Research Square

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Left Anterior Insular Lesions Result in Impaired Recognition of Facial Expressions of Negative Emotions

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Abstract

Single case studies about patients with unilateral insular lesions reported deficits in emotion recognition from facial expressions. However, there is no consensus about both the actual extent of impairments and the role of lesion lateralization. To investigate associations of brain lesions and impairments in a facial emotion recognition task, we used voxel-based lesion-symptom mapping (VLSM) in a group of 29 stroke patients in the chronic stage, 16 with left and 13 with right hemispheric lesion. Recognition accuracy was impaired for fearful and angry expressions in patients with left hemispheric lesions compared to 14 matched healthy controls. VLSM analyses revealed that lesions centered around the left insula were associated with impaired recognition of emotional facial expressions. We here demonstrate a critical role for the left insula in decoding unpleasant emotions from facial expressions and therefore present further evidence for a broader role for the insular cortex not restricted to disgust processing.

Introduction

Impaired social cognition affects the individual's capability to process social information which is highly relevant for adequate social functioning (1). In patients surviving severe brain damage following stroke social withdrawal had been shown to persist unrelated to an actual degree of physical impairment (2). Social integration is an important factor for improved functional outcome (3) and therefore the consideration of social-cognitive disturbances is of particular importance when treating deficits following stroke.

The correct encoding of emotions from facial expressions of fellow human beings is a core function for successful social interaction, given that facial expressions communicate the emotional states and intentions of the emitter (4). Such abilities can be easily assessed in experimental settings, typically using pictures of prototypical facial expressions of emotions (5). Impairments in facial emotion recognition in stroke patients have been described at both chronic and subacute stages (6, 7). Moreover, impaired emotion recognition accuracy was associated with social withdrawal (8), relationship dissatisfaction (9) and problematic changes in behavior such as losing one's temper or impulsivity in stroke cohorts (10).

The insular cortex seems to be crucially involved in decoding of emotions from facial expressions (11). Some evidence suggests that the left insula is particularly involved in decoding disgust from facial expressions (12, 13). However, other findings derived from single case reports on lesions covering the left insula are not always consistent, either failing to show significant impairments in recognizing disgust from facial expressions (14), or failing to show any impairment of emotion recognition in faces in general even when the insula is bilaterally damaged (15). A mostly preserved recognition accuracy in a patient with a right hemispheric lesion including the insula was also described (16). Similarly, a further patient with such a lesion showed normal emotion recognition performance in a paradigm where morphing faces were presented (from neutral to an emotional expression) (17).

However, compared to controls the patient needed more morphing steps for recognizing expressions of disgust and surprise. A general impairment regarding the recognition of negative facial expressions was also documented for another patient with a right hemispheric lesion including the insula (18). While case studies might provide valuable insight into emotion recognition, studies including larger patient samples are important to better understand the association between specific brain lesions existing after a stroke and functional performance. In addition, studies that assess emotion recognition performance and relate the function explicitly to insular lesions following stroke are scarce. Actually, in recent approaches lesions were not restricted to the insular cortex while results on lesion laterality and recognition impairments were inconsistent (19, 20).

Taken together, there is a disagreement about the nature of facial emotion recognition impairments in patients with insular lesions. Additionally, it remains unclear whether such impairments are more associated with the laterality of the lesions. So far, available data suggest that recognition impairments are expected to be more pronounced in patients with left insular lesions – particularly for negative emotions which are more difficult to categorize than happy faces (21). However, a better understanding for the association between behavioral performance and lesion localization is needed.

Therefore, we performed a prospective study in 38 patients in the chronic stage following unilateral brain lesions due to stroke with and without involvement of the insula using a facial emotion recognition paradigm and extensive neuropsychological testing. Comparisons based on group categories such as affected hemisphere consider the spatial resolution of the actual brain lesion less precisely and, hence, can result in null findings (22). Therefore, we also applied a voxel-wise lesion-symptom mapping analysis (VLSM) to provide a better characterization of the lesions and to describe in more detail the association between structural damage and recognition performance (23).

Finally, data of 29 patients with either left (LL; n = 16) or right hemispheric lesions (RL; n = 13) were used for analyses. Fourteen healthy controls (HC) matched for age and gender were included for comparisons of recognition performance and neuropsychological testing which comprised examinations of verbal intelligence and comprehension, alertness, verbal and visuospatial memory, executive functioning, facial blindness, and a questionnaire for depression. Recognition of emotional facial expression was tested using stimuli of the FACES database including 12 pictures showing facial expressions for each of four basic emotions and also neutral expressions (24; for the time course of one facial recognition run see Fig. 1A). Correct recognition (accuracy in %) and mean time required for correct recognitions were assessed. Since we assumed that time required for correct recognitions is an important and sensitive variable we merged both accuracy and duration for categorization in one recognition performance variable. Actually, correcting accuracy measures is a standard approach in rating performance studies (25). All patients underwent structural cranial MR-imaging including a high resolution T1 and a Flair sequence and lesion maps were manually drawn by an experienced neuroscientist/neurologist (ML; sum lesion map presented in Fig. 1B) and used for voxel-based lesion-symptom mapping (VLSM) analysis after advanced normalization optimizing normalization processes also for brains with lesions. The Non-Parametric Mapping Toolbox was used for statistical comparisons realized for whole-brain and region-of-

interest analyses (bilateral insular cortex) corrected for multiple comparisons. Since previous reports already identified the relevance of the insular cortex for emotional facial expression identification we expected a significant association of recognition performance with lesions in that structure in our VLSM analyses.

Results

Patients were comparable with healthy controls for most of the neuropsychological measures (see Table 1). Only for the Trail Making Test (TMT A) significant differences were found. Bonferroni-adjusted post-hoc tests showed that patients with right hemispheric lesions performed slower than healthy controls ($p = .036$).

Table 1
Characteristics of the group

	HC	LL	RL	Statistics
No. of participants	14	16	13	-
Age in years	62.3 (15.6)	63.3 (13.6)	65.3 (13.9)	$F = 0.155$, $p = .857$
Gender (F:M)	8:6	5:11	4:9	$p = .311$
Handedness (L:R)	0:14	1:15	1:12	$p = .752$
Months since stroke	-	33.0 (36.1)	35.5 (36.6)	t=-0.187, $p = .853$
Lesion volume cm³	-	20.0 (35.4)	19.7 (14.1)	$t = 0.033$, $p = .974$
NIHSS (median)*	-	3	4	$MW = 60$, $p = .346$
School years	10.3(1.3)	10.3 (0.7)	9.6 (1.6)	$F = 1.266$, $p = .293$
MWT-B	29.1 (3.6)	27.0 (4.8)	28.6 (5.6)	$F = 0.857$, $p = .432$
Simple reaction in ms	360 (68)	375 (87)	343 (51)	$F = 0.688$, $p = .508$
AAT	55.6 (4.4)	53.9 (4.5)	54.2 (3.5)	$F = 0.617$, $p = .545$
CVLT	52.2 (12.4)	48.6 (12.3)	44.5 (14.2)	$F = 1.210$, $p = .309$
TMT A in s	33.9 (11.6)	45.8 (15.9)	51.6 (23.6)	$F = 3.646$, p **= .035**
TMT B in s	84.1 (44.7)	118.7 (45.8)	110.8 (49.9)	$F = 2.180$, $p = .126$
STROOP in s	86.2 (21.8)	108.2 (33.1)	92.2 (17.5)	$F = 2.985$, $p = .062$
Benton	7.1 (1.5)	5.8 (1.8)	6.3 (1.4)	$F = 2.332$, $p = .110$
FAB	94.3 (7.3)	92.8 (9.5)	93.5 (6.3)	$F = 0.129$, $p = .879$
BDI	9.0 (7.9)	5.8(6.0)	8.8(6.0)	$F = 1.072$, $p = .352$

Mean values are presented with standard deviation in brackets. HC = healthy control, LL = left hemispheric lesion, RL = right hemispheric lesion, F = female, M = male, L = left, R = right, NIHSS = median of the National Institute of Health Stroke Scale score assessed at admission to hospital, MWU = Mann-Whitney U statistic, MWT-B = number of correctly recognized words, AAT = score of the verbal comprehension task, CVLT = number of all correctly remembered nouns of the California Verbal Learning Task, TMT A/B = Time required for the Trail Making Test A/B, STROOP = time required for the STROOP interference task, Benton = number of correct drawings, FAB = percentage of correct trials in the facial identity discrimination task, BDI = sum score of the Beck Depression Inventory II. *NIHSS scores were not available for 4 patients (LL = 2, RL = 2).

There was no difference in recognition performance between patients and controls in general ($F(1, 41) = 1.017$, $p = .319$) but also when laterality of lesion was considered ($F(2, 40) = 1.019$, $p = .370$). The LL group performed worse than the HC group for expressions of fear ($t(28)$=-1.761, $p = .045$) and anger

($t(28)$=-2.095, p = .023), while no significant differences were found between the RL group and HC group (see Fig. 1C and Table 2).

Table 2
Comparisons of recognition performance

	HC	Patients		LL		RL	
	Mean (SD)	Mean (SD)	vs. HC	Mean (SD)	vs. HC	Mean (SD)	vs. HC
Fear	34.3(9.4)	29.4(13.3)	.113	27.7(11.0)	**.045**	31.5(15.9)	.293
Anger	37.5(12.8)	32.2(22.1)	.205	27.4(13.3)	**.023**	38.0(29.1)	.476
Disgust	32.0(9.9)	29.2(15.5)	.272	29.0(15.0)	.265	29.5(16.7)	.317
Neutral	41.7(16.5)	39.7(21.1)	.381	39.9(22.4)	.405	39.5(20.3)	.379

Recognition performance (accuracy in % divided by the time in s needed for correct decisions) of healthy controls and patients (in sum and separated for left and right hemispheric lesions) for emotional and neutral expressions. Mean values are presented with standard deviation in brackets, HC = healthy controls, LL = patients with left-hemispheric lesions, RR = patients with right-hemispheric lesions, vs. HC = p value of the single comparison with HC using independent-samples t-tests (according to our directional hypotheses one-tailed p values are reported).

When applying VLSM for the analysis of lesion specificity for impairments of recognition performance, an explorative analysis (0.001 uncorrected, see Fig. 2) demonstrated that impaired facial expression recognition performance was predominantly associated with left sided brain lesions centered around the left insula. In particular, impaired recognition of fear was associated with lesions of the left lateral insula cortex. Impaired recognition of anger was associated with lesions of the left superior anterior and inferior posterior insula. Impaired recognition of disgust was associated with lesions of the left ventrolateral prefrontal cortex, more anterior to the anterior insula. Also, lesions of the left insula were associated with the recognition of neutral expressions. When correcting for multiple comparisons in a region-of-interest analysis (ROI; bilateral insular cortex), impaired recognition performance for anger and neutral expressions correlated significantly with clusters of voxels in the left insular cortex.

In Table 3, corresponding peak coordinates (referring to MNI space) and numbers of voxels are reported for significant z values corrected for multiple comparisons (FDR correction).

Table 3
Lesion sites associated with impaired recognition performance (ROI analysis)

Expression	Site	Number of voxels	Peak voxel	Z	MNI coordinates		
					x	y	z
Anger	L ant/post IC	250	ant IC	2.415	-33	-1	13
Neutral	L post IC	241	post IC	2.246	-39	-5	-4

Coordinates are reported for the peak region and refer to MNI space. Only voxels with significant z values corrected for multiple comparisons are considered. Z = maximum z value found in the peak region, L = left, ant = anterior, post = posterior, IC = insular cortex.

Discussion

In the present work stroke patients with unilateral left and right hemispheric lesions which frequently included the insula were examined using a facial emotion recognition paradigm while recognition accuracy and reaction time were assessed. In this prospective study we applied both a group comparison between patient groups with left and right hemispheric lesions and healthy controls, and a voxel-based lesion-symptom mapping to investigate the specificity of lesioned brain regions for facial recognition impairment. We enrolled our patients during the acute stage following stroke and asked them to participate in the experiment at a later chronic stage. Together with a comprehensive neuropsychological testing – ensuring that left and right hemispheric lesion groups and matched controls performed comparable for other dimensions such as vision, speech and language, and cognition – we were able to specifically test facial recognition disturbances with a careful control of possibly biasing other impairments.

Exploratory single comparisons suggested that left hemispheric lesions affected recognition performance especially for negative emotional facial expressions (fear and anger) which is in contrast to findings which relate recognition capabilities rather with the right hemisphere (26, 27). Nevertheless, our results are in line with findings by Young et al. (28) who found recognition impairments primarily in patients with left hemispheric lesions following traumatic brain injuries. Actually, fear and anger expressions are difficult to discriminate (29) and impaired recognition for these emotions is typically found in stroke patients (6, 30).

We did not observe impairments in disgust recognition in our patients which is in line with previous findings (7, 31) though also impaired capabilities have been reported (32). In accordance with previous work (6, 21), happiness was the easiest expression to identify compared to negative facial expressions and accurately recognized by our patients. This might be due to the fact that happiness was the only positive expression applied in our study (29). For later studies it might be interesting to use further positive facial expressions (e.g. surprise) to decrease a potential ceiling effect (33).

A more in-depth analysis using VLSM (whole brain), a strategy superior to a gross classification of stroke patients to groups before (34), showed that impaired recognition performances particularly for fear and anger expressions were associated with lesions located predominantly in the left insula. Using ROI analyses (bilateral insular cortex) and correcting for multiple comparisons, a correlation between regions in the left insula and impairments in anger recognition performance was still observable. Our findings support previous work which has revealed similar recognition impairments in patients with lesions of the left insula (14, 33, 35).

Impairment in the recognition of disgust or fear did not stand the correction for multiple comparisons (Table 1). Uncorrected results (Fig. 2) showed highest significance for the recognition of fear in the left medial insula (MNI-coordinates: -34, -1, 15) and for the recognition of disgust for the left ventrolateral prefrontal cortex (vlPFC; MNI-coordinates: -28, 27, 13). The vlPFC area is known to process multidimensional emotional stimuli with respect of the perceived emotional intensity in man (for prosody see 36; for emotional gestures see 37) and monkey (38).

Considering the correction for multiple comparisons, our results corroborate Boucher et al. (33) who found intact disgust recognition in patients with unilateral insular surgery, however they contradict previous findings of impaired disgust recognition in patients with left insular lesions (12, 13). More importantly, our findings question the idea that the insula is primarily relevant for disgust processing (39). Interestingly, our VLSM analysis showed that impairments in recognition of neutral expressions were also associated with lesions in the left insula, hence, corroborating findings by Fusar-Poli et al. (11).

In fact, the insula has a central function in the perception and evaluation of body signals, which is highly critical for the activation of subjective experiences of emotional states but also for the encoding of emotional information displayed for example in facial expressions (40). The anterior and posterior regions of the insula differ not only in terms of their cytoarchitecture, but also in terms of their afferent and efferent connections. While the posterior part of the insular cortex is connected to the thalamus, the somatosensory cortex and the superior temporal gyrus, the anterior insula maintains close connections to the limbic system, particularly to the amygdala, the anterior cingular and prefrontal cortex and the basal ganglia (41). Whereas the posterior insula is responsible for the representation of various visceral functions and physiological body processes (40), the anterior insula is more involved in the evaluation of these body processes, which then forms the basis for various emotional and motivational states. Therefore, according to our data it appears that lesions especially in the left insular cortex cannot that easily be compensated especially for those expressions that are difficult to identify even for healthy participants. In fact, correctly identifying expressions of fear and anger was among the most difficult tasks as shown in a recent work on emotion recognition (42). In contrast, lesions of the right insula might not affect emotion recognition as also previously shown (16).

Limitations

Patients with right hemispheric lesions showed visual search deficits (assessed with the TMT A test). However, since all of the effects for facial emotion recognition were located in the left hemispheric lesion group this did not have an impact on our results. Although post-stroke depression is a common finding (43), self-reported depression severity was comparable between patients and healthy controls with scores reflecting absent or mild symptoms. Thus, depression can be ruled out as a confounding factor biasing social cognition performance in our analyses. Our study comprised a variety of examinations on several days. It therefore cannot be ruled out that especially highly-motivated and well-recovered patients showed willingness for participation, which was critically noted just recently (7). A selection bias could be reflected by relatively small lesion sizes in our sample (mean = 19.9cm³), compared to another recent study (20). This might explain why effects were not that prominent in our study and that impairments were rather selective in contrast for example to findings by Braun et al. (6).

Conclusion

To our knowledge, this is the first study to examine emotion recognition performance including analyses of lesion-symptom mapping for three basic emotions in a stroke cohort that comprehensively contained unilateral lesions of the left and right insula. Our results show that at least selective impairments in social cognition are present even in well-recovered patients with less severe strokes. Moreover, we show that these deficits could be especially related to lesions of the left anterior insular cortex and the adjacent vlPFC, corroborating previous findings of clinical case reports and imaging studies on healthy participants. In the light of well-documented negative consequences for the patients' life after brain lesions of various etiologies, we therefore suggest not only that more weight should be placed on possible social cognition impairments in the treatment of strokes in general, but, most especially, that patients with left lesions of the insular cortex should be treated as a high risk group who are in particular prone to social disturbances. Further approaches might also include structural and functional connectivity information to identify hubs for specific emotional processing within the insula (44).

Methods

Participants

We examined 38 patients suffering from a stroke following an ischemic or hemorrhagic cerebrovascular accident, recruited from the stroke unit of the University Medicine Greifswald. Inclusion criteria were adult patients (age > 18 years) in the chronic stage following a stroke (at least 5 months after a stroke) with diagnosed initial impairment and unilateral lesions as assessed in the initial CT or MRI scan of the brain performed in the first week after stroke. The exclusion criteria were low consciousness or arousal level, age > 90 years, presence of relevant cognitive deficits, schizophrenia, a history of neurodegenerative disorders, epilepsy, brain traumas or tumors. For six patients, structural images could not be collected due to contraindications for MRI. Two patients terminated the examination due to personal reasons. The data of one patient was not considered for analyses, as poor performance was consistently apparent in neuropsychological tests on visual-spatial processing especially in the light of a relatively young age of

58 years which might reflect a generally impaired vision (this patient's test scores vs. mean values of the patients considered in the study ± SD: Stroop Color-Word Interference Test: 140s vs 101.1s ± 28.0; numbers* of uncorrected errors in the Stroop Test: 22 vs 2.4 ± 3.2; Trail Making Test A: 99s vs 48.4s ± 19.6; Trail Making Test B: 153.6s vs 115.1s ± 47.0; Benton visual retention test: 4 vs 6.0 ± 1.6; *for one patient the number of errors in the Stroop Color-Word Interference Test was not available). Finally, data of 29 patients with either left (LL; n = 16) or right-hemispheric lesions (RL; n = 13) was used for analyses (see Table 1). Three patients reported intake of psychotropic medication in the past (antidepressants = 1) or at present (antidepressants = 1, herbal sedatives = 1). Five patients reported that they undertake (n = 1) or had undertaken psychotherapeutic treatment (n = 4). Fourteen healthy participants (HC) with no history of diagnosed neurological or psychiatric disorders were recruited through community advertisement as age-matched controls. One of them reported the infrequent intake of sedatives for the treatment of sleep disorders. All patients and healthy controls reported normal or corrected-to-normal vision. The study was conducted according to the standards as defined in the Declaration of Helsinki and had been approved by the Ethics Committee of the University Medicine Greifswald (BB29/09b). All participants signed written informed consent forms and were financially compensated.

Procedure

The study presented here is part of a comprehensive examination which took place on three days mostly realized within a week. On the first day, the participants were welcomed to the laboratory facility of the Department of Psychology of the University of Greifswald and briefed in detail about the planned experimental procedure. They signed the informed consent form and completed various questionnaires and neuropsychological tests. The second day of examination took place at the MRI facility of the Department of Radiology of the University Medicine Greifswald in which the MRI investigation was performed. On the third day, emotion recognition experiments were conducted. For emotion recognition experiments participants were seated in a comfortable chair with arm rests in a dimly lit and sound-attenuated room. Stimulus presentation was realized with a computer screen 1.5m in front of them. After the experimental procedure, the participants were debriefed.

Testing

The National Institute of Health Stroke Scale score (45) assessed at admission to the stroke unit was obtained from medical records (this score was not available for four patients). All other tests and MRI were performed in the chronic stage following stroke. These comprised testing of handedness and level of education, clinical information including diagnoses, age of lesion (in months). As cognitive deficits are relatively common after a stroke (46) a variety of neuropsychological tests were administered in order to examine various facets of brain functions: verbal intelligence with the German multiple-choice word test MWT-B (47), alertness with the simple reaction task of the NeuroCogFX software (48), verbal comprehension with the Aachen Aphasia Test (49), verbal memory with the German version of the

California Verbal Learning Test (50), executive functioning with the Trail Making Tests A (numbers) and B (numbers and letters) of the CERAD-Plus (51), susceptibility to interference with the German version of the Stroop Color-Word Interference Test (52), visuospatial memory with the Benton Visual Retention Test (53), facial blindness with a computerized adaption of the facial identity discrimination task of the Florida Affect Battery (54) using pictures showing neutral facial expressions taken from the FACES database (24). Severity of depression was assessed using the German version of the Beck Depression Inventory II (55).

Recognition of facial emotion expressions

Forty-eight pictures of faces of both genders with emotional expressions (fear, anger, disgust, happiness) taken from the FACES database (24) were used. They were converted to gray-scale images and standardized regarding size and brightness using Photoshop CS4 (Adobe Systems Inc., San Jose, CA, USA) and Matlab 7.7 (MathWorks Inc., Natick, MA, USA). An elliptic mask was applied so that only the face was visible. We used twelve pictures for each emotion (six female faces) and twelve pictures of faces with neutral expressions (six female faces). After the presentation of a picture (6s) five labels with the German words for neutral, anger, fear, disgust and happiness appeared at the bottom of the screen. Participants were instructed to identify the emotional expression by pressing the corresponding buttons (1 to 5) on a keyboard using the dominant hand. During the rating, the facial expression was presented continuously, and response time was not restricted. Before the presentation of the next facial expression, a resting period (3s) was realized, during which a fixation cross was shown starting directly after the intensity rating. Stimulus orders were randomly created for each participant. Presentation of stimuli and recording of ratings were realized using Presentation software (Neurobehavioral Systems, Inc.).

MRI

All participants underwent an MRI investigation, including T1 and T2* weighted structural images. Structural scans were collected with a 3T Magnetom Verio MRI scanner (Siemens, Erlangen, Germany) using a 12-channel head coil. T1-weighted imaging for lesion mapping was carried out using a sagittal 3D MPRAGE with 176 slices, a spatial resolution of 0.98×0.98×1 mm^3. The field of view was 250×250 $mm^{2,}$ corresponding to an acquisition matrix of 256×256. Repetition time was 1690 ms, echo time 2.52 ms, total acquisition time 3:50 min. For T2*-weighted imaging, we used a Flair sequence with 45 axial slices of 3 mm thickness with 0.6 mm gap, field of view: 220 mm corresponding to an acquisition matrix of 320×240; Repetition time was 10000 ms; echo time 107 ms; total acquisition time 2:42 min. Lesions were manually drawn by an experienced neuroscientist/neurologist (ML; using MRIcron; (56) on structural T1-weighted images, adding the Flair-images if necessary for lesion localization, and confirmed by medical reports.

Experimental design and the statistical tests

Demographic variables, neuropsychological measures and BDI scores of patients and healthy controls were compared using analyses of variance (ANOVAs) with *Group* (HC, RL, LL) as between-subjects factor. In case of significant main effects, post-hoc comparisons with Bonferroni corrections were computed. Greenhouse-Geisser corrections were applied when the assumption of sphericity was violated. Distributions of gender and handedness were compared using Fisher's exact tests. Lesion volume and age (months) were compared between LL and RL using independent-samples *t* tests. NIHSS scores were compared using a Mann-Whitney *U* test.

Similar to healthy controls stroke patients recognized facial expressions of happiness almost perfectly (100 ± 0% vs. 98.0 ± 5.3%). Because of this ceiling effect, recognition performance of happy faces was not considered for further analyses. We calculated a performance factor for facial recognition by dividing recognition accuracy in percent by the mean response time (in s) needed for correct recognitions for each emotion since combining behavioural accuracy and required time is a common procedure (25). These performance factors were examined using a repeated measures (rm) ANOVA with *Group* (stroke patients, HC) as between-subjects factor and *Emotion* (fear, anger, disgust) as within-subjects factor. A further rmANOVA was conducted where lesion laterality was considered (i.e. *Group*: LL, RL, HC).

Also, single comparisons between patient groups and healthy controls were conducted using independent-samples *t* tests for emotional and neutral expressions. As we expected impaired performances in stroke patients one-tailed *p* values were reported. All analyses were conducted with IBM SPSS Statistics 22 (Armonk, NY, USA). Bee swarm plots were created using R (57) and the beeswarm package (58).

Comparisons based on group categories such as affected hemisphere consider the spatial resolution of the actual brain lesion less precisely and, hence, can result in null findings (22). Therefore, we also applied a voxel-wise lesion-symptom mapping analysis (VLSM) to provide a better characterization of the lesions and to describe in more detail the association between structural damage and recognition performance (23).

For the VLSM analysis the Advanced Normalization Tools (ANTs, v2.2.0(59)) were used to register and spatially normalize the T1-weighted images into MNI space (MNI ICBM152 6th generation). For this purpose, the antsBrainExtraction script calculated a skull-stripped version of each T1-weighted image. Afterwards, antsRegistration was used to create the necessary transformations (rigid to affine to SyN (diffeomorphic)) from individual subject space into MNI space (60). The hand-drawn lesion mask images were included as constraints for a precise registration, while minimizing brain topology changes due to non-linear warping. The individual lesion mask images were transformed into MNI space by applying the GenericLabel-Interpolator of ANTs. A voxel-based lesion-symptom mapping was realized with the Non-Parametric Mapping Toolbox (delivered with MRIcron) for each of the three emotion categories displayed in the facial expressions and also for neutral expressions by conducting Brunner Munzel rank tests for each voxel to compare recognition accuracy between patients having a lesion in that voxel and patients having no lesion in that voxel. Computations were realized for whole-brain and region-of-interest analyses

(bilateral insular cortex). The insular cortex map was created using the Neuromorphometrics atlas (Neuromorphometrics, Inc.; http://neuromorphometrics.com/). Only voxels lesioned in at least 15% of the participants (n = 4) were included. To correct for multiple comparisons, threshold Z-values were adjusted using the false discovery rate (FDR) correction (23). Alpha was set at .05 for all statistical analyses.

Declarations

Data availability

Lesion maps and tables of recognition performance can be downloaded on GitHub/martinlotze/facial_recognition.

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Author Contributions

KK performed patient measurement, data analyses, wrote of the first draft of the manuscript and corrected the manuscript. JW provided support for designing the study and the patients testing, for data analyses and statistics and wrote and corrected the manuscript. BvS helped in study planning, patient selection and corrected the manuscript. AH helped in organizing the study, selecting the test material and correcting and writing the manuscript. ML helped organizing the study, supervised measurement and data evaluation, and wrote and corrected the manuscript.

Competing interests

The authors report no competing interests.

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Figures

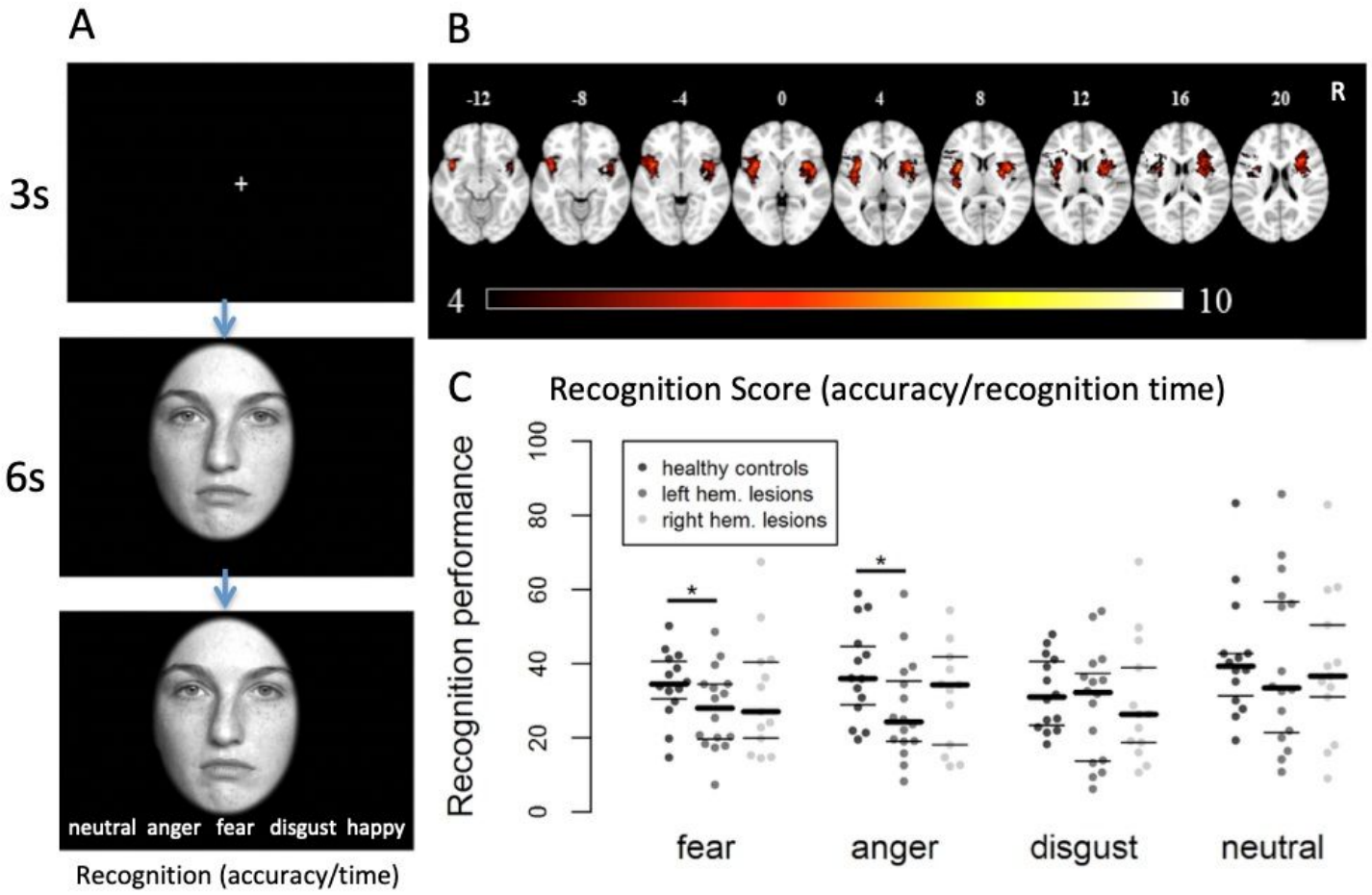

Figure 1

Testing method, patient lesions and behavioral results for healthy controls and left and right hemispheric lesioned patients. A. Facial recognition testing procedure: a fixation cross presented for three seconds was followed by the presentation of the face for another six seconds. Recognition accuracy and time was recorded afterwards. B. Sum lesion map of all stroke patients included (color coding below) C. Swarm plots showing individual recognition performances of healthy controls and patients. Thick horizontal lines represent median values, thin horizontal lines represent quartiles. Asterisks indicate significant single comparisons ($p < .05$).

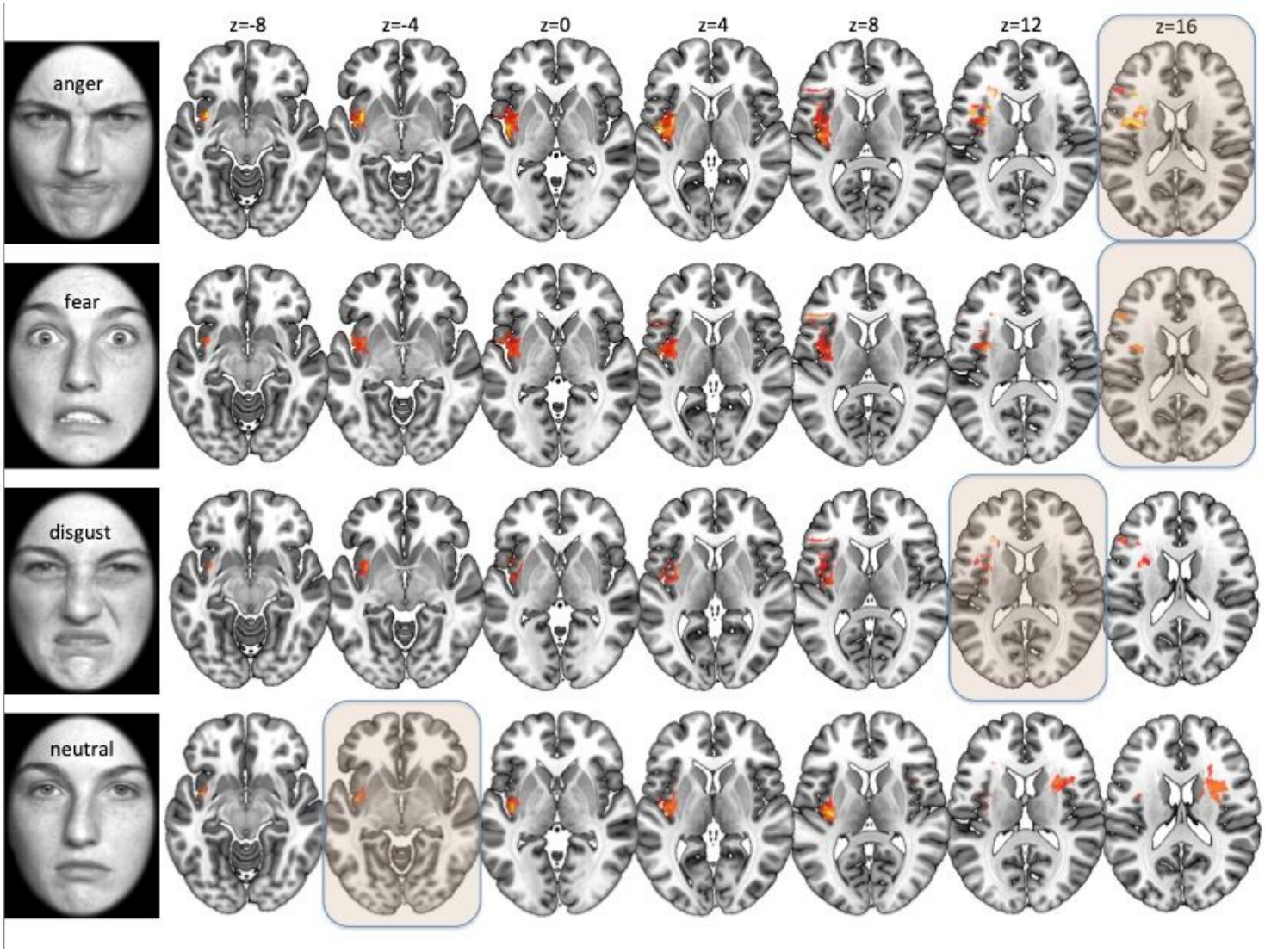

Figure 2

Example for an emotional face presented and demonstration of the results of voxel-based lesion-symptom mapping (VLSM; p=0.001 uncorrected for display purpose) in a group of 29 stroke patients corresponding to the respective emotional expression. Location of transverse slices is provided as z-values in MNI-coordinates on the top. Orange transparent overlay indicate the nearest slice for highest significant voxels. For anger recognition performance VLSM showed highest significance in the superior anterior insula (MNI-coordinate: -35, 0, 17). For fear VLSM showed highest association of impairments with left medial insula lesions (MNI-coordinate: -34, -1, 15). For disgust left ventrolateral prefrontal cortex

were most relevant in the VLSM (MNI-coordinate: -28, 27, 13). For recognition performance of neutral faces left posterior insula showed highest association in VLSM (MNI-coordinate: -41, -6, -6). Only VLSM for anger and neutral facial recognition survived statistics corrected for multiple comparisons in the insula (see Table 3).