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Behavioral and neuroanatomical correlates of facial emotion processing in post-stroke depression

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ABSTRACT

Background: Emotion processing deficits are known to accompany depressive symptoms and are often seen in stroke patients. Little is known about the influence of post-stroke depressive (PSD) symptoms and specific brain lesions on altered emotion processing abilities and how these phenomena develop over time. This potential relationship may impact post-stroke rehabilitation of neurological and psychosocial function. To address this scientific gap, we investigated the relationship between PSD symptoms and emotion processing abilities in a longitudinal study design from the first days post-stroke into the early chronic phase.

Methods: Twenty-six ischemic stroke patients performed an emotion processing task on videos with emotional faces (`happy,` `sad,` `anger,` `fear,` and `neutral`) at different intensity levels (20%, 40%, 60%, 80%, 100%). Recognition accuracies and response times were measured, as well as scores of depressive symptoms (Montgomery-Åsberg Depression Rating Scale). Twenty-eight healthy participants matched in age and sex were included as a control group. Whole-brain support-vector regression lesion-symptom mapping (SVR-LSM) analyses were performed to investigate whether specific lesion locations were associated with the recognition accuracy of specific emotion categories.

Results: Stroke patients performed worse in overall recognition accuracy compared to controls, specifically in the recognition of happy, sad, and fearful faces. Notably, more depressed stroke patients showed an increased processing towards specific negative emotions, as they responded significantly faster to angry faces and recognized sad faces of low intensities significantly more accurately. These effects obtained for the first days after stroke partly persisted to follow-up assessment several months later. SVR-LSM analyses revealed that inferior and middle frontal regions (IFG/MFG) and insula and putamen were associated with emotion-recognition deficits in stroke. Specifically, recognizing happy facial expressions was influenced by lesions affecting the anterior insula, putamen, IFG, MFG, orbitofrontal cortex, and rolandic operculum. Lesions in the posterior insula, rolandic operculum, and MFG were also related to reduced recognition accuracy of fearful facial expressions, whereas recognition deficits of sad faces were associated with frontal pole, IFG, and MFG damage.

Conclusion: PSD symptoms facilitate processing negative emotional stimuli, specifically angry and sad facial expressions. The recognition accuracy of different emotional categories was linked to brain lesions in emotion-related processing circuits, including insula, basal ganglia, IFG, and MFG. In summary, our study provides support for psychosocial and neural factors underlying emotional processing after stroke, contributing to the pathophysiology of PSD.

1. Introduction

Deficits in emotion processing are common in stroke patients (Abbott et al., 2014; Aben et al., 2020; Adams et al., 2019; Luo et al., 2022; Yuvaraj et al., 2013). Such impairments may interfere with social rehabilitation as dealing with social and emotional cues, such as facial expressions, is essential for interactions and social bonding (Adolphs, 2008). Notably, depressive-affective disorders such as major depression

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(MD) are also known to hinder specific socio-emotional processing (Bourke et al., 2010). Stroke patients can also suffer from depressive symptoms, commonly described as post-stroke depression (PSD). Meta-analyses and reviews report a prevalence of PSD between 18 % and 33 % (Hackett & Pickles, 2014; Medeiros et al., 2020). Of note, an enhanced sensitivity of processing negative facial emotion expressions (such as sad or angry faces), is known to promote a mood-congruent emotional state of sadness in depression (Bourke et al., 2010; Peckham et al., 2010). However, data are scarce on whether depressive symptoms post-stroke increase emotion processing of negative faces.

Many studies reported biased emotion processing towards negative facial expressions in MD, e.g., impaired recognition accuracy, longer response times, and selective attention for emotionally valenced stimuli (Bourke et al., 2010; Leppänen, 2006; Peckham et al., 2010). While evidence for a general impairment of emotion processing in depression is less abundant, reviews and meta-analyses instead indicate preferred processing of negative stimuli (e.g., sad and angry faces), reduced processing of positive stimuli (e.g., happy faces), and a tendency to attribute more negative meaning to neutral stimuli. Studies showed that attention to sad facial expressions, in the sense of faster response times, and greater accuracy were predominant in MD compared to controls (Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, et al., 2004; Van Vleet et al., 2019) especially in subtle expressions (Bomfim et al., 2019; Surguladze et al., 2004) and even after recovery (Joormann & Gotlib, 2007). Likewise, findings also suggested that depressive patients exhibit a longer attentional engagement for angry faces compared with non-depressed persons (Leyman et al., 2007).

Generally, stroke patients are also often impaired in emotion recognition, especially those with right-hemispheric infarcts (Yuvaraj et al., 2013). Importantly, in contrast to MD patients, stroke patients often show an overall deficit in recognition compared to healthy controls (Braun et al., 2005; Luo et al., 2022; Nijsse et al., 2019; O'Connell et al., 2021; Tippett et al., 2018; van den Berg et al., 2021). To date, only a few studies have investigated the question of to what extent PSD symptoms are associated with deficits in emotion processing. Montagne et al. (2007) demonstrated in an emotion recognition task, including dynamic face stimuli with different intensity levels, that depressed stroke patients showed lower accuracy than those without depressive symptoms in recognizing anger, disgust, happiness, and sadness. Furthermore, stroke patients with depressive symptoms required more intense emotions to correctly identify angry, sad, and happy faces compared to patients without depressive symptoms. Likewise, de Souza et al. (2021) observed a significant correlation between a better recognition of sad faces and increasing levels of depression in stroke patients. However, data remain scarce concerning the effect of PSD on emotion processing abilities of dynamic facial expressions and how these phenomena develop over time.

Notably, most emotion processing studies in stroke patients found impaired emotion recognition accuracy in patients with right-hemispheric lesions compared to left-hemispheric lesions (Yuvaraj et al., 2013). The networks responsible for the cognition and processing of emotions comprise cortical and subcortical regions, including occipital-temporal cortices, which play a role in forming perceptual representations of the facial signal, and the amygdala, hippocampus, orbitofrontal cortex (OFC), basal ganglia, insula, cingulum, striatum, and somatosensory cortex for representing the emotional value of the expression (Craig, 2009; Damasio, 2003; Gasquoine, 2014; Leppänen, 2006; Palomero-Gallagher & Amunts, 2022; Pessoa & Adolphs, 2010; Phan et al., 2002). These areas also show structural or functional brain changes (Davidson et al., 2002; Phillips, 2003), e.g., in responses to emotional faces in depressed patients (Fu et al., 2008; Lee et al., 2008a; Peluso et al., 2009; Surguladze et al., 2005). Therefore, these brain regions may also mediate emotion recognition deficits. A structural MRI study reported that acute stroke patients with lesions in the right amygdala or right anterior insula showed a significantly worse recognition accuracy of happy and angry faces than patients with other lesion locations (Tippett et al., 2018). Nevertheless, whether lesions of specific regions are related to a recognition deficit of specific emotional valence contributing to a general emotion recognition network is poorly examined.

To our knowledge, only one lesion-symptom mapping study has thus far investigated the relationship between specific emotion processing deficits and lesion sites in stroke patients. A recent study by van den Berg et al. (2021) investigated facial emotion recognition and found significant lesion-symptom associations in right-hemispheric regions, including the insula, putamen, and rolandic operculum, as well as the middle and superior frontal gyrus (anger), caudate nucleus (disgust), superior corona radiata white matter tract, superior longitudinal fasciculus and middle frontal gyrus (happiness), and inferior frontal gyrus (sadness). The authors concluded that emotion recognition is represented in the brain within a network, including nodes and interconnections of specific basic emotions (van den Berg et al., 2021).

Given the scarcity in the research field, this study aimed to investigate the association between emotion processing abilities of real-life evolving dynamic facial expressions and depressive symptoms in stroke patients in a longitudinal study design. In addition to previous literature, a novelty aspect is that we assessed patients in the early stage post-stroke and observed how emotion processing and depression develop over time. We used an emotion processing task, where videos of face stimuli of different emotional intensities were presented to the participants. Healthy participants were included as a control group. Furthermore, we performed multivariate support-vector regression lesion-symptom mapping (SVR-LSM) analyses to explore which specific lesioned brain sites are associated with specific emotion recognition deficits (van den Berg et al., 2021). In a follow-up assessment (3–6 months), when PSD symptoms are thought to peak (Hackett & Pickles, 2014), patients replicated the experimental task, and depressive symptoms were examined again to evaluate how emotion processing abilities and lesion-symptom associations developed over time.

We hypothesized that stroke patients show worse emotion recognition accuracy in the task than controls. We further assumed that increased PSD symptoms will lead to an increased emotion processing towards negative emotions (specifically sad and angry faces) in the sense of increased recognition accuracy and a faster response time in the task and impaired processing of positive stimuli (i.e., happy faces). Moreover, at the neural level, we hypothesized to detect brain lesions in regions related to the recognition deficits of distinct emotion categories.

2. Materials and methods

2.1. Participants

Right-handed first-ever stroke patients were recruited from the Department of Neurology, University Hospital of Cologne, Germany. Examination took place on average ten days post-stroke (*range* 3–20 days). Inclusion criteria were: (i) legal capacity, (ii) no severe comorbid neurological or psychiatric disorders including preexisting depression, (iii) sufficient sight, (iv) no severe cognitive impairment, neglect, or aphasia according to neurological examination. Healthy participants matched in age and sex were recruited as a control group. Seven stroke patients needed to be excluded due to inability to finish the task or incorrect performance. Three healthy controls were excluded due to mild depressive symptoms upon formal testing. The final sample included 54 participants ($n = 26$ S patients, $n = 28$ healthy controls). Twelve stroke patients had lesions in the left hemisphere (LH), and 14 lesions were on the right hemisphere (RH). All stroke patients were right-handed, and one control participant was left-handed (see Table 1 for demographics and sample characteristics).

Assessments took place at the Department of Neurology, Cologne. Stroke patients were examined at the bedside during hospitalization. All participants gave informed written consent following the local ethics committee and the Declaration of Helsinki (revised in 2008). Controls

Table 1
Overview of the demographic and clinical characteristics of the sample.

	Stroke patients n = 26	Controls n = 28	
Demographics			
Sex (f:m)	14:12	11:17	$\chi^2{}_1 = 1.150$, $p = 0.284$
Age (mean, years) (±SD)	67.3 (12.05)	69.5 (8.5)	$F_{1,52} = 0.693 p = 0.409$
Examination post-stroke (mean, days) (range)	10.3 (3–20)		
Lesion Side (left:right)	12:14		
Handedness (left:right)	0:26	1:27	$\chi^2{}_1 = 0.946$, $p = 0.331$
Neurological impairment			
NIHSS early (mean) (±SD)	5.31 (4.25)		
NIHSS follow-up (mean) (±SD)	2.64 (2.17)		
Depressive symptoms			
MADRS global score early (mean) (±SD)	9.42 (8.01)	0.96 (1.37)	$F = 30.302$, $p < 0.001$, $\eta_p^2 = 0.368$
MADRS global score follow-up (mean) (±SD)	8.69 (7.18)		

NIHSS: National Institutes of Health Stroke Scale, MADRS: Montgomery-Åsberg Depression Rating Scale, χ^2: chi-square, η_p^2: Eta-Square effect size. One patient received anti-depressive medication (Citalopram 20 mg/day) due to acute depressive symptoms. MADRS scores in the early stage post-stroke were: no depression ($n = 13$), mild depression ($n = 10$), moderate depression ($n = 3$), and severe depression ($n = 0$). MADRS scores in the follow-up >3 months later were: no depression ($n = 13$), mild depression ($n = 12$), moderate depression ($n = 1$), and severe depression ($n = 0$) (Herrmann et al., 1998). Please note that for the NIHSS $_{\text{follow-up}}$, data from n = 22 patients could be assessed.

received an expense allowance of 15€ and travel expenses (e.g., taxi). Likewise, patients were paid for their travel expenses for the follow-up measurements.

2.2. Design of dynamic face stimuli

For the emotion processing task, dynamic face stimuli of different intensities were designed using the static pictures from the FACES database, Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany (Ebner et al., 2010). Dynamic face stimuli were chosen for this study design over static images because we aimed to depict a realistic emotional expression. Facial interactions in everyday life are typically dynamic and changing, which is why recent research has shown the importance of dynamic information in facial emotion processing (Holland et al., 2019). A study by Kamachi et al. (2013) even revealed that dynamic facial features can enhance both, emotion classification accuracy and perceptions of emotional intensity. We selected four model stimuli (2 females) showing the facial expression of happiness, sadness, anger, fear, and a neutral expression. We chose middle-aged models as older raters recognized these most accurately (Holland et al., 2019), and this rater group was most similar in age to our patient sample. Then we morphed the stimuli out of the static images to create a video presenting an evolving facial emotion expression using the software MorphAge (v5.0.3) for MacOS, similar to the creation of the Dynamic FACES, an extension of the original FACES database (Holland et al., 2019). The neutral facial expression and the final expression (e.g., happiness at 100 % intensity) were used to create the morph. In this way, we created facial expressions of different intensities by terminating the transition at 20 %, 40 %, 60 %, 80 %, and 100 %. Each video lasted 3 s (sec). Emotion expressions started with the neutral image and evolved linearly, reaching the final expression within 1 sec (Holland et al., 2019) – shown for 2 sec. Neutral faces did not have intensity levels, so we morphed the transition from the same neutral in two data sets provided by the database to create the dynamic video. A total of 100 videos were created in 2048×2560-pixel resolution with a frame rate of 30 fps.

2.3. Experimental design

The experiment was designed using PsychoPy3 v.2020.2.0 based on Python (Peirce et al., 2019) and implemented on a 17′ Lenovo touch-screen Windows laptop. The picture resolution was 1920×1080 pixels with 11.5×14 cm on the screen. In the task, participants gave their answers by tapping on the touchscreen.

The experimental design of the emotion processing task was presented in Fig. 1. Participants were seated in front of the screen at 1 m distance. Each trial started with a countdown of three seconds (digits on screen), followed by the dynamic facial expression stimuli. Before the task, participants received written and oral instruction and completed a training run of five trials. Participants could choose the appropriate emotion on the touchscreen after the stimuli appeared. Answer buttons were shown in fixed order beneath the stimulus: happy, sad, angry, fearful, neutral. The stimulus of facial expression disappeared after 3 s, and participants had an additional 6 s to choose the appropriate emotion category, resulting in a maximum of 9 s for answering per trial. Importantly, as participants were asked to correctly identify the emotion category (even if relatively uncertain), they were further instructed to respond as fast as possible. For task execution, participants used the dominant/non-affected hand. A break of individual length was set after every ten trials.

The task consisted of a 5x5 factorial design with the factors EMOTION (happy, sad, angry, fearful, neutral) and INTENSITY (20 %, 40 %, 60 %, 80 %, 100 %). Note that four stimuli models from the FACES database were chosen to express the facial emotions at different intensity levels. This design resulted in 100 identically structured trials. Further, neutral emotional expressions did not contain any intensity levels. Thus, five equal neutral video stimuli were presented per stimuli model for an equal number of all emotion categories. Trials were presented in a pseudo-random order, with consecutive trials never showing the same model and the same emotion category to prevent habituation.

2.4. Behavioral assessments

To quantify depressive symptoms, we used the Montgomery-Åsberg Depression Rating Scale (MADRS) interview, which includes ten items of depression rated by an experimenter (Herrmann et al., 1998; Montgomery & Asberg, 1979). According to published guidelines, each item must be answered based on several questions. Items include for example sadness, motivational and cognitive deficits, somatic symptoms, and anxiety, each scored on a scale from zero to six, evaluated by several detailed interview questions (Williams & Kobak, 2008). It measures the severity of depressive symptoms based on the patient's condition with higher scores indicating more severe depression (ranging from 0 to 60). To quantify neurological impairment after a stroke, we used the National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989). The scale provides an observer-rated global score based on 11 items, including e.g., the level of consciousness, arm and leg motor impairment, facial paresis, visual field test, ataxia, and aphasia. Symptoms are evaluated on an ordinal scale ranging from 0 (normal) to 2, 3, or 4, depending on the item (maximally impaired).

2.5. Follow-up assessment

For follow-up assessment, patients were re-invited >3 months post-stroke (M = 155.04 days, SD = 34.11). This time was referred to as the early chronic stage when PSD symptoms are thought to peak (Hackett & Pickles, 2014). Follow-up assessment included the same experimental assessments as during hospitalization. Data from n = 26

Fig. 1. Experimental design of the emotion processing task. Trials started with a countdown (3 s) leading to the stimuli presentation phase in which the video displayed the evolvement of the facial expression (3 s). When starting with the presentation phase, participants were allowed to select the corresponding emotion category (happy, sad, angry, fearful, neutral) up to 6 s after the presentation (3 s). Participants were instructed to respond as fast as possible. The stimuli in the figure illustrate an evolvement of an ANGRY facial expression with a final intensity of 80 %.

patients (100 %) could be obtained upon follow-up, yet four patients disapproved or could not attend in person, so depression scores (MADRS) were assessed via telephone interview.

2.6. Data pre-processing

Data from the emotion processing task were processed using SPSS 28 (IBM Corp, Armonk, NY, USA). First, we created variables, including information about emotion category (EMOTION) and intensity level (INTENSITY). Neutral stimuli did not include any intensity levels. Variables were created for the dependent variables: (i) recognition accuracy (in %) and (ii) response time. The response time variables were formed relative to the average response time over all trials for each participant. Thus, the reported response times are normalized to the participant's individual speed, which might be impaired due to the stroke, e.g., through hemiparesis. This procedure allows a more accurate comparison of response time effects independent of stroke impairment.

In another task, we provided a scale for each video to measure the participant's explicit emotional intensity rating. All included stroke patients ($n = 26$) and healthy controls ($n = 28$) additionally completed the intensity rating task. Moreover, we computed confusion matrices to illustrate which emotion categories were mistaken for which other emotion categories (type of mistakes) during emotion recognition in the task. See the Supplementary for this additional information.

2.7. Statistical analysis

For the emotion processing task, recognition accuracy and response time were analyzed using mixed-design ANOVA with the within-subject factors EMOTION (happy, sad, angry, fearful) and INTENSITY (20 %, 40 %, 60 %, 80 %, 100 %) and the between-subject factor GROUP including stroke patients and controls. Significant interactions were further investigated using Bonferroni-corrected post-hoc simple effect analyses. As neutral facial expressions did not involve any intensity levels, a separate *t*-test was calculated to compare effects between groups in the dependent variables (i.e., recognition accuracy and response time). Significant effect sizes were determined by partial eta-squared (η_p^2) and Cohen's *d* as provided by SPSS. To assess potential sex differences in emotion processing (Alaerts et al., 2011; Hoffmann et al., 2010; Lambrecht et al., 2014), we computed mixed-design ANOVAs per experimental group (i.e., stroke group and control group), with Bonferroni-corrected simple effect analyses for significant interactions, with the between-subject factor SEX including females and males and the within-subjects factors EMOTION and INTENSITY (see Supplementary material).

Further correlational analyses were computed to investigate associations between task performance parameters and depression in the stroke subgroup. We observed that emotional expressions within the subgroup with intensities of 60 % – 100 % were recognized as equally accurate. Therefore, to increase statistical power for the correlational analyses, we combined the scores for recognition accuracy of 20 % and 40 % to 'low-intensity level' and the scores of 60 %, 80 %, and 100 % to 'high-intensity level' for each emotional category. For example, the variable for the recognition accuracy of happy faces of low intensities included the average of both accuracies of 20 % and 40 % in recognizing happy faces. Spearman correlations (R_{Sp}) were computed for the ordinal scaled dependent variable' recognition accuracy' (low intensity and high intensity), and Pearson correlations (R_P) were calculated for the interval scaled dependent variable' response time.' Correlations were considered significant at $p < 0.05$ (two-sided), except for associations between depression (MADRS) and parameters including negative emotions (sad, angry, fearful) according to the hypothesis of increased processing of negative emotions, where more depressed patients show a better performance in mood-congruent emotional stimuli (one-sided $p < 0.05$) (Bourke et al., 2010; Gilboa-Schechtman et al., 2004; Gotlib et al., 2004a; Gotlib et al., 2004b; Lee et al., 2008b; Leyman et al., 2007; Takizawa et al., 2020; Van Vleet et al., 2019). False discovery rate (FDR) correction for multiple testing was applied for each set of a dependent variable correlation analysis (Benjamini & Hochberg, 1995). To investigate depression-related effects in stroke patients from a group-analysis approach, we further computed one-way ANOVAs using similar emotion processing parameters as described above for dependent variables and PSD vs non-PSD as a grouping variable. We grouped patients by using the MADRS cut-off value for non-PSD (no depression 0–6) and PSD (minimum of mild depression ≥7) (Herrmann et al., 1998). The results are reported in the Supplementary material.

To compare emotion processing parameters in the early stage and at follow-up (>3 months post-stroke), we performed paired-sample t-tests of both time points' overall recognition accuracy and absolute response time. To further evaluate the potential effects of specific emotion categories and intensity levels over time, we executed a mixed-design ANOVA per parameter similar to the above-described mixed-design ANOVA with the extra within-subjects factor TIME (early stage, >3 months later). Additionally, we aimed to substantiate the effects of early depressive symptoms on task performance parameters in the follow-up assessment. Therefore, we performed correlational analyses for significant behavioral parameters and depressive symptoms between the early stage and >3 months later ($p < 0.05$, one-sided). FDR correction was applied to all correlation analyses in the follow-up computations.

Lastly, the effect of lesion side on task performance parameters (i.e., overall recognition accuracy, overall absolute response time), depressive symptoms (MADRS), and stroke severity (NIHSS) were examined using separate independent t-tests. Correlational analyses (R_P) were used to calculate the associations between lesion volume (m^3) and stroke severity and performance parameters.

2.7.1. Lesion mapping and pre-processing

For all patients, anatomical MRI scans obtained during the clinical routine were available to map the stroke lesion based on diffusion-weighted imaging (DWI; TR = 4076 ms, TE = 95 ms, 22–24 axial slices, voxel size = $1.8\times3.0\times6$ mm^3) and fluid-attenuated inversion recovery images (FLAIR; TR = 6000 ms, TE = 100 ms, 36–40 axial slices, voxel size = $1.4\times1.1\times4$ mm^3). Lesion maps were manually drawn onto DWI volumes, showing the anatomical extent of the (sub)acute ischemic lesion. Lesion drawings underwent quality control by a second reviewer. DWI, FLAIR, and binary lesion masks were then spatially normalized to a standard template (1x1x1 mm) in the space of the Montreal Neurological Institute (MNI) by using the unified segmentation approach with masked lesions in SPM12 (https://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB R2020a (The MathWorks Inc, Natick, MA, USA) and FMRIB Software Library (FSL). Unlike many other lesion-symptom mapping studies in stroke research, lesions were not systematically flipped to a particular hemisphere, i.e., information on inter-hemispheric differences in lesion location was preserved.

2.7.2. Support-vector regression lesion-symptom mapping (SVR-LSM)

In six different multivariate SVR-LSM analyses, we investigated lesion-recognition deficit associations between each specific emotion category's recognition accuracy and overall recognition accuracy at the early-stage post-stroke. For this, a MATLAB-based toolbox was used (DeMarco & Turkeltaub, 2018) based on an SVR-LSM implementation introduced by Zhang et al. (2014). Support vector regression (SVR) is a particular case of support vector machines, which are employed to solve binary classification problems, e.g., whether a disease is either present or absent (Rehme et al., 2015a; Rehme et al., 2015b). Complementary, SVR allows the prediction of continuous variables (and their variability) based on the lesion status of multiple voxels.

Controlling for lesion volume is crucial in lesion-symptom mapping because patients with larger lesions tend to show more significant deficits (DeMarco & Turkeltaub, 2018; Price et al., 2017). Thus, after correcting both the behavioral scores and the lesioned voxels for lesion volume, the interpretation of SVR-LSM results allows answering questions about whether the behavior of interest is more strongly related to lesions in a particular brain area relative to all other brain regions rather than a mere correlative interpretation of whether lesions are associated with the behavior of interest (DeMarco & Turkeltaub, 2018). Therefore, lesion volume was regressed from both the lesion maps and the behavioral variables for all SVR-LSM analyses. A minimum lesion threshold of three lesions per voxel was used, as 10 % of the sample size is suggested as the minimum threshold to ensure sufficient lesion overlap (Sperber & Karnath, 2017). Notably, the analysis design is one-tailed. Thus, the analyses were set to be negatively tailed based on the assumption that lesion presence was associated with a greater deficit, i.e., worse emotion recognition accuracy.

For model estimation, five-fold cross-validation was used. Statistical significance was determined by a non-parametric approach using 10,000 permutations. A voxel was considered significant when passing a threshold of $p < 0.005$. Final permutation-based voxel-wise thresholded p-maps were smoothed using a 2 mm isotropic Gaussian smoothing kernel in SPM12 to reduce cluster independence of neighboring lesion voxels. Significant anatomical structures were classified using the Harvard-Oxford Cortical and Subcortical structural atlases as implemented in FSL and the SPM Anatomy Toolbox. In addition to the SVR-LSM analyses investigating lesion-symptom associations in the early stage post-stroke, we performed SVR-LSM analyses with behavioral data at the follow-up assessment. We aimed to investigate whether acute brain lesions are associated with emotion recognition deficits not only early after stroke but also after >3 months, and thus, may precede chronic emotional processing impairments. The details, analyses, and results are described in the Supplement material.

3. Results

Demographic and clinical characteristics of the sample are summarized in Table 1.

3.1. Emotion processing task

3.1.1. Recognition accuracy

When analyzing the accuracy of emotion recognition, the mixed-model ANOVA yielded a main effect of INTENSITY ($F_{1,52} = 330.768$, $p < 0.001$, $\eta_p^2 = 0.864$). Both groups (stroke patients and controls) recognized stimuli better with increasing emotion intensity. Furthermore, a significant main effect of EMOTION ($F_{1,52} = 37.674$, $p < 0.001$, $\eta_p^2 = 0.420$) showed that happy expressions were most accurately recognized ($M = 84.63$ %, $SD = 11.15$), followed by angry ($M = 82.5$ %, $SD = 13.38$), fearful ($M = 68.15$ %, $SD = 22.35$), and sad expressions ($M = 59.17$ %, $SD = 21.65$). Post-hoc simple effect analyses revealed that the recognition of happy and angry expressions differentiated significantly from fearful and sad expressions ($F_{3,50} = 40.528$, $p < 0.001$), but not between happy and angry expressions ($p = 1.000$) or between fearful and sad expressions ($p = 0.091$).

Moreover, we observed a main effect of GROUP ($F_{1,52} = 12.110$, $p = 0.001$, $\eta_p^2 = 0.189$), with stroke patients recognizing emotions significantly less accurately than controls. Likewise, a significant interaction effect between GROUP and EMOTION ($F_{1,52} = 3.309$, $p = 0.030$, $\eta_p^2 = 0.060$) indicates a worse recognition accuracy of stroke patients than controls in sad ($F_{1,52} = 7.744$, $p = 0.007$, $\eta_p^2 = 0.130$), fearful ($F_{1,52} = 10.197$, $p = 0.002$, $\eta_p^2 = 0.164$), and happy emotional expressions ($F_{1,52} = 4.075$, $p = 0.049$, $\eta_p^2 = 0.073$) (Fig. 2A) as revealed by the simple effect analyses. Besides, there was a trend for statistical significance in the correct recognition of neutral faces between groups ($t_{52} = 1.871$, $p = 0.067$, $d = 0.510$). We identified a significant three-way interaction, where stroke patients recognized specific emotions of different intensity levels significantly worse than controls. These results are reported in the supplementary material. There was neither a significant interaction between GROUP and INTENSITY ($p = 0.622$) nor between EMOTION and INTENSITY ($p = 0.130$). An overview of the effects of the mixed-model ANOVA on the recognition accuracy, response times, and subjective intensity rating are provided in Supplementary Table 1.

3.1.2. Response time

In Fig. 2B the results of the relative response times of stroke patients and controls per emotion category are displayed. When analyzing the differences in relative response time between groups, we found a significant main effect of EMOTION ($F_{1,52} = 32.020$, $p < 0.001$, $\eta_p^2 = 0.381$) showing that happy faces were recognized the fastest ($M = 3.73$ s, $SD = 0.34$), followed by angry ($M = 3.79$ s, $SD = 0.33$), sad ($M = 4.12$ s, $SD = 0.29$), and fearful facial expressions ($M = 4.36$ s, $SD = 0.40$). Post-hoc simple effect analyses revealed significant differences in response time between all pairs of emotion categories ($F_{50,3} = 24.003$, $p = 0.001$–0.006), except for the response times between happy and angry faces (p = 1.000). Response times to neutral facial expressions were not significantly different between groups ($t_{52} = 1.466$, $p = 0.149$). The response time analyses indicated a significant main effect of INTENSITY ($F_{1,52} = 43.949$, $p < 0.001$, $\eta_p^2 = 0.458$) with higher intensity levels corresponding to reduced response time. There was neither a significant main effect of GROUP ($p = 0.149$) nor a significant interaction between EMOTION and GROUP ($p = 0.594$) for relative response time.

3.2. Stroke group analysis

The number of days between the stroke and the first examination date did not correlate with depressive scores or performance in the task (i.e., recognition accuracy and response time). Stroke severity, as assessed by the NIHSS, did not affect depressive symptoms (MADRS) in the stroke sample ($p = 0.213$), and neither stroke severity nor depression influenced overall recognition accuracy (all $p > 0.267$).

Correlation analyses within the stroke group showed a negative association between the MADRS score and the response time to angry

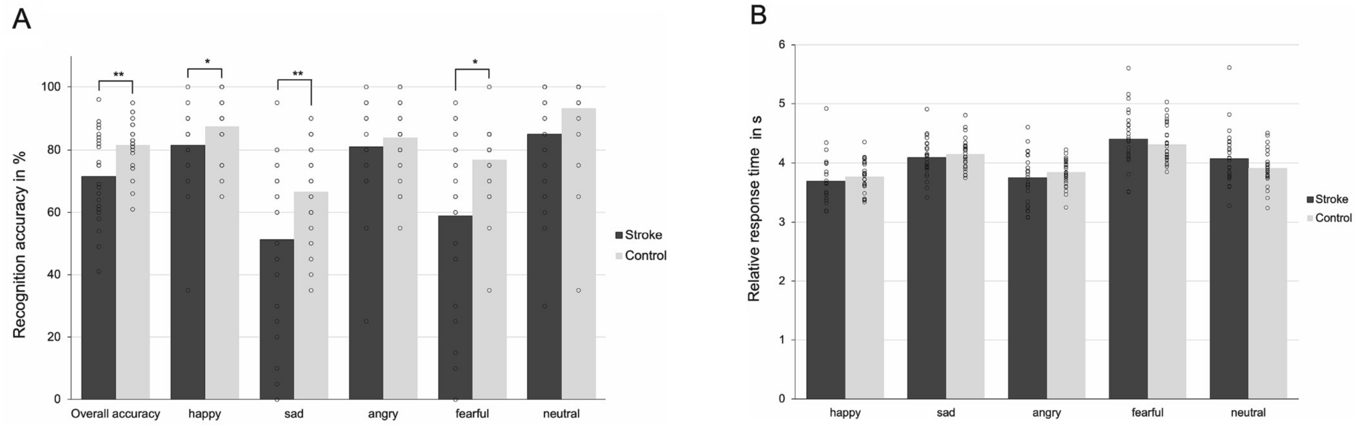

Fig. 2. A: Emotion recognition accuracy scores for stroke patients (black) and controls (grey). Overall accuracy and per emotion category. Stroke patients showed significantly worse overall performance, especially in recognizing happy, sad, and fearful facial expressions. Open circles indicate individual scores. ** $p < 0.01$, * $p < 0.05$. B: Relative response time scores for stroke patients (black) and controls (grey). Open circles indicate individual scores. Results showed no differences between groups, but relative response times varied significantly between specific emotion categories. For displaying purposes no significance bars are displayed. Significant differences between emotions are described in the text.

emotions (irrespective of intensity level) in the early stage post-stroke (R_P = -0.620, $p = 0.005$, FDR-corrected). This finding indicates that more depressed patients responded significantly faster to angry faces (Fig. 3A). We also observed a positive correlation between the MADRS score and the recognition accuracy of low intense, sad facial expressions ($R_{Sp} = 0.527$, $p = 0.027$, FDR-corrected), indicating a better recognition performance of more depressed stroke patients (Fig. 3B). No other correlations between emotion processing parameters of the other emotion categories (happiness, fearful, and neutral) and the MADRS score were observed. Also, there was no effect of lesion side (LH/RH) on depression, overall recognition accuracy, and overall absolute response time (all $p >$ 0.310).

Patients in the first days after stroke performed overall significantly worse in the emotion processing task (overall recognition accuracy and overall absolute response time) compared to >3 months later (overall recognition accuracy: $t_{21} = 2.887$, $p = 0.009$, $d = 0.615$, early stage: 71.14 % correct responses, follow-up assessment: 76.27 % correct responses; absolute response time: $t_{21} = 2.355$, $p = 0.028$, $d = 0.502$, early stage: 3.30 sec, follow-up assessment: 3.01 sec). In the mixed-models ANOVAs, evaluating the effects of specific emotion categories and intensity levels over time, no interaction between EMOTION or INTENSITY and TIME could be observed for recognition accuracy and response times (all $p > 0.229$). Thus, the task performance did not improve relative to a specific emotion or intensity level. Impairments due to stroke (NIHSS) significantly reduced over time ($t_{21} = 4.692$, $p < 0.001$). The MADRS score did not change significantly in the follow-up assessment compared to the early stage post-stroke ($p = 0.587$).

We performed additional correlational analyses to investigate characteristics of task performance parameters in the follow-up assessment based on previous behavioral results. Of note, MADRS scores at early stage showed a strong positive correlation with MADRS scores at follow-up ($R_P = 0.607$, $p < 0.001$). We found faster response times to angry facial expressions >3 months later to be negatively associated with MADRS scores in the follow-up assessment (R_P = -0.435, $p = 0.042$, FDR-corrected, Fig. 3C). We observed a non-significant correlational trend between the MADRS score at follow-up and the recognition accuracy of low intense sad faces at follow-up ($R_{Sp} = 0.325$, $p = 0.084$, FDR-corrected, Fig. 3D). Overall, these findings indicate that behavioral results observed in the early stage after stroke persist to some degree into the chronic stage at follow-up. However, associations are overall weaker (response time to angry faces) and non-significant (recognition accuracy of low intense sad faces) at follow-up.

3.3. SVR-LSM

The average lesion volume was 33.12 cm^3 (SD = 62.40 cm^3, $range$ = 0.46 cm^3 − 291.43 cm^3). There was no effect of lesion side (left, right) on task performance parameters (i.e., overall recognition accuracy, overall absolute response time; $p = 0.349$, $p = 0.609$, respectively), depression symptoms (MADRS; $p = 0.310$), or stroke severity (NIHSS; $p = 0.453$) and no associations between lesion volume (in cm^3) and NIHSS ($p = 0.647$) or task performance parameters ($p > 0.220$).

To investigate lesion-symptom associations of emotion recognition abilities at the early-stage post-stroke, we performed several multivariate SVR-LSM analyses. In Fig. 4, we depict the overlap map of the lesion coverage included in the analyses. It displays all lesion regions, which had a lesion threshold of a minimum of three lesions per voxel (red to yellow) and those, which indicated less than three lesions per voxel (blue). The analyses revealed that deficits in *overall* recognition accuracy were associated with damage in the rolandic operculum, insula (anterior and posterior), OFC, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), putamen, frontal operculum, and pre- and post-central gyri (Fig. 5). Also, deficits in correctly identifying *happy* facial expressions were associated with damage in the frontal pole, anterior insula, OFC, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), putamen, frontal operculum, and pre- and post-central gyrus (Fig. 6). Furthermore, reduced recognition accuracy for *fearful* expression was related to lesions in the posterior insula, frontal pole, rolandic operculum, and MFG. Recognition deficits of *sad* faces were associated with damage in the frontal pole, IFG, and MFG. No significant lesion voxels were related to reduced recognition of *angry and neutral* faces. Brain regions of lesion-symptom associations are provided in Table 2. In the SVR-LSM analyses at follow-up assessment, similar emotion categories to those in the early stage exhibit significant lesion-symptom associations (i.e., overall recognition accuracy, happy, fearful, sad). These results and detailed information are reported in the Supplementary material).

4. Discussion

In this study, we compared the emotion processing of dynamic face stimuli in stroke patients and healthy controls. We revealed specific lesion-symptom associations for the overall emotion recognition accuracy and distinct emotion categories. We found that more severe symptoms of PSD correlated with an increased emotion processing of more negative emotions, including sadness and anger. Thus, we observed that depressive symptoms after stroke facilitated the processing of socially negatively valenced face stimuli. Our findings are in line

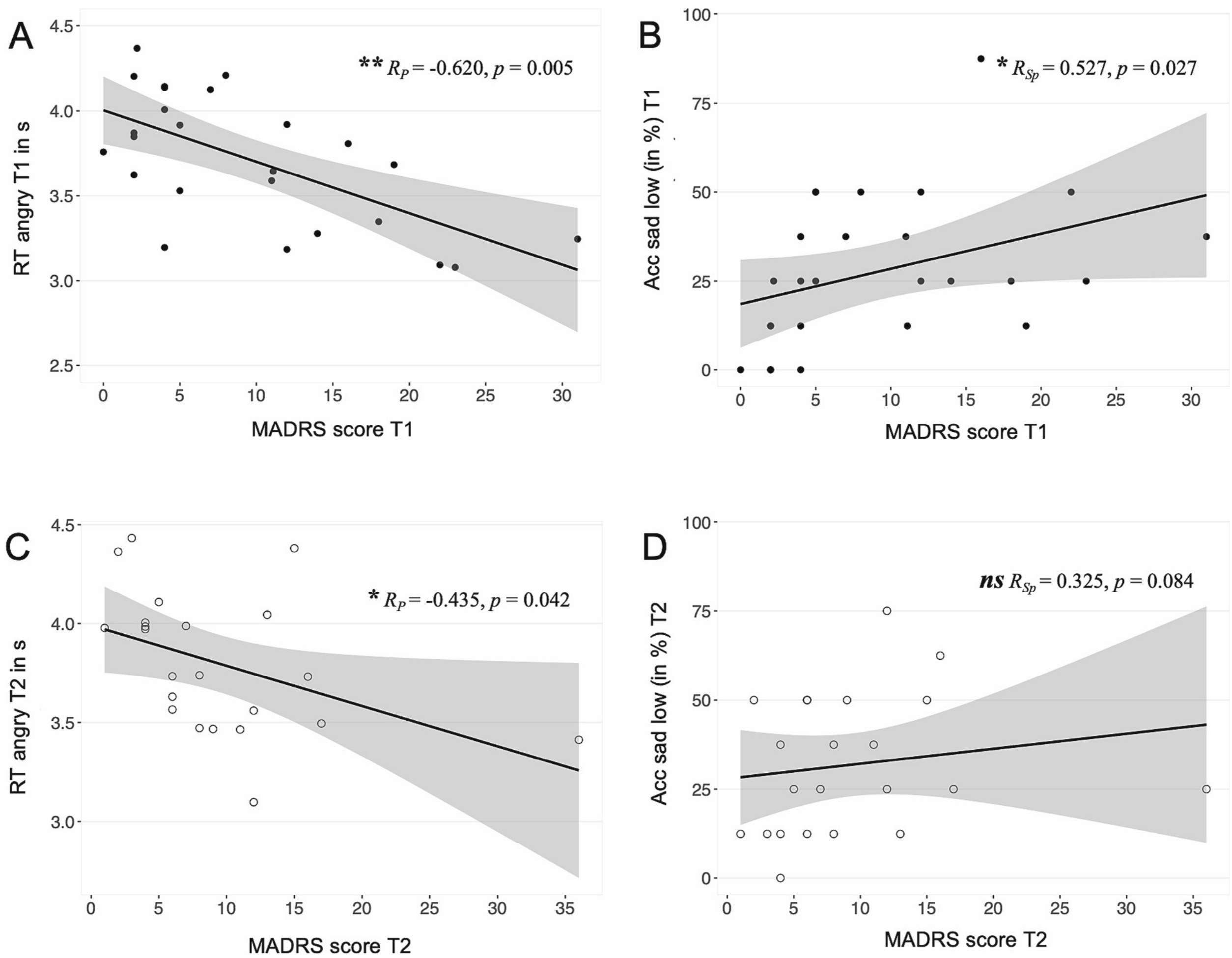

Fig. 3. Relationships between performance in the emotion processing task and depressive symptoms (MADRS score) of stroke patients in the early stage post-stroke and at follow-up. A: Negative correlation between the response time to angry facial expressions and the MADRS score in the early stage after stroke (R_P = -0.620, p = 0.005), with more depressed patients responding faster. B: Positive correlation between the recognition accuracy of sad facial expressions in low-intensity levels (in %) and the MADRS score in the early stage after stroke (R_{Sp} = 0.527, p = 0.027). C: Negative correlation between the response time to angry facial expressions at follow-up assessment and the MADRS score at follow-up assessment (R_P = -0.435, p = 0.042). D: Non-significant correlational trend between the recognition accuracy of sad facial expressions in low-intensity levels (in %) at follow-up assessment and the MADRS score at follow-up assessment (R_{Sp} = 0.325, p = 0.084). Filled dots in the plots indicate the behavioral parameter of the emotion processing task early after stroke (T1), and empty dots show the behavioral parameter at follow-up (T2). Corresponding correlation coefficients and p values are displayed in the plots (** $p < 0.01$, * $p < 0.05$, ns = not significant). All p-values are corrected for multiple testing (FDR). RT = response time, s = seconds, Acc = recognition accuracy.

with the model of negative emotion processing in major depression disorder (Bourke et al., 2010; Leppänen, 2006; Peckham et al., 2010). Notably, emotion processing deficits in our cohort of stroke patients were associated with lesions to an emotion processing network, including inferior and middle frontal regions, insula, and parts of basal ganglia. Our findings suggest that behavioral, psychological, and neural aspects after stroke constitute potential risk factors for developing and maintaining PSD.

4.1. Emotion recognition

We found that stroke patients showed worse overall recognition accuracy compared to controls. This finding supports previous literature on emotion recognition of facial emotion expressions in stroke patients (Abbott et al., 2014; Aben et al., 2020; Adams et al., 2019; Luo et al., 2022; Yuvaraj et al., 2013). After stroke, cognitive functions such as executive dysfunction, attention, processing speed, and visuospatial processing are frequently disrupted (Hachinski et al., 2006; Nys et al., 2007). Emotional or social recognition impairment often accompanies cognitive dysfunctions (Aben et al., 2020). Although it is well established that impaired emotion recognition and processing are critical predictors of rehabilitation outcome and quality of life after stroke (Blonder et al., 2012; Cooper et al., 2013; Dombovy et al., 1986; Langer et al., 1998; Yeates et al., 2016), as well as markers of depression (Bourke et al., 2010), such deficits are often not detected in the clinical routine (Henry et al., 2015). This lack of detection might be due to an unawareness of this phenomenon or missing or insensitive tools to identify patients' deficits when they are relatively subtle (Aben et al., 2020; Henry et al., 2015; Spikman et al., 2013). Therefore, examining patients regarding potential impairments in emotional recognition and social dysfunction seems to be important in clinical practice. Acknowledging neural correlates of emotional recognition deficits can facilitate considering early interventions such as medication, social skills training, psychotherapy, and psychoeducation.

4.2. Negative emotion processing in PSD

Our findings demonstrated an increased emotional processing of angry and sad faces in more depressed stroke patients. Specifically, angry faces were recognized faster, and sad faces of low intensity were recognized more accurately. This result aligns with findings that MD patients showed more robust emotional responses to an expression of

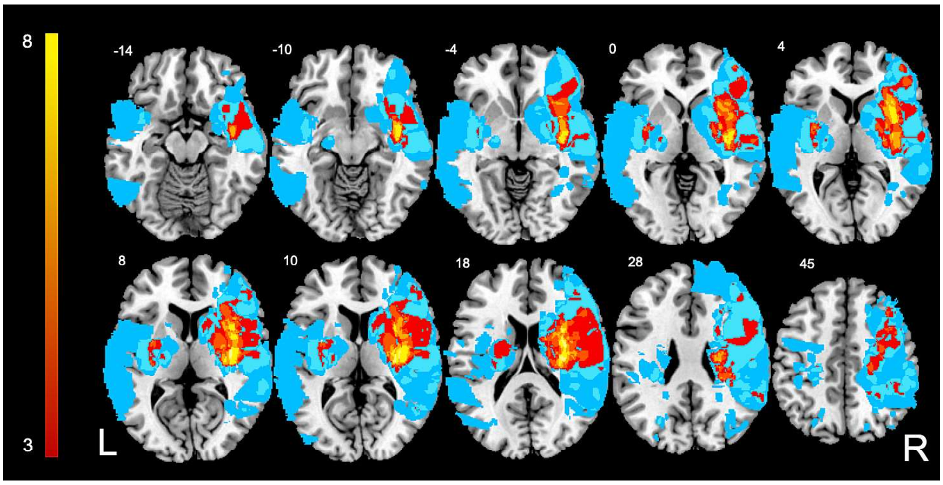

Fig. 4. Overlap map of the lesions included in the SVR-LSM analyses ($n = 26$) on axial slices. Colors indicate the number of overlapping lesions (red to yellow). Analyses included voxels only when a minimum of three patients had a lesion in this voxel. Blue voxels were not included in the SVR-LSM. Coordinates indicate the corresponding z-value in Montreal Neurological Institute (MNI) space. L, left; R, right.

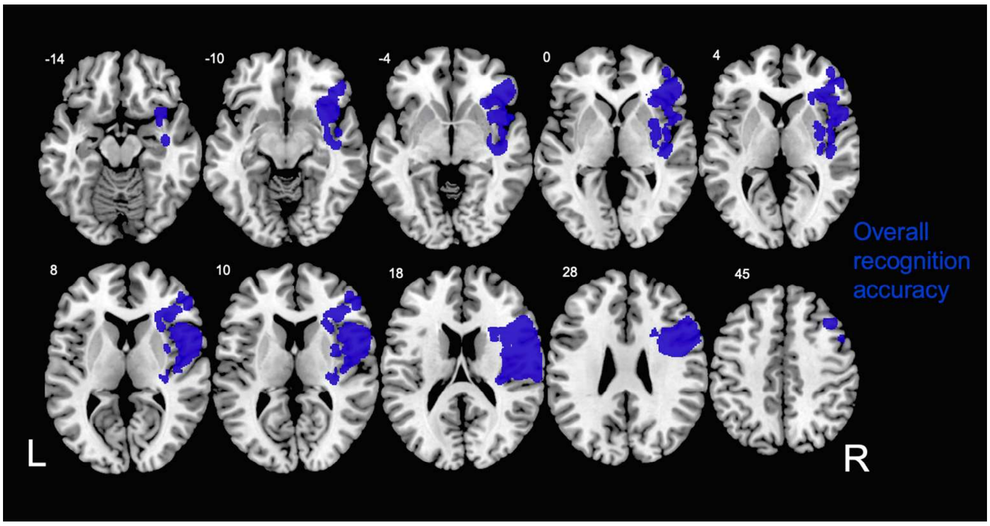

Fig. 5. Results of the SVR-LSM analyses depicting lesion-symptom associations of the overall emotion recognition accuracy in the emotion processing task (blue). Colored brain regions in the figures indicate voxels with a significant lesion-symptom association, which survived permutation testing with 10.000 permutations. Results were thresholded with a voxel-wise threshold set to $p < 0.005$ and smoothed using a 2 mm isotropic Gaussian smoothing filter. Coordinates indicate the corresponding z-value in Montreal Neurological Institute (MNI) space. L, left; R, right.

rejection (i.e., angry cues) (Leyman et al., 2007; Gilboa-Schechtmann et al., 2004). Furthermore, the response was facilitated for sadness in more depressed stroke patients, which is well in line with previous literature showing that MD patients are more prone to mood-congruent cues, representing the patients emotional state (Bomfim et al., 2019; Surguladze et al., 2004; Van Vleet et al., 2019). Our findings suggest that negative emotion processing may be a characteristic feature of PSD similar to MD. These associations between negative emotion processing and depressive symptoms persisted to a lesser extent in the chronic stage post-stroke, particularly in the faster response time towards angry expressions. Of note, in our sample we identified associations of depression and emotion processing parameters for angry and sad faces only. For instance, happy emotions were processed and recognized independent of depression level after stroke. This is contrary to some findings in the literature of MD, which showed differences in the discrimination accuracy and the intensity threshold in recognizing happy emotions compared to controls (Joormann & Gotlib, 2006; Surguladze et al., 2004). Furthermore, in our experimental design, it is important to acknowledge the possibility that for instance a stroke patient with depressive symptoms may accurately recognize a specific emotion but exhibit delayed response times on this emotion. These opposing influences could introduce conflicting effects of depression on the dependent variables, potentially distorting its effects.

Interestingly, depressive symptoms at follow-up assessment were not more pronounced than at early stage as indicated by previous analyses and reviews (Hackett & Pickles, 2014, Medeiros et al., 2020). We assume this may be attributed to the fact that our study included patients with relatively mild neurological impairments, also at follow-up assessment. Patients included in the experiment possessed specific remaining functionalities, such as cognitive and language abilities, as well as motor and physical functioning enabling them to endure the tasks and experimental assessments. We assume that patients with more severe neurological impairments, not especially represented in our sample, might exhibit more intense depressive symptomatology as suggested by studies and reviews like Singh et al. (2000), Towfighi et al. (2017), Robinson & Jorge, 2016), which would also affect depression after 3 months post-stroke. Increased functional impairments may relate to more severe PSD symptoms after hospital discharge due to challenges and

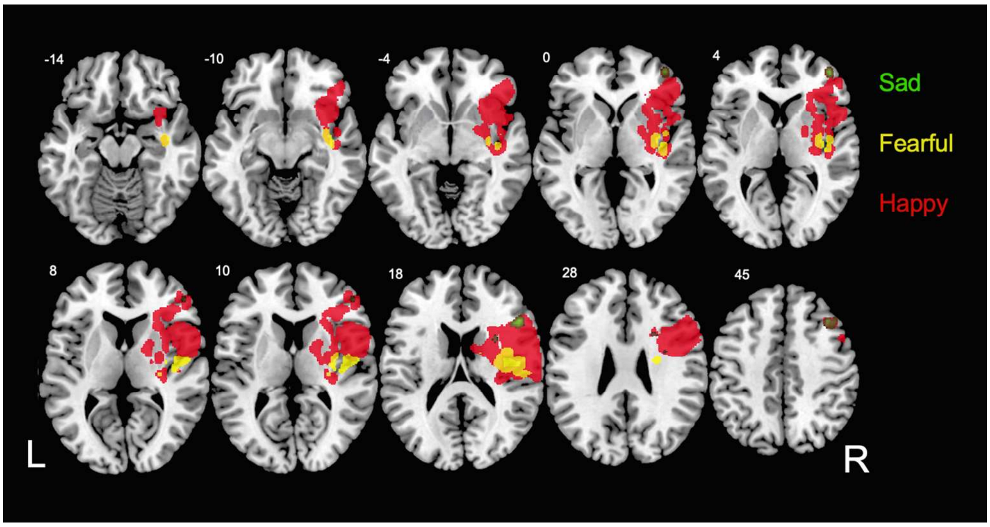

Fig. 6. Results of the SVR-LSM analyses depicting lesion-symptom associations of emotion recognition accuracy in happy (red), fearful (yellow), and sad (green) faces in the emotion processing task. Colored brain regions in the figures indicate voxels with a significant lesion-symptom association, which survived permutation testing with 10.000 permutations. Results were thresholded with a voxel-wise threshold set to $p < 0.005$ for each emotion and smoothed using a 2 mm isotropic Gaussian smoothing filter. Coordinates indicate the corresponding z-value in Montreal Neurological Institute (MNI) space. L, left; R, right.

Table 2
SVR-LSM results for the recognition accuracy deficits of happiness, fear, sadness, and overall accuracy in the emotion processing task. Brain regions are provided with corresponding standardized Z-values at peak lesion-symptom associations and MNI coordinates. Regions are labeled using the Harvard-Oxford Cortical Structure Atlas and the SPM Anatomy Toolbox. Voxels were thresholded at $p < 0.005$.

Lesion regions	z-value	MNI coordinates		
		x	y	z
Happiness				
Inferior frontal gyrus (IFG)	3.54	50	13	10
Middle frontal gyrus (MFG)	3.53	48	15	34
Precentral gyrus	3.52	55	8	26
Orbitofrontal cortex (OFC)	3.51	35	24	−6
Anterior insula	3.39	33	23	−3
Putamen	3.27	32	4	1
Frontal operculum	3.18	45	24	1
Frontal pole	2.75	44	49	2
Fear				
Rolandic Operculum	3.70	46	−12	17
Posterior insula	3.32	37	−16	16
Frontal pole	2.49	44	49	2
Middle frontal gyrus (MFG)	1.37	43	24	43
Sadness				
Inferior frontal gyrus (IFG)	2.44	48	23	19
Frontal pole	2.40	44	49	2
Middle frontal gyrus (MFG)	1.63	40	20	43
Overall				
Rolandic operculum	3.70	46	−12	17
Posterior insula	3.50	37	−17	16
Inferior frontal gyrus (IFG)	2.84	55	13	9
Middle frontal gyrus (MFG)	2.80	48	18	36
Orbitofrontal cortex (OFC)	2.76	37	27	−6
Frontal pole	2.59	44	49	2
Anterior insula	2.58	33	23	−1
Putamen	2.39	31	4	1
Frontal operculum	2.14	43	20	0

restrictions in daily life.

Montagne et al. (2007) demonstrated in a facial emotion recognition task with different emotion intensity levels that chronic stroke patients (>5.5 months post-stroke) with depressive symptoms showed lower accuracy than stroke patients without depressive symptoms in recognizing the emotions anger, disgust, happiness, and sadness. Furthermore, stroke patients with depressive symptoms required more intense emotions to recognize anger, sadness, and happiness correctly. In contrast, we found a lower emotion threshold to respond to sad emotions in more depressed patients accurately. Another study assessed individuals with subthreshold depression (i.e., significant depressive symptoms not fulfilling the diagnostic criteria for depression) and healthy controls using a recognition task with faces distorted by different levels of visual noise (Mei et al., 2020). The study found that individuals with depressive symptoms showed lower recognition thresholds for sad faces (i.e., more effective discrimination of images with higher visual noise intensity) than controls. Importantly, this finding was observed two months later, too, and individuals with lower recognition thresholds for sadness were less likely to show improvements in depressive symptoms at follow-up. As the sample in our study showed, on average, only mild depressive symptoms, too, the recognition of subtle sad emotions might be a tipping point in developing and maintaining depression.

Overall, these behavioral results add to the evidence that psychological processes are involved in the development and maintenance of PSD. Furthermore, the SVR-LSM approach unraveled some neural correlates that may contribute to worse emotion processing. Together, psychological and neural factors are involved in the pathophysiology of PSD.

4.3. *Lesion-symptom mapping of the recognition accuracy*

A worse recognition accuracy of happy, sad, and fearful faces after stroke was observed in the emotion recognition task (Fig. 2A). In the SVR-LSM analyses, these deficits in recognition accuracy early after stroke were associated with distinct lesioned brain areas (Fig. 6). Results indicated that emotion recognition depended predominantly on the right-hemispheric frontal and insular regions and the putamen. Moreover, distinct emotion categories were linked to specific brain regions and emotion-overlapping regions, including brain regions involved in overall recognition capabilities. Significant overlapping regions included the frontal pole, IFG, and MFG (related to overall emotion recognition, including happiness, sadness, and fear), the putamen (related to happiness and fear), and the insula (happiness, fear). The more anterior part of the insula and the OFC and frontal operculum were related to poorer happiness recognition, whereas the posterior insula and the Rolandic operculum were related to fear recognition. Our results showed that poorer overall recognition accuracy of emotions highly overlapped with lesion-symptom associations for specific emotions, so we likely revealed parts of an emotion processing network. This network consists of a distributed network with reciprocal interactions between cortical and subcortical regions, including occipito-temporal cortices for perceptual face representations, as well as amygdala, hippocampus, OFC, basal ganglia, insula, cingulum, striatum, and somatosensory cortex for representing the emotional value (Leppänen, 2006; Palomero-Gallagher & Amunts, 2022; Pessoa & Adolphs, 2010). Especially the insula is suggested to play a significant role in processing socio-emotional stimuli (Harrison et al., 2010; Kurth et al., 2010; Phillips et al., 1998). It interconnects with many other brain structures, such as frontal cortex areas and subcortical structures, including the amygdala (Damasio, 2003; Gasquoine, 2014). A structural MRI study by Tippett et al. (2018) observed that acute stroke patients with lesions in the right amygdala or right anterior insula performed significantly worse in happy and angry facial emotion recognition than patients with other lesion locations. As it has been suggested that emotional impressions are represented in the insula (Craig, 2009; Phan et al., 2002), our results support the view that lesions to insular regions are accompanied by distorted emotion recognition.

To our knowledge, this is the first study using a multivariate voxel-based lesion-symptom mapping approach to examine emotion recognition of dynamic emotional stimuli in early-stage stroke patients. A recent large-scale study investigating subacute and chronic ischemic stroke patients used a multivariate lesion-symptom method, too, and identified recognition accuracy deficits in anger, happiness, sadness, and disgust to be related to fronto-temporal regions, including the insula, Rolandic operculum, and putamen (van den Berg et al., 2021). Our sample showed a poorer recognition of sad faces related to frontal regions, including the frontal pole, IFG, and MFG. Van den Berg et al. (2021) also identified a poorer recognition of sadness as exclusively associated with the IFG. Likewise, an fMRI study observed cortical hyperactivity (medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC)) in patients with an anxiety disorder when confronted with sad faces compared to controls (Labuschagne et al., 2012). Also, damage to the right mPFC, ACC, and temporal areas, including IFG and MFG, was related to a worse ability to recognize negative emotions in traumatic brain injury patients (Dal Monte et al., 2013). Together with our findings, this suggests that specifically frontal cortical areas might play a key role in processing sadness. As we found PSD is related to altered processing of sadness, too, likely an interplay of frontal lesions, depressive symptoms, and negative emotional processing might affect each other and facilitate the development and persistence of PSD. Furthermore, a bias in processing and recognizing negative emotions in healthy and depressed populations is associated with rumination tendencies involving repetitive thinking about negative feelings and their consequences (Owens & Gibb, 2016; Raes et al., 2006; Suslow et al., 2019), while rumination in depression is further related to altered frontal activation and volume encompassing IFG, cingulum, PFC, and OFC (Burkhouse et al., 2017; Cooney et al., 2010; Kühn et al., 2012). Our results demonstrate that recognition deficits of sadness showed lesion-symptom associations in frontal regions only, suggesting that altered processing of sadness might influence rumination predispositions, potentially exacerbating depressive states.

In contrast to van den Berg et al. (2021), we found a worse fear recognition related to lesions in the posterior insula. Likewise, in a PET study, fear processing in healthy controls induced a decreased activation in the posterior insula (Damasio et al., 2000). While broad literature and early studies reported the amygdala to be crucial in the processing and recognition of fearful faces (Adolphs et al., 1995; McFadyen et al., 2019; Morris et al., 1996), we did not identify such a lesion-symptom association. This lack of an association might be because our lesion coverage in the sample was too little to assess the potential effects of an amygdala lesion on facial recognition abilities (van den Berg et al., 2021).

Our SVR-LSM results of emotion recognition deficits at follow-up assessment revealed similar emotion categories associated with lesioned brain regions (i.e., overall recognition accuracy, happy, fear, and sad) to those in the early stage post-stroke. Details are described in the Supplementary material. Generally, SVR-LSM results at both time-points showed lesion-symptom associations between recognition accuracy and damaged voxels in the RH only, regardless of emotion category. Although lateralization in emotion processing remains a topic of debate, a large meta-analysis found evidence for the right lateralization, especially for facial stimuli (Yuvaraj et al., 2013). However, our results must be interpreted cautiously, as lesion coverage was lower in the left hemisphere (Fig. 4). This lower lesion coverage might be because a left-hemispheric stroke is more likely to induce severe aphasia, which was an exclusion criterion for our study. Overall, our significant SVR-LSM findings extend the literature on neural correlates of emotional face recognition in stroke patients, especially on studies using multivariate lesion-symptom approaches.

According to our findings regarding emotional processing, it seems likely that a combination and interconnection of psychosocial (worse emotional responsiveness and negative emotion processing) and neural factors affect the pathophysiology of PSD. Moreover, besides emotional-cognitive capabilities and structural and functional impairments in specific brain regions, studies and meta-analyses identified the level of functional disability after stroke as an important correlate of PSD (Medeiros et al., 2020; Robinson & Jorge, 2016; Singh et al., 2000; Towfighi et al., 2017). Further research should aim at disentangling the effects of these parameters and how they affect emotional processing. Likewise, specific recruitment and categorization of PSD and non-PSD patients as well as unipolar depressed patients without stroke as a control group allow a more direct evaluation of correlates and consequences of PSD pathophysiology and emotion processing on behavioral and neural levels. Comparing depressive stroke patients with unipolar depressed patients seems promising to distinguish emotion processing deficits unique to stroke or depression. Ideally, this comparison should include stroke patients with minimal acute neurological or motor impairments, to enhance sample comparability. This would give important insights into therapeutic approaches regarding social interactions and emotional bonding for stroke patients, especially but not limited to the acute stage after stroke. Lastly, one limitation refers to the non-optimal sex balance between stroke and control groups, although group differences were not statistically significant. The imbalance arises due to the exclusion of several subjects as a consequence of incorrect task performance, mild cognitive impairments in the stroke group, as well as depressive symptoms in control participants. However, we found no effect of sex on our central emotional processing parameters. As sex potentially influences emotion processing (Alaerts et al., 2011; Hoffmann et al., 2010; Lambrecht et al., 2014), this issue should be considered with caution in the context of emotion tasks.

4.4. Conclusion

The findings extend previous literature on behavioral and neural aspects of PSD. Depression after stroke facilitates the processing of socially negatively valenced emotional stimuli. As negative emotion processing maintains depressive symptoms and deteriorates rehabilitation, interventions, and therapies after stroke, one should aim at stabilizing socio-emotional networks and coping strategies. Additionally, we identified an emotional-processing network including the insula as well as inferior and middle frontal regions and parts of basal ganglia related to deficits in the recognition of distinct emotions. Our findings yield essential insights into how lesions in specific brain regions early after a stroke can selectively affect the recognition abilities of particular emotions. These may, in turn, promote specific behavioral disturbances (e.g., depressive symptoms and negative emotion processing), which should be investigated in future studies on lesion-symptom mapping and PSD.

CRediT authorship contribution statement

Janusz L Koob: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maximilian Gorski:** Writing – review & editing, Investigation. **Sebastian Krick:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Maike Mustin:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Gereon R. Fink:** Writing – review & editing, Resources. **Christian Grefkes:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Anne K. Rehme:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2024.103586.

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