing post-stroke recovery in structural imaging data, however, are confronted with different methodological issues. First, standard voxel-based lesion-symptom mapping analyses (Bates et al., 2003; Rorden, Karnath, & Bonilha, 2007) can only be performed with one behavioral score at a time (either acute or chronic score). The analysis based on acute scores is useful to determine lesion-symptom associations in the acute stage, the analysis with chronic scores identifies lesion locations related to persisting deficits. Patients with recovered deficits, however, are treated as healthy in the chronic stage, and thus they confound the chronic lesion analysis and their lesion anatomy is difficult to analyze (Karnath, Rennig, Johannsen, & Rorden, 2011). This can be overcome by using a longitudinal lesion-mapping approach based on a repeated-measures analysis of variance (ANOVA), which is implemented in a newly developed statistical tool for the analysis of interaction effects in non-parametric data (NIX-toolbox) (Dressing et al., 2018; Schmidt et al., 2019). This approach allows differentiating between lesion related to persisting deficits in the chronic stage and lesions, which induce a deficit during the acute stage, but allow recovery over time. Second, recovery after stroke examines a dynamic process, which requires concisely defining the timeframe in which recovery is studied. To determine the difference between acute and chronic lesion patterns and to identify lesion locations, related to chronic, i.e., persisting deficits, it seems reasonable to compare the acute (until day 10) with the chronic stage (later than six months) (Bernhardt et al., 2017), in which the patient reached a stable state of recovery. To address these points, in this study we used a prospective longitudinal voxel-based lesion-symptom mapping (VLSM) approach (NIX-toolbox) based on acute imaging data in a large sample of 90 carefully selected stroke patients with singular left-hemisphere ischemic infarcts. Patients were examined during the acute stage (4.74 ± 2.73 days post stroke) and during the chronic stage (14.3 ± 15.39 months post stroke) with the majority of patients examined later than 6 months post stroke. We aimed to find clues on (i) how the anatomy of lesions may support or hamper recovery in the various forms of apraxic deficits; and (ii) what we may learn about compensation within the praxis network or the existence of critical lesions in this domain.

2. Methods

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

2.1. Patients

Patients consecutively admitted to the Stroke Unit of the Clinic for Neurology and Clinical Neuroscience, University Medical Centre Freiburg from 2011 to 2017 were screened for eligibility to participate in the study. The patient-specific inclusion criterion was the presentation of a first-ever ischemic stroke in the territory of the middle cerebral artery. Exclusion criteria in the acute stage as reported previously (Beume et al., 2015; Dressing et al., 2018; Hoeren et al., 2014) were (i) contraindications for MRI, (ii) inability to tolerate MRI or behavioral examination (e.g., severely reduced general health status), (iii) age > 90 years, (iv) interfering cognitive impairment (e.g., dementia or severe depression), (v) poor German language skills, (vi) compliance issues (e.g., withdrawal of consent), (vii) technical or organizational problems (e.g., rapid transfer to another ward or hospital), (viii) previous ischemic or hemorrhagic infarction, (ix) structural brain changes (e.g., severe brain atrophy, extensive white matter changes, previous traumatic brain injury), (x) widespread hemodynamic alterations (e.g., carotid occlusion with insufficient collateralization as revealed by ultrasound). A total of 187 left-hemisphere stroke patients was included at the acute stage. Patients with severe object recognition deficits (based on performance in subtest 11 of the Birmingham Object Recognition Battery for object recognition (Riddoch & Humphreys, 1993)) were excluded retrospectively ($n = 7$). All patients underwent a standard treatment and rehabilitation program according to the Guidelines of the German Society of Neurology.

Of those, 90 patients were followed up after at least four months after stroke in a dedicated post-stroke care program. Exclusion criteria in the chronic stage were a re-infarction (identified clinically or on MRI; $n = 0$). Thus, the final sample comprised longitudinal data from 90 stroke patients who were examined twice, during the acute stage [Ex 1: 4.74 ± 2.73 days post stroke (range 1–10 days)] and the chronic stage [Ex 2: 14.3 ± 15.39 months post stroke (range 4–66 months)], but the majority of patients (74%) was examined later than 6 months post stroke. Demographic and basic clinical data of the patients are presented in Table 1.

Data from the acute stage of a subset of the patients were previously published (Dressing et al., 2018; Hoeren et al., 2014; Martin et al., 2016). Normative evaluations for all tests were based on previously published data from 29 elderly subjects [age 72.0 ± 7.2 years (range 54–87 years); male/female: 15/14] (Hoeren et al., 2014).

The study was approved by the local ethics committee (EK281/13) and conducted in accordance with the Declaration

Table 1 – Demographic and basic clinical data.

	Mean \pm SD or n	Range
Male/Female	62/28	
Age (y), acute examination (Ex1)	63.21 ± 13.97	21–86
Age (y), chronic examination (Ex2)	64.46 ± 13.61	22–87
Lesion volume (ml)	27.78 ± 33.11	.96–134.96
Acute therapy ^a	44/32/14	
NIH stroke scale on admission	8.09 ± 5.77	0–24
NIH stroke scale on discharge	2.92 ± 2.99	0–14
NIH stroke scale on chronic examination (Ex2)	2.14 ± 2.47	0–11
modified Ranking Scale on discharge	2.00 ± 1.32	0–5
modified Ranking Scale on chronic examination (Ex2)	1.69 ± 1.02	0–5

^a 0 = none, 1 = iv lysis; 2 = mechanical thrombectomy (\pm intravenous lysis).

of Helsinki of the World Medical Association. Full written consent was obtained from all patients or their legal guardians before participation. No part of the study procedures or analysis plans was pre-registered prior to the research being conducted.

2.2. Clinical and behavioral testing

We performed the same behavioral testing twice, in the acute and chronic stages. Although this might lead to repeated testing effects and ceiling effects, as the test has to be suitable for both time points, we chose this approach as allowing the greatest possible comparability of the deficits in the different phases after stroke. 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.

2.2.1. Apraxia

Imitation of meaningless hand and finger postures (in the following referred to as meaningless imitation) was tested with an adaptation of a previously published test (Goldenberg & Strauss, 2002). The test comprised 20 meaningless hand and finger postures (10 positions of the hand relative to the head with invariant finger position and 10 finger postures). Patients always used the left (ipsilesional) hand. The postures were presented with the contralateral hand compared to the patient like in a mirror; to reduce memory load the posture was continuously presented.

Pantomime of tool use was assessed with a modified version of the test developed by Bartolo and colleagues (Bartolo, Cubelli, & Della Sala, 2008). Patients were asked to mime the use of 14 objects, depicted as line drawings. The task was demonstrated through two example items (for example and test items see Supplement). The drawing of the current item was kept in view for the entire time while the patient pantomimed its use. Patients performed the pantomime with their right (contralesionally) hand, in case of a severe paresis

with their left hand. To examine object recognition abilities patients completed subtest 11 of the Birmingham Object Recognition Battery for object recognition (Riddoch & Humphreys, 1993).

2.2.2. General stroke-related deficits

The overall impairment was evaluated by the National Institute of Health Stroke Scale (NIHSS) and the modified Ranking Scale (mRS) (Wilson et al., 2005).

2.3. Scoring and error classification for apraxia tests

Apraxia testing (imitation and pantomime) was performed by specially trained occupational therapists with long-standing experience in working with stroke patients and supervised by A.D. For scoring, performances were videotaped and evaluated separately by two raters (M.M. and A.D.). The items which had been scored differently by the two raters were jointly reviewed by both raters and a consensus rating was established that was used for subsequent analyses. Patients who either declined being recorded on video or could not be filmed due to technical reasons were scored directly by the examining occupational therapist (Ex 1 $n = 6$; Ex 2 $n = 4$). All examiners were familiarized with the scoring system.

In the imitation task, each item was scored with two points when correct at the first try and one point at the second try (max. 40 points). In the pantomime task, each item was scored as either correct (1 point) or incorrect (0 points). Errors in pantomime were classified according to a model of Rothi and Heilman (Rothi et al., 1997) as either *concept errors*, including semantic errors (e.g., brushing teeth instead of combing hair), perplexity (e.g., showing no response) and unrecognizable response (e.g., amorphous, back-and-forth or side-to-side movements without resemblance to the action), or *production errors*, referring to overall recognizable actions that were flawed in terms of the hand configuration, orientation, distance, or movement errors. If a single item was scored as being conceptually wrongly performed, it was not scored regarding production errors. A tool use pantomime production and concept summary score were established based on the number of errors (max. 14 points each with low scores reflecting a high number of errors).

2.4. Assessment of recovery

Binarized measures (impaired, unimpaired) for imitation and pantomime tests were obtained, based on the performance of 29 normal, age-matched individuals (Hoeren et al., 2014). Impaired performance was defined as performance below the 5th percentile of the normal control group. Based on these cut-off scores patients were classified as impaired or unimpaired in the acute stage. The patients who were impaired during the acute stage were further classified as either recovered or impaired during the chronic stage, resulting in three groups in the chronic stage (unimpaired, recovered, impaired).

Additionally, the ratio of the actual recovery during the chronic stage (maximum score - chronic score) and the

maximum possible recovery at the first examination (maximum score - acute score) was calculated and is reported as *percent of maximum possible change-score* (Moss & Nicholas, 2006). Proportional scores enable the detection of recovery despite inter-individual variability in absolute scores and allow better comparability between differently scaled test scores.

2.5. Image preprocessing and lesion delineation

2.5.1. Image acquisition

Lesion analyses were based on images acquired in the acute stage. Structural imaging data were obtained on a 1.5 T Avanto ($n = 17$) or a 3 T Trio scanner ($n = 73$) (Siemens, Healthcare, Erlangen Germany). Detailed parameters of image acquisition are provided in the Supplement.

2.5.2. Lesion delineation

As previously reported (Dressing et al., 2018; Hoeren et al., 2014) the ischemic lesions were first delineated on the diffusion-weighted images based on intensity thresholds using a customized region-of-interest toolbox implemented in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>). Subsequently, the lesion delineations were further refined manually by specially trained assistants, who were blind to the patient's behavioral results. In one case with no available DWI sequence, the lesion was directly drawn on the FLAIR image. Prior to normalization, the exact correspondence between lesion map and lesion was checked (M.M., L.B., or A.D.). Lesion mapping and inspection were performed in MRICron (<https://www.nitrc.org/projects/mricron>). For normalization, the diffusion-weighted images (or the FLAIR image) and corresponding lesion maps were co-registered to the anatomical T1 scan ($n = 86$), or when no T1 scan was available ($n = 4$), to the FLAIR images. The T1 (or FLAIR) scans were segmented using the VBM8 toolbox (r435; <http://dbm.neuro.uni-jena.de/wordpress/vbm/download/>), and deformation field parameters for nonlinear normalization into the stereotactic Montreal Neurological Institute (MNI) standard space were obtained using the DARTEL approach (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) implemented in VBM8 (Ashburner, 2007). Following normalization, the individual lesion maps were again inspected and compared to the lesions in native subject space to ensure that the extent of the ischemic damage was accurately delineated in MNI-space.

2.6. Data analysis

2.6.1. Statistical analyses of behavioral data

Basic statistical analyses of the behavioral data were performed using the Statistical Package for the Social Sciences (SPSS) version 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). To analyze the number of patients, who were impaired and unimpaired in the acute stage, and to compare the number of patients, who recovered and who remained impaired, χ^2 tests were calculated. To compare

the percent of maximum possible change-scores the Kruskal–Wallis test with post-hoc pair-wise Dunn–Bonferroni correction was used. Correlations between test scores and demographic/clinical data were determined using Spearman’s rank-order correlation.

2.6.2. Analyses of longitudinal changes in behavior and related lesion correlates

Longitudinal behavioral and lesion analyses were performed based on an extension of the non-parametric Brunner–Munzel rank test (Munzel & Brunner, 2002) for multi-factorial designs with within- and between-subject factors. An analysis of variance (ANOVA)-type test statistic was chosen, which is based on an $F_{(df, \infty)}$ -distribution and robust even for small sample sizes. We performed a two-way repeated-measures ANOVA with behavioral performance in single apraxia tests as dependent variable, the within-subject factor time [acute (examination 1, Ex 1), chronic (examination 2, Ex 2)], and the between-subject factor lesion at voxel-level (lesion, no-lesion). In this analysis, the main effect lesion reveals lesion clusters that lead to impaired behavioral performance irrespective of the time stage. The interaction effect time \times lesion detects lesion clusters that were associated with changes in behavioral measures over time. In the present study, interaction effects were related to two patterns, i.e., either to a significant change in behavioral performance (recovering deficits) or conversely to a behavioral deficit, which remains impaired over time, compared to the rest of the cohort (persisting deficit). The analyses were performed using the open-source NIX-toolbox (‘Non-parametric Interaction Effects’; <https://github.com/kainitschke/NIX>) implemented in MATLAB, which enables voxel-wise testing of interaction effects in non-normally distributed data (Dressing et al., 2018; Schmidt et al., 2019). Significant results are thresholded at an FDR-corrected threshold of $p < .01$ at the voxel level.

To identify lesion locations leading to chronic deficits we additionally performed a lesion-symptom mapping analysis with behavioral scores at examination 2. We used a mass-univariate approach (Rorden et al., 2007) and, as shortcomings of mass-univariate approaches have been discussed recently (Karnath, Sperber, & Rorden, 2018), we complementarily performed a support-vector-regression based multivariate analysis, which allows us to determine lesion–behavior relationship which is less dependent on anatomical lesion distribution and differences in statistical power due to varying numbers of patients with lesions in each voxel. The mass-univariate analysis uses the Brunner–Munzel test for continuous behavioral variables (Rorden et al., 2007) implemented in the Non-Parametric Mapping toolbox (the statistical package included with MRICron; version 12/12/2012). Following previous studies (Dressing et al., 2018; Goldenberg & Spatt, 2009; Hoeren et al., 2014) we report results of the mass-univariate VLSM on the threshold of $p < .05$ FDR-adjusted. To improve comparability with the results from the longitudinal analysis the threshold of $p < .01$ FDR-adjusted is additionally indicated. The multivariate analysis was performed with the SVR-LSM toolbox (DeMarco & Turkeltaub, 2018; GitHub - atdemarco/svrlsmgui: A graphical multivariate lesion-symptom mapping toolbox) based on the approach of (Zhang, Kimberg, Coslett, Schwartz, & Wang, 2014). The SVR-LSM toolbox generates a voxel-wise map of raw regression β

values. The resulting SVR- β values were thresholded at $p < .005$ based on 10,000 permutations.

Lesion volume is a potential confounding factor in studies with stroke patients (Hope, Seghier, Leff, & Price, 2013). Correction for lesion volume was performed by regressing lesion volume out of both, the image and behavioral data (‘regress on both’) in the multivariate analysis. Results of the mass-univariate analysis and the longitudinal lesion-mapping analysis are not corrected for lesion volume. In our study only a mild to moderate correlation between lesion size and test scores (Supplement Table 1) was present. Previously it could be shown that in this constellation lesion volume correction produces smaller, but not spatially displaced results (DeMarco & Turkeltaub, 2018). Therefore, we assume that the results of the mass-univariate and the longitudinal lesion-mapping analysis are not solely driven by the factor lesion volume.

For all analyses, only voxels damaged in at least 5% of the sample were entered in the analysis. This sample size was recommended as sufficient affection (Sperber & Karnath, 2017) and was also used in previous VLSM studies (Hoeren et al., 2014; Watson & Buxbaum, 2015), although it faces the limitation of inflated z-scores and potentially false-positive results in voxels where only a small number of patients shows a lesion (Medina, Kimberg, Chatterjee, & Coslett, 2010).

For visualization, results are displayed on an in-house average template of 50 normalized T1 scans from a sample of normal subjects [age 47 ± 20.75 years (range 22–84 years); male/female 25/25] (Beume et al., 2015) as slice and rendering images. Images were generated using MRICron (<https://www.nitrc.org/projects/mricron>). For identification of anatomic regions, the Automated Anatomic Labeling (AAL) labeling atlas (Tzourio-Mazoyer et al., 2002) was used.

2.7. Data availability statement

Data and lesion maps registered to the reference map are available on demand as patients did not consent to the free distribution of their data. Readers seeking access to this data should contact the corresponding author. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must complete a formal data-sharing agreement. A copy of the consent form signed by the participants is available on demand; please refer to the corresponding author (A.D.).

3. Results

3.1. Behavioral recovery of apraxic deficits

During the acute stage (Ex 1), patients were impaired in meaningless imitation, tool use pantomime production, and tool use pantomime production concept to a similar extent (Fig. 1A, Examination 1: $\chi^2_{(2)} = 1.872$, $p = .392$, $\phi = .083$). However, the number of patients, who were initially impaired and either recovered or remained impaired in the chronic stage differed significantly between the tests (Fig. 1A Examination 2: $\chi^2_{(2)} = 6.490$, $p < .05$, $\phi = .243$). This became also

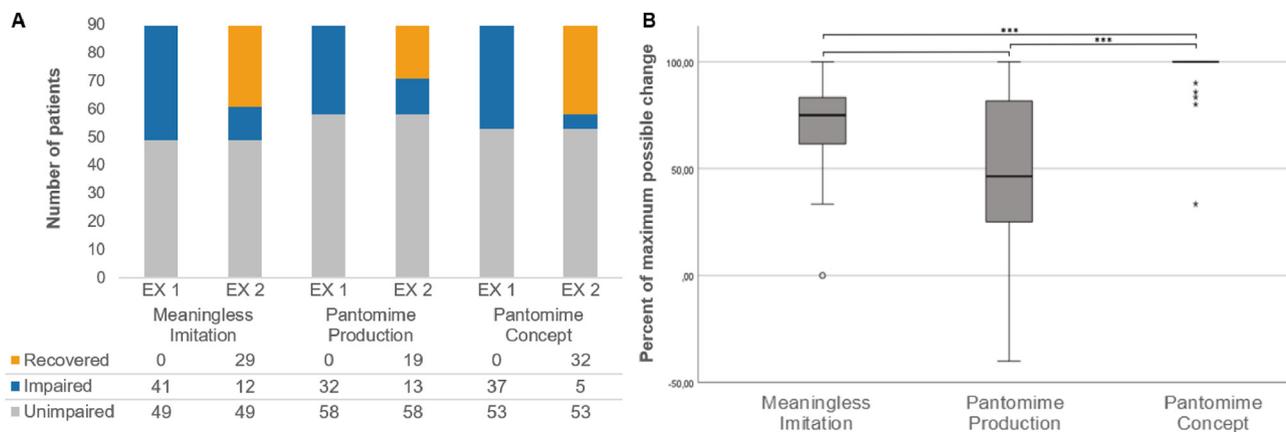


Fig. 1 – Behavioural recovery from apraxia. A: The bar diagram indicates the number of patients in the acute (Ex 1) stage without deficit (unimpaired, grey) and with deficit (impaired, blue), and number of patients in the chronic stage (Ex 2) without deficit (unimpaired, grey), with persisting deficit (impaired, blue) and with recovered deficit (recovered, orange) for meaningless imitation, pantomime production and pantomime concept errors. **B:** The boxplot illustrates the distribution of the percent of maximum possible change-scores for meaningless imitation, pantomime production and pantomime concept errors. Box and whisker plots indicate median and interquartile range (IQR) with first (25 percentile) and third (75 percentile) quartiles. The score was calculated as the ratio of the actual recovery in the chronic stage (maximum score – chronic score) and the maximum possible recovery at the first examination (maximum score – acute score), and indicates how complete the recovery is over time was for each test. Significant differences in the post-hoc tests are labelled with asterisks (***) ($p < .001$).

evident in the different percent of maximum possible chance-scores in the patients, who were impaired during the acute stage (Fig. 1B). Here, in particular, concept errors showed an almost complete recovery compared to tool use pantomime production and meaningless imitation ($H_{(2)} = 42.724$, $p < .001$). Single error types for the category of production and concept errors in the acute and chronic stage are listed in the Supplement (Supplement Fig. 1). Note that conceptual errors mainly comprised perplexity and unrecognizable movements (Supplement Fig. 1). Correlations between age, lesion size, clinical scores, and apraxia test scores in the acute and chronic stage showed only mild to moderate correlations, detailed results are presented in Supplementary Table 1. Between-group comparison of patients who were initially unimpaired, recovered, or showed chronic apraxia for the dependent variables age, lesion size, and the clinical test scores (NIHSS, mRS) are presented in Supplementary Table 2.

3.2. Lesion distribution

The lesion distribution reflected the territory of the left middle cerebral artery and showed a maximum overlap centered on the lenticular nucleus/external capsule, which included perisylvian white matter (Fig. 2).

3.3. Main effects and recovery effects in longitudinal voxel-based lesion-symptom mapping

To identify anatomical structures typically related to chronic or recovering apraxic deficits we used a longitudinal VLSM approach with a two-way repeated-measures ANOVA design.

3.3.1. Lesion locations related to apraxia in the acute and chronic stage

The main effect for lesion identified lesion clusters which are related to impaired performance in the acute and/or the chronic stage for each test.

Impaired imitation of meaningless postures was significantly related to lesions of the dorso-dorsal stream (Fig. 3A). Lesions comprised the LOTC ($F_{(1,\infty)} = 50.957$, $p < .01$) extending into visual area V6, superior and inferior parietal lobe (SPL; $F_{(1,\infty)} = 45.813$, $p < .01$, IPL; $F_{(1,\infty)} = 48.509$, $p < .01$) and the posterior parts of the superior temporal gyrus (pSTG; $F_{(1,\infty)} = 27.280$, $p < .01$) and sulcus (pSTS; $F_{(1,\infty)} = 11.258$, $p < .01$). No regions were found using lesion volume as covariate.

Both, production (Fig. 3B) or concept deficits (Fig. 3C) in tool use pantomime were related to lesions in the supramarginal gyrus (SMG) of the anterior IPL (production: $F_{(1,f\infty)} = 22.846$, $p < .01$); concept: $F_{(1,\infty)} = 50.197$, $p < .01$, and the posterior STG (production: $F_{(1,\infty)} = 14.840$, $p < .01$; concept: $F_{(1,\infty)} = 13.278$, $p < .01$) in the ventro-dorsal stream. Lesions in concept errors in tool use pantomime extended to middle temporal gyrus (MTG; concept: $F_{(1,\infty)} = 13.958$, $p < .01$). See Table 2 for cluster information.

3.3.2. Lesion locations related to good or poor recovery

The interaction effect lesion \times time of the two-way repeated-measures ANOVA allowed the detection of lesions that were either related to good or poor recovery.

Imitation deficits in patients who did not recover over time compared to the rest of the cohort were associated with middle superior temporal gyrus lesions (STG; $F_{(1,\infty)} = 21.311$, $p < .01$; Fig. 4A). Lesions in the ventral premotor cortex (PMV)

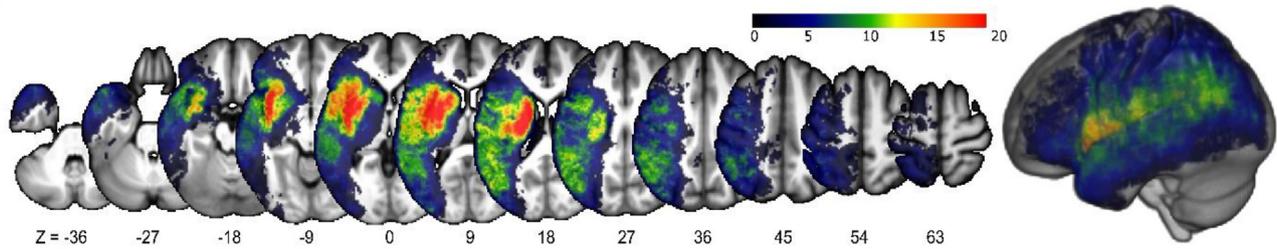


Fig. 2 – Lesion overlap. Lesion overlap of 90 patients with left hemisphere stroke included in the study. The binarized lesion maps are displayed as overlay on an in-house template and show the lesion distribution in the left hemisphere. Color bar represents the number of patients with lesions in a particular voxel, e.g., red indicates an overlap of 20 out of 90 subjects.

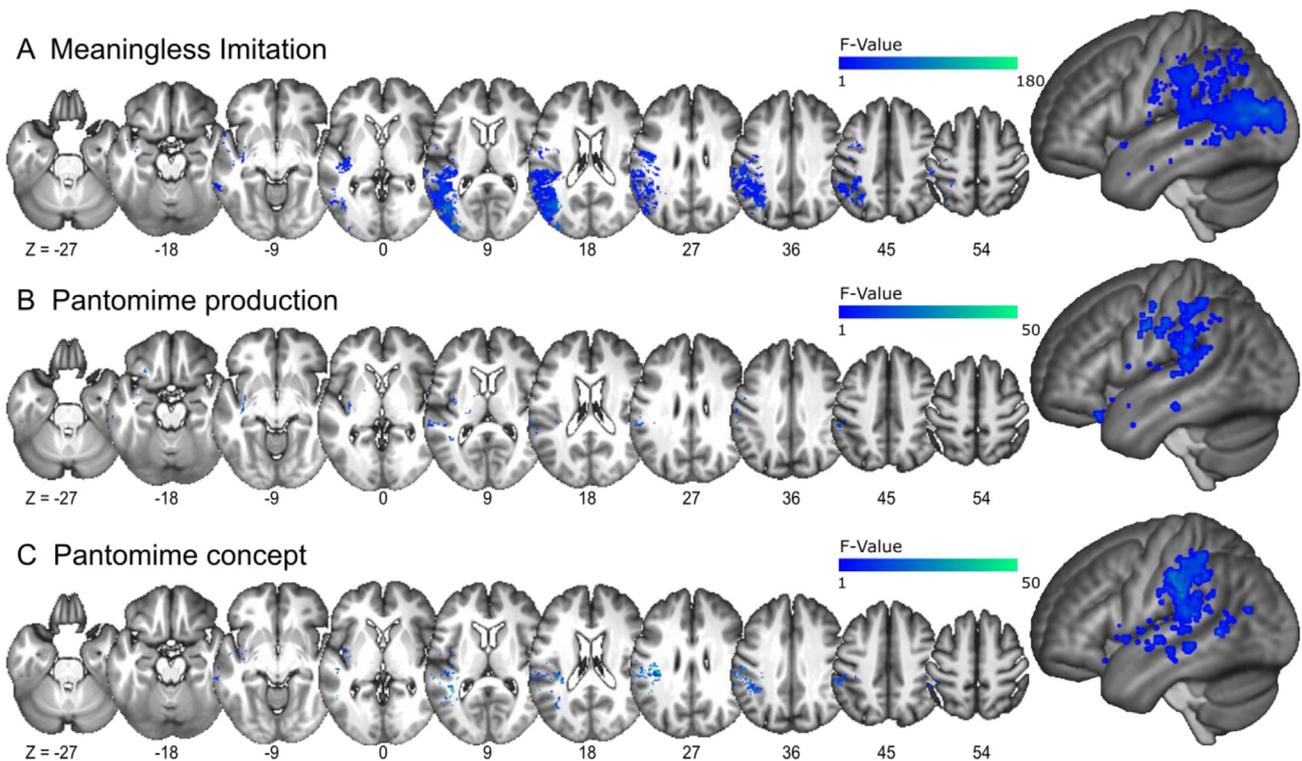


Fig. 3 – Main effect for lesion. Results of the two-way repeated-measures ANOVA for the main effect lesion. Lesion cluster marked in blue convey a significant difference in behavior between patients with versus without a lesion in the corresponding voxel irrespective of the time of examination for meaningless imitation (A), pantomime production (B) and pantomime and concept (C) deficits. Results are thresholded at $p < .01$ FDR corrected for multiple comparisons. As significant interaction effects confound the main effect, lesion maps are masked for those voxels, where a significant interaction effect for lesion \times time was present in the repeated measures ANOVA (see results in Fig. 4).

were associated with production deficits during pantomime of tool use which persisted until the chronic stage ($F_{(1,\infty)} = 13.509$, $p < .01$; Fig. 4B).

On the contrary, for pantomime concept deficits we detected lesion clusters related to good recovery (Fig. 4C). The lesion clusters were located in the left angular gyrus (AG; $F_{(1,\infty)} = 40.962$, $p < .01$), the posterior parts of SMG, and (peri-) insular structures ($F_{(1,\infty)} = 56.359$, $p < .01$). No lesion cluster

was related to poor recovery. See Table 2 for cluster information.

3.3.3. Lesion locations related to apraxia in the chronic stage
We also analyzed which lesions correlated with deficits in the chronic stage by performing multivariate lesion-symptom mapping with the performance in the chronic stage (Ex 2) as the behavioral variable. These analyses corroborated the

Table 2 – Cluster information.

AAL label	Mean center of cluster (XYZ)		
Main effect lesion			
Meaningless Imitation			
Left supramarginal gyrus	−53.0	−33.0	35.0
Left angular gyrus	−38.0	−63.0	41.0
Left middle occipital gyrus	−47.0	−69.0	2.5
Left superior temporal gyrus	−63.0	−30.0	9.0
Pantomime Production			
Left superior temporal gyrus	−64.5	−39.0	13.5
Left supramarginal gyrus	−65.0	−27.0	20.0
Pantomime Concept			
Left middle temporal gyrus	−61.5	−22.5	−19.5
Left superior temporal gyrus	−57.0	−10.5	1.5
Left supramarginal gyrus	−63.0	−27.0	20.0
Interaction effect lesion × time			
Meaningless Imitation			
Left superior temporal gyrus	−63.0	−18.0	6.0
Pantomime Production			
Left precentral gyrus	−54.0	3.0	6.0
Pantomime Concept			
Left supramarginal gyrus	−57.0	−46.5	31.5
Left angular gyrus	−52.0	−53.0	33.0
Left insula	−36.0	4.5	−3.0
Multivariate VLSM analysis			
Meaningless Imitation			
Left inferior parietal lobe	−31.0	−41.0	43.0
Left superior parietal lobe	−27.0	−52.0	49.0
Left middle occipital gyrus	−37.0	−66.0	17.0
Left middle temporal gyrus	−36.0	−64.0	15.0
Pantomime Production			
Left superior temporal gyrus	−58.0	−30.0	18.0
Left supramarginal gyrus	−52.0	−31.0	26.0
Left postcentral gyrus	−50.0	−17.0	31.0
Pantomime Concept			
Left middle temporal gyrus	−50.0	−41.0	1.0
Left superior temporal gyrus	−63.0	−39.0	16.0
Left superior temporal gyrus	−58.0	−13.0	5.0
Left supramarginal gyrus	−50.0	−28.0	29.0
Left temporal pole	−49.0	15.0	−11.0

results of the repeated measures ANOVA (Figs. 3 and 4). Imitation deficits remained until the chronic stage after LOTC and superior parietal lesions (Fig. 5A). Production errors persisted after SMG, postcentral, and pSTG lesions (Fig. 5B). Conceptual errors in tool use pantomime persisted after SMG and superior and middle temporal gyrus (pSTG, MTG) lesions (Fig. 5C). The mass-univariate VLSM analysis (Supplement Fig. 2) yielded comparable results; whereby the middle temporal lesion cluster related to persisting imitation deficits was only detected in the mass-univariate analysis. See Table 2 and Supplement Table 3 for cluster information.

4. Discussion

This is the first longitudinal study that investigated recovery from apraxia and the corresponding lesion correlates in a large cohort of stroke patients, who were examined during the acute and chronic stage. We detected a diverging course of recovery in relation to apraxic deficits on the behavioral level

and could identify task-dependent lesion correlates for persisting or recovering apraxic deficits using a novel longitudinal voxel-based lesion-symptom mapping approach. Imitation deficits recovered only partly. Chronic imitation deficits were related to lesions at the entrance of the dorso-dorsal stream (LOTc and pSTG/STS). Tool use pantomime production errors recovered least. Anterior SMG seems to represent the most critical lesion for these deficits during the acute and chronic stages. Lesions to the more frontal part of the ventro-dorsal stream (PMv, postcentral gyrus) were additionally associated with a poor recovery in tool use pantomime production. Conceptual errors in tool use pantomime tended to resolve completely over time when related to AG and (peri-)insular lesions, and only rarely persisted after temporal lesions (MTG, STG) and SMG lesions. An overview of the results is shown in Fig. 6. In the context of the network for motor cognition, these lesion patterns show different task-dependent mechanisms of good or poor recovery in apraxia: critical lesions for each task are leading to chronic deficits; conversely, lesions outside the key structures of the network only lead to temporary network dysfunction and are related to a good recovery.

Methodically, our longitudinal lesion mapping approach is based only on acute imaging data and combines them with acute and chronic behavioral data. Reasons supporting the usage of only acute lesion data are reduced morphological changes in shape, location, and quantity of brain tissue (e.g., enlargement of the ventricles, translation of anatomical landmarks) (Karnath et al., 2011; Martin et al., 2016).

4.1. Critical lesions in entrance areas of the dorso-dorsal stream relate to chronic imitation deficits

Imitation deficits in the acute and chronic stage related to areas known from previous studies (Achilles et al., 2019; Goldenberg, 2001; Hoeren et al., 2014; Peigneux et al., 2000; Rumiati et al., 2005), including LOTc, posterior parietal cortex extending into AG/SMG, and pSTG/pSTS (Fig. 3A), which grossly constitute the dorso-dorsal stream, relevant for the on-line guidance of movements (Binkofski & Buxbaum, 2013; Kalénine et al., 2010; Rijntjes et al., 2012; Rizzolatti & Matelli, 2003; Vingerhoets, 2014; Vry et al., 2012). In the chronic stage lesion clusters in the LOCT and pSTG/pSTS showed a special relevance for chronic imitation deficit (Figs. 4A and 5A).

In the context of actions, LOTc integrates different aspects (“perception, understanding and production” (Lingnau & Downing, 2015)) of movements, and provides input into the dorsal and ventral processing stream (Lingnau & Downing, 2015). LOTc processes visuospatial information of movements into the dorso-dorsal stream (Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003; Mishkin, Ungerleider, & Macko, 1983) and is commonly attributed to visuospatial mapping (Ajina, Kennard, Rees, & Bridge, 2015; Born & Bradley, 2005; Peigneux et al., 2000; Rizzolatti & Matelli, 2003), coding of spatial features of visually perceived objects (Culham & Kanwisher, 2001; Faillenot, Decety, & Jeannerod, 1999) and gestures (e.g., the spatial relationships of the body parts involved) (Goldenberg, 1995, 2009; Goldenberg & Hagmann, 1997). LOTc also comprises regions located at the junction and connected with ventro-dorsal and ventral stream (e.g., posterior MTG) (Weiller et al., 2021), potentially coding for

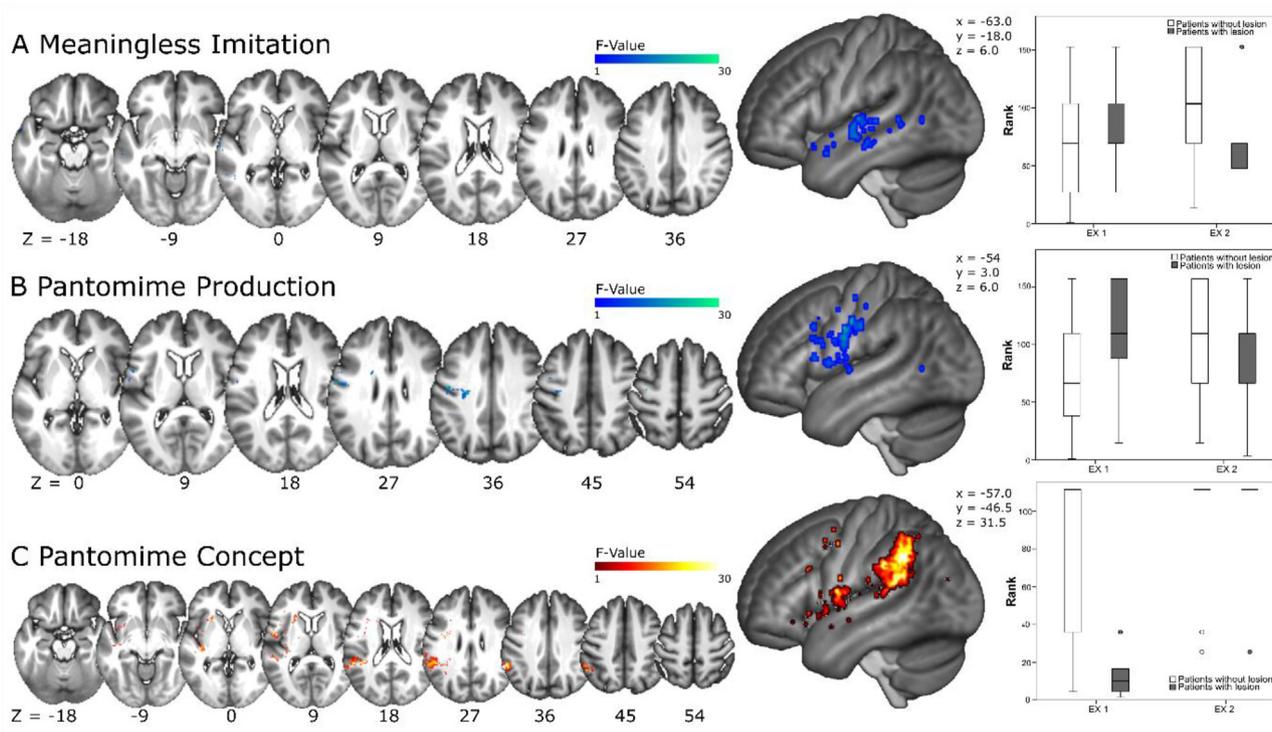


Fig. 4 – Interaction effect lesion \times time. Results of the longitudinal repeated measures ANOVA for the interaction effect of lesion \times time. In the upper rows (A meaningless imitation and B pantomime production) voxels with significant interaction effects between lesion status and time, which are related to non-recovering deficits are marked in blue. Boxplots illustrate the behavioural data from patients with (grey bar) and without (white bar) lesions at the left superior temporal (A; $-63.0/-18.0/6.0$) and left ventral premotor cortex (B; $-54.0/3.0/6.0$) peak voxels. In the lower row (C pantomime concept) voxels related to good recovery are marked in red. As indicated by post hoc tests those lesion cluster had a significant effect on deficits which did recover. The boxplots illustrate the behavioural performance of patients with (grey bar) and without (white bar) lesions in the left angular gyrus/posterior supramarginal gyrus ($-57.0/-46.5/31.5$). Results are presented at the threshold of $p < .01$ FDR corrected for multiple comparisons.

body representations in actions as well as for the processing of hand postures (Bracci, Cavina-Pratesi, Connolly, & Ietswaart, 2016; Downing et al., 2001, 2006; Goldenberg & Karnath, 2006; Lingnau & Downing, 2015; Orlov, Makin, & Zohary, 2010). Concluding, LOTC lesions are susceptible to cause lasting imitation deficits as LOTC provides input information for imitation in all processing streams, and holds integrative functions for movements and the body parts involved.

Also, pSTG and pSTS were related to chronic imitation deficits in our (Fig. 5A) and previous studies (Rumiati et al., 2005; Tessari, Canessa, Ukmar, & Rumiati, 2007). In movements pSTG/pSTS contribute to the identification of motion in space and in time (Beauchamp, 2015; Beauchamp, Lee, Argall, & Martin, 2004; Decety, Chaminade, Grè, & Meltzoff, 2002). In the language system, pSTG represents the origin of the dorsal stream, projecting via the acute fascicle to parietal and frontal regions (Catani, Howard, Pajevic, & Jones, 2002). It provides temporal (Rauschecker, 2012) and spatial information, e.g., the location of sound (Ahveninen, Kopčo, & Jääskeläinen, 2014) in auditory processing. Thus, a domain-general function for temporal analysis in pSTG/pSTS at the entrance of the dorso-dorsal stream in movement production

and language can be assumed, providing essential information to complete this task, which cannot be compensated.

The lesion cluster related to acute and chronic imitation deficits also involved AG and SMG (Fig. 3A), but these lesions were not present at the chronic stage (Fig. 5A) only. The role of inferior parietal regions for imitation of hand and finger postures has been discussed in previous studies: it has been proposed that IPL provides stored information about the involved body parts (body-part knowledge) of the observed postures (Goldenberg, 1995, 1999, 2009; Goldenberg & Karnath, 2006). The finding, that lesions to this region were not strongly associated with chronic deficits of meaningless imitation (Fig. 5A) might indicate that lacking body part information mainly plays a role during the acute stage.

Further, chronic meaningless imitation deficits were related to MTG and middle STG lesions, the association however was only detected in the mass-univariate analysis (Supplement Fig. 2). This finding is less intuitive as the ventral stream does not belong to the regions usually related to meaningless imitation and might be driven by the fact that, due to the vascularization of the MCA territory, involvement of the temporal lobe is systematically associated with large

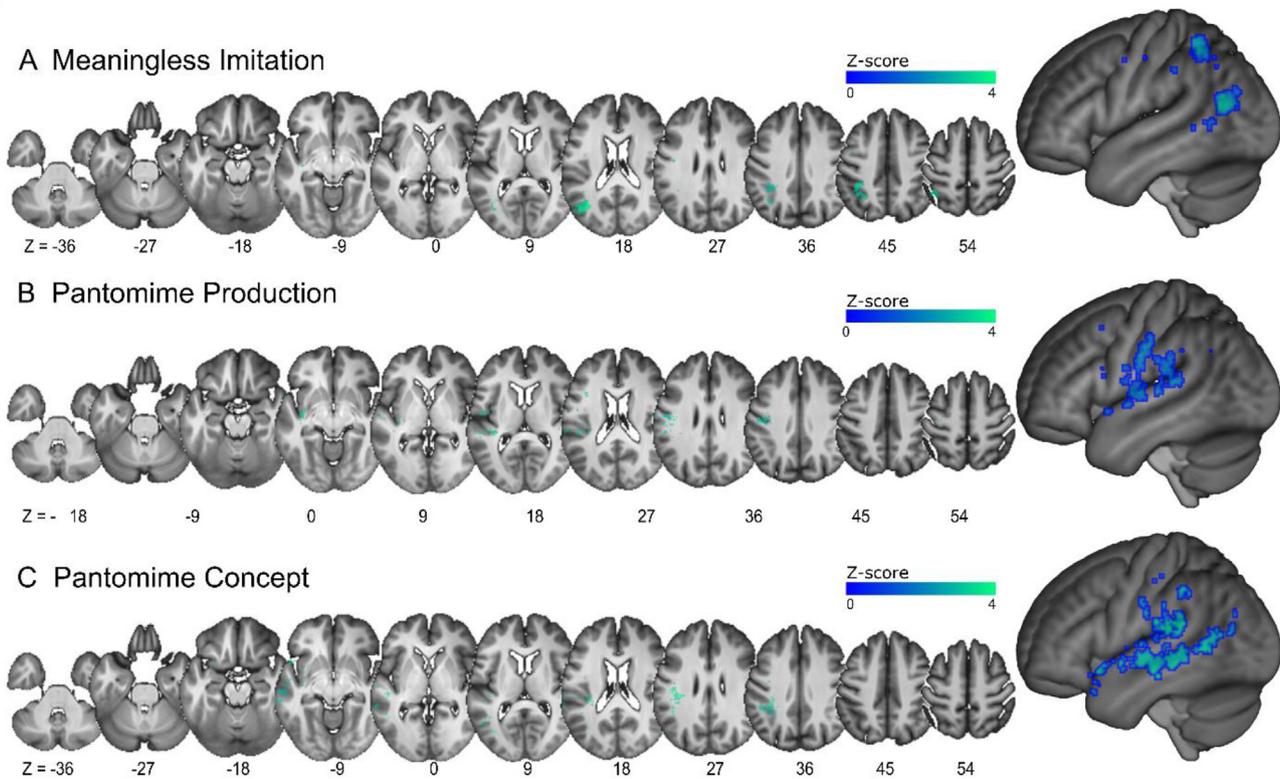


Fig. 5 – Multivariate lesion symptom mapping (SVR-LSM). Results of the multivariate support-vector-regression lesion-symptom mapping (SVR-LSM) analysis for impaired performance in the meaningless imitation (A) and pantomime production (B) and concept errors (C) during the chronic stage (Examination 2). Color bar indicate Z-scores. Voxels shown in blue-green are significant on a voxel-based threshold of $p < .005$.

lesions. The interpretation of this finding can only be speculative and is grounded on the domain-general function of the ventral stream, which is the processing of internal and abstract information for higher motor functions such as imagery of a movement (Vry et al., 2012), abstract conceptual thought (Patterson, Nestor, & Rogers, 2007; Shallice & Cooper, 2013), and on a computational level the capacity to relate behavioral elements based on item structure (Weiller et al., 2009, 2011, 2021). It also facilitates learning of unknown movements by understanding (Menz, Blangero, Kunze, & Binkofski, 2010). Thus, the result could indicate that extensive damage to the ventral stream might hamper the ability to compensate imitation deficits due to deficits in understanding and analyzing the meaningless posture abstractly.

4.2. The supramarginal gyrus is essential for tool use

Deficits in tool use tasks (production and conceptual errors in tool use pantomime) were related to lesions of aSMG and pSTG at both timepoints (Fig. 3B/C, Fig. 5B/C, Fig. 6). aSMG and pSTG together with PMv/posterior IFG (BA 6, BA 44) are connected along SLF III and form the ventro-dorsal stream (Binkofski & Buxbaum, 2013; Caspers et al., 2011; Cloutman, Binney, Morris, Parker, & Lambon Ralph, 2013; Makris et al., 2005; Vry et al., 2012). aSMG stores stable information about tools and movement “blueprints” (Binkofski & Buxbaum, 2013; Goldenberg

et al., 2003; Goldenberg & Spatt, 2009; Hoeren et al., 2014; Kalénine et al., 2010; Niessen et al., 2014; Orban & Caruana, 2014; Rijntjes et al., 1999). Lesions of SMG were related to deficient tool use (pantomime) in the acute (Hoeren et al., 2014) and chronic stage (Buxbaum et al., 2014; Goldenberg, 2009; Niessen et al., 2014). The unique association of the SMG with skilled movement explains the long-term impairment in tool use pantomime in patients with lesions in this region and indicates that the brain has only restricted capacity to compensate for a deficit when specific anatomical structures are damaged. As the right SMG probably does not contribute to the processing of skilled actions (Dressing et al., 2020), compensation through the contralesionally homolog also seems not possible. The importance of the SMG for skilled actions has already been proposed by Liepmann (Liepmann, 1908) and follows the concept of the “critical lesion” for a specific task.

Our data further stress the critical importance of the whole ventro-dorsal stream for tool use, as not only SMG but also PMv lesions impacted on incomplete long-term recovery in tool-related pantomime (Fig. 4B). PMv receives information from aSMG and anterior intraparietal sulcus via the ventro-dorsal and dorso-dorsal stream and combines spatio-temporal information and motor programs (Buxbaum et al., 2014; Heilman, Rothi, & Valenstein, 1982; Rijntjes et al., 1999). In healthy subjects, PMv is crucial for coordination of hand shape and orientation during grasping and movement production

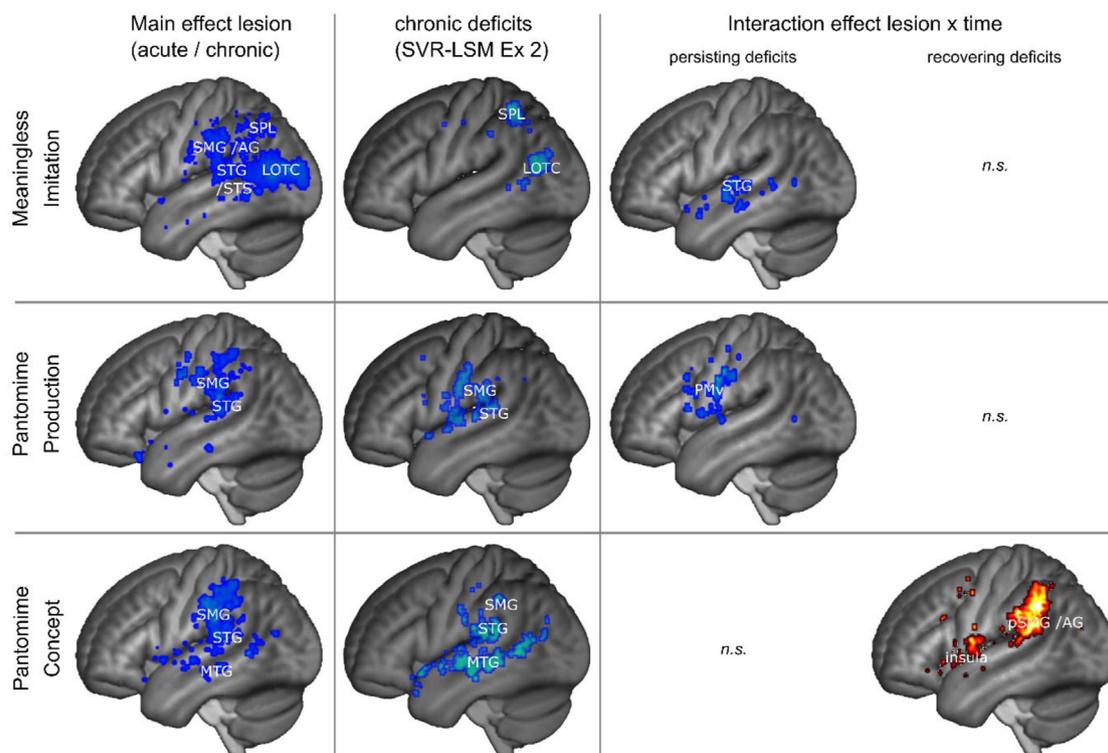


Fig. 6 – Overview of the lesion mapping results. The figure shows the results of the voxel-wise analyses (column 1: longitudinal repeated measures ANOVA - main effect lesion; column 2: multivariate SVR-LSM analysis at examination 2; column 3: longitudinal repeated measures ANOVA - interaction effect lesion \times time) for the different behavioural scores obtained in the study. For more detailed depictions of the results including Z-scores, axial slices, color bars, and legends, see Figs. 3–5. AG; angular gyrus; LOC: lateral occipitotemporal cortex; MTG: middle temporal gyrus; n.s.: no significant results; PMv: ventral premotor cortex; (p)SMG: (posterior) supramarginal gyrus; SPL: superior parietal lobe; STG: superior temporal gyrus; STS: superior temporal sulcus.

(Davare, Kraskov, Rothwell, & Lemon, 2011; Hamzei et al., 2016; Jacobs, Danielmeier, & Frey, 2010). Therefore, deficits in these functions as part of the ventro-dorsal stream reduce the possibility to restore tool use production errors.

4.3. Conceptual errors were related to ventral stream lesions or a temporary network dysfunction

Patients with conceptual errors in tool use pantomime are perplexed and often not able to start any useful movement. However, they recovered dramatically in most cases in our cohort (Fig. 1); only a minority of patients remained impaired. We detected two mechanisms that lead to these two different courses of recovery. First, lesions to SMG and STG, as well as of MTG, were related to a persisting inability to pantomime the use of a tool (Figs. 3C, 5C and 6). The association of SMG and STG lesion for chronic conceptual errors in pantomime is consistent with the view that all tool-related tasks are based on the intactness of the corresponding movement blueprint (see discussion about the SMG above). The association of ventral stream lesions (MTG) for pantomime of tool use in the chronic stage is in line with acute stage studies (Hoeren et al., 2014; Martin et al., 2017). Pantomime relies on the processing of a symbolic gesture in the absence of the corresponding tool,

which requires an additional cognitive process that modulates the representation of the movement and guides movement planning in the ventral processing stream (Vry et al., 2015). Conceptual errors in tool use pantomime arise from the inability to correctly associate tools with actions due to a disturbance of the semantic system for action (Cubelli, Marchetti, Boscolo, & Della Sala, 2000; Rothi et al., 1997; Vry et al., 2015), a function of temporal lobe regions (Buxbaum & Kalénine, 2010; Kalénine & Buxbaum, 2016; Vry et al., 2015; Weiller et al., 2011). This explains why chronic conceptual errors in pantomime of tool use occur due to temporal (i.e., ventral) lesions.

On the other hand, the patients, who recovered over time had AG/pSMG or (peri-)insular lesions (Fig. 4C). AG is a multimodal association cortex (Geschwind, 1965; Seghier, 2013), serves as an interface between modalities, and has been suggested to map perceptual input to distributed semantic knowledge (Binder, Desai, Graves, & Conant, 2009; Seghier, 2013). An alternative but not mutually exclusive view is that the angular gyrus is part of a network engaged in top-down-control of semantic processing in other regions (Corbett, Jefferies, & Lambon Ralph, 2009). AG is widely connected along dorsal (SLF II and III) and ventral routes (ECF, IFOF) (Frey, Campbell, Pike, & Petrides, 2008; Makris et al.,

2005; Obleser, Wise, Dresner, & Scott, 2007; Umarova et al., 2010; Vry et al., 2012) to frontal regions, and along the middle longitudinal fasciculus (mdLF) with the temporal lobe towards ATL (Makris et al., 2009, 2013). Lesions to this highly interconnected supramodal region may damage the access to the network of motor cognition and lead to perplexity and unrecognizable movements, but leave key structures of the network in the ventro-dorsal and ventral stream intact. A similar mechanism can be proposed for pSMG, which, unlike the aSMG, holds more connection to the temporal lobe (Caspers et al., 2011; Cloutman et al., 2013). (Peri-)insular white matter lesions also led to conceptual errors, which recovered well (Fig. 4C). This finding corroborates the results of the only existing longitudinal voxel-based lesion-symptom mapping study in apraxia (Kusch et al., 2018), where insular lesions were related to short-term recovery. In the periinsular white matter, the long ventral association tracts (IFOF, ECF, UF) are traversing through the extreme capsule. This bottleneck allows the iterative exchange of information between temporal, parietal, and inferior frontal areas (Rijntjes et al., 2012; Saur et al., 2008). Periinsular lesions, therefore, might lead to a temporary functional disturbance of the whole stream but do not lead to persisting apraxia as core cortical regions of the network are intact. The initially severe but recovering conceptual errors in tool use pantomime therefore might be an example for temporary remote network dysfunction which leads to disproportional recovery resolves over time as the key structures of the network are intact and regain their function.

4.4. Limitations

Apraxia can impair patients in their everyday living, which has previously been shown (Donkervoort, Dekker, & Deelman, 2006; Hanna-Pladdy, Heilman, & Foundas, 2003; Sunderland & Shinner, 2007). However, mapping these deficits is difficult as apraxia is a complex deficit in cognitive motor functions, which is not mirrored in classic clinical outcome scores. Neither the NIH stroke scale (which only accounts for cognitive deficits in the domain of language and visuospatial attention), nor the mRS, which focuses on basic motor abilities (i.e., paresis) depict complex functions of everyday living, which are impaired by apraxic errors. This might explain the lack of correlation between apraxic deficits and outcome (mRS) or clinical scores (NIHSS) in the chronic stage in our study.

5. Conclusion

Although a thorough understanding of a stroke patient requires the consideration of structural lesion information, description of the functional status of the brain, and information about the patients' behavior (Dressing et al., 2019) we may learn about recovery from the comparison of the acute versus chronic the state even without information about the functional activation of the network. The present lesion and longitudinal behavioral data reveal different recovery

patterns and underlying mechanisms of good or poor recovery dependent on the apraxia test.

Of clinically high relevance are those lesions which will always hamper recovery over time, as these patients might profit from tailored rehabilitation strategies. In all tasks lesion to critical regions [input regions in the dorsal stream (LOCT and pSTG/pSTS) for meaningless imitation; ventro-dorsal stream lesions for tool use; ventral stream regions for conceptual aspects of tool use pantomime] were related to chronic deficits. This shows that the concept of a critical lesion for functional restitution, which is known from the domain of language and motor function (Weiller et al., 2015) also applies to apraxia. We also identified lesion correlates which explained the initially severe impairment but almost complete recovery in patients with severe pantomime deficits (conceptual errors). Lesions located in the angular gyrus at the entrance of the ventro-dorsal and ventral stream or in the (peri-)insular white matter likely induce only a temporary network dysfunction. These findings might be generalized to other network-based cognitive functions like language and visuospatial attention and can help to estimate the clinical course of recovery already in the acute stage based on the stroke lesion location.

Author credit statement

Author credit statement: AD, MM, CK, MR, and CW contributed to conceptualization of the experiments; AD, MM, MCM, CSMS, LAB and DK recruited and tested the patients; AD, MM, CK, and HU were responsible for the imaging data and data curation; AD, KN and CK performed the analysis; AD, CK, MR and CW contributed to the analysis and interpretation of the results; AD, MR and CK wrote the manuscript, all authors provided critical feedback and helped shape the research, analysis and manuscript.

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Declaration of competing interest

H.U. received honoraria for lectures from Bracco, Bayer, Union Chimique Belge (UCB) pharma, Eisai, and Stryker. The other authors report no conflicts.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cortex.2021.06.001>.

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