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ORIGINAL ARTICLE

Modulation of bodily response to chill stimuli by impaired structural connectivity of the left insula: a functional and lesion quantification study in stroke patients

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Abstract

Background and purpose: The insula has important functions in monitoring and integrating physiological responses to a personal experience of multimodal input. The experience of chills in response to auditory stimuli is an important example for a relevant arousing experience coupled with bodily response. A group study about altered chill experiences in patients with insula lesions is lacking.

Methods: Twenty-eight stroke patients with predominantly insula lesions in the chronic stage and 14 age-matched controls were investigated using chill stimuli of both valences (music, harsh sounds). Group differences were analyzed in subjective chill reports, associated bodily responses (skin conductance response), lesion mapping, diffusion-weighted imaging and functional magnetic resonance imaging. Other neuropsychological deficits were excluded by comprehensive testing. Diffusion-weighted imaging was quantified for four insula tracts using fractional anisotropy.

Results: The frequency of chill experiences was comparable between participant groups. However, bodily responses were decreased for the stroke group. Whereas there was no association of lesion location, a positive association was found for the skin conductance response during aversive sounds and the tract connecting anterior inferior insula and left temporal pole in the stroke group. Similarly, functional magnetic resonance imaging activation in areas hypothesized to compensate for damage was increased with bodily response.

Conclusions: A decoupling of felt arousal and bodily response after insula lesion was observed. Impaired bodily response was related to an impaired interaction of the left anterior insula and the temporal pole.

KEYWORDS
arousal, chill, emotion, harsh sounds, insula, music, shiver, stroke

Witt L. and Klepzig K. made equal contributions.

INTRODUCTION

The insular cortex (IC) has an important function in monitoring body responses and processing emotional experiences [1]. In fact, activation of the IC was observed during chill responses [2] which comprise both strong emotional experiences and profound bodily reactions [3]. In a case report on a patient with left hemispheric complete arteria media stroke also covering the IC anecdotal evidence was provided on decoupled bodily response and subjective chill experience during chill evoking acoustic stimuli [4]. Using the same chill stimuli and experimental design patients were enrolled in the chronic stage following stroke with predominantly insula lesions. Patients should be impaired in subjective chill experiences and bodily responses towards chill inducing pleasant and unpleasant acoustic stimuli compared to matched healthy controls (HCs). Using voxel-based lesion-symptom mapping (VLSM) impairments should be associated with lesions located in the IC. In addition, patients should show a reduced integrity of white matter structure of the insula. The integrity should be positively correlated with impaired responses towards chill stimuli. Brain areas which are able to compensate the damage of the IC (contralesional insula or BA47) or are interconnected to the insula by tracts with reduced white matter integrity should exhibit changes in functional magnetic resonance imaging (fMRI) activation during the presentation of chill inducing stimuli. There should be a positive association between blood-oxygen-level dependent (BOLD) magnitudes and impaired responses towards chill stimuli.

METHODS

Participants

Data on 28 stroke patients (10 females; mean age 63.4 years ±13.2) in the chronic stage recruited from the stroke unit of the University Medicine Greifswald and 14 HCs were included (ethical commitment number ML_012015_rev; see Figure S1). Neuropsychological tests were conducted to rule out cognitive impairments affecting results. See Table 1 for detailed characteristics of the examined groups.

Demographical, neuropsychological and psychopathological characteristics

Participants were asked about their level of education (school years) and handedness. Clinical data of stroke patients were extracted from medical reports. All participants underwent a variety of neuropsychological tests: the German multiple-choice word test MWT-B1 for verbal intelligence, the simple reaction task of the NeuroCogFX software for alertness, the Aachen Aphasia Test for verbal comprehension, the German version of the California Verbal Learning Test for verbal memory, the Trail Making Tests A (numbers) and B (numbers and letters) of the CERAD-Plus for executive functioning, the German version of the Stroop Color Word Interference Test for susceptibility to interference, and the Benton Visual Retention Test for visuospatial memory. Depression was assessed with the Beck Depression Inventory II. One patient did not complete the MWT-B and the Stroop test and hence was not considered for the corresponding analyses. Another patient omitted two items from the Beck Depression Inventory II, however, data were considered.

TABLE 1 Participants' characteristics.

	Healthy controls	Stroke patients	Statistics
No. of participants	14	28	–
Age in years	62.3 (15.6)	63.4 (13.2)	$t = -0.234$, $p = 0.816$
Gender (F:M)	8:6	10:18	$\chi^2 = 1.75$, $p = 0.186$
Handedness (L:R)	0:14	2:26	$p = 0.545$
Months since stroke	–	32.7 (32.8)	–
Lesion volume (cm^3)	–	24.3 (32.5)	–
School years	10.3 (1.3)	10.0 (1.2)	$t = 0.777$, $p = 0.441$
MWT-B	29.1 (3.6)	27.3 (5.0)	$t = 1.232$, $p = 0.225$
Simple reaction (ms)	360 (68)	360 (76)	$t = -0.019$, $p = 0.985$
AAT	55.6 (4.4)	53.6 (4.1)	$t = 1.395$, $p = 0.171$
CVLT	52.2 (12.4)	48.4 (10.1)	$t = 1.069$, $p = 0.291$
TMT B/A ratio	2.5 (0.8)	2.4 (0.9)	$t = 0.192$, $p = 0.849$
Stroop in seconds	86.2 (21.8)	101.3 (28.6)	$t = -1.733$, $p = 0.091$
Benton	7.1 (1.5)	5.9 (1.8)	$t = 2.194$, $p = \mathbf{0.034}$
BDI	9.0 (7.9)	7.5 (6.0)	$t = 0.700$, $p = 0.488$

Note: Mean values are presented with standard deviation in parentheses.Abbreviations: AAT, Aachen Aphasia Test, score of the verbal comprehension task; B/A ratio, TMT-B/TMT-A; BDI, Beck Depression Inventory II; Benton, number of correct drawings; CVLT, California Verbal Learning Task, number of all correctly remembered nouns; F, female; L, left; M, male; MWT-B, multiple-choice word test, number of correctly recognized words; R, right; Stroop, time required for the Stroop interference task; TMT, Trail Making Test.

Experimental design and data acquisition

The MRI session included T1- and T2-weighted whole head scans to assess lesion locations and lesion map creation, diffusion imaging to quantify white matter structural integrity, and an examination on chill responses using fMRI.

During the examination on chills six excerpts of classical music pieces were played whilst analyses focused on certain passages especially apt to evoke pleasant chills (lengths between 7.2 and 11.5 s) [3]. For two excerpts (Albinoni, Barber) such passages have not been identified in previous research. Hence, sections (length of 7 s each) were chosen for these excerpts where chills were frequently reported in our HC sample. Additionally, to induce unpleasant chills harsh sounds (e.g., fingernails scraping a blackboard, cutting styrofoam) of a similar duration (7.5–9.9 s) were played which were embedded in further excerpts of classical music (see Tables S1 and S2 for the applied chill stimuli). All stimuli had a total duration of 90s each. Amplitude normalization and fade-in/out effects were realized using Adobe Audition CS3.0 (Adobe Systems Inc.). After each stimulus white noise was played (30 s). Stimuli were presented using Presentation software (Neurobehavioral Systems) and MRI-capable headphones (MR confon). Chill responses during music and harsh sounds were assessed using recordings of skin conductance response (SCR) indicating chill-associated bodily arousal [3] and subjective chill reports (Supplement 1.1). Chills were explained as having bodily sensations like goose bumps, tingling, shivers down the spine, a lump in the throat or palpitation [5,6]. A broad range of bodily manifestations was presented since it was found that pleasant and unpleasant chills differ in terms of associated sensations [7]. Details on MRI can be found in Supplement 1.2.

Magnetic resonance imaging data preprocessing

Diffusion-weighted imaging (DWI) data processing was performed using FSL (v6.0.4, Analysis Group, FMRIB) and the Advanced Normalization Tools (ANTs, v2.3.5.dev212-g44225) [8,9,10]. T1w images were brain extracted and (non)linearly registered to the DWI b0 image as well as to the MNI152 NLIN 6th gen. template space including the patients' lesion masks to improve registrations. A concatenated transformation (MNI [Montreal Neurological Institute] → T1w → DWI) for transformation of regions of interest (ROIs) or atlases from MNI space into subject space was calculated. Eddy-current-related distortions and subject movement in the DWIs were corrected [11], outlier slices were replaced [12]. The diffusion tensor and diffusion-related indices were calculated (FSL dtifit), as well as distributions on diffusion parameters at each voxel (FSL BedpostX). A diffusion tensor imaging (DTI) quantification of insula tracts interconnecting the dorsal and ventral anterior and posterior parts of the insula for both hemispheres was done using fractional anisotropy (FA) with the mask generation and analyses recently described [13]. For details on DWI preprocessing see Supplement 1.4.

Functional MRI data were preprocessed using ANTs, too, and comprised motion correction, unwarping via a nonlinear registration of the average fMRI time course image to the T1w image, spatial normalization into MNI template space and Gaussian smoothing using a kernel of 8 mm full width at half maximum. For detailed VLSM and fMRI preprocessing see Supplement 1.3, 1.5.

Statistical analyses

Characteristics of groups were compared using independent samples *t* tests, a chi-squared test (gender) and a Fisher's exact test (handedness).

Differences in chills per minute and SCR were tested using repeated measures analyses of variance (rmANOVAs) with Valence as within-subjects variable (music, harsh sounds) and Group as between-subjects variable (HCs, stroke patients). Lesion mapping was performed to examine the relation between specific brain sites and SCR (see Supplement 1.6) [14]. Differences in averaged FA were examined using rmANOVA with Side (left, right) as within-subjects variable and Group as between-subjects variable. Independent samples *t* tests were computed to compare the FA of specific tracts (see Supplement 1.7). For fMRI analyses the same time windows were used as for the SCR and chill reports focused on harsh sounds as relevant impairments were found in that condition. fMRI activation magnitude was then assessed using SPM12 and related scripting (marsbar; averaged beta-response per ROI) in preselected ROIs which were hypothesized to compensate the damage of the IC and ROIs interconnected by the tract that was found to be associated with clinical impairment of chill response. Differences between BOLD responses were examined via rmANOVA with ROI as within-subjects variables (ipsilesional insula, contralesional insula, BA47, left temporal pole) and Group as between-subjects variables (see Supplement 1.8). To further examine impairments in the patients' response towards chill stimuli (i.e., lowered SCR during harsh sounds) associations with structural integrity and the corresponding BOLD response using Spearman's rank correlations were computed (see Supplements 1.7 and 1.8). Analyses were conducted using SPSS 22 (IBM). Alpha was set at 0.05. Plots were created using SPSS 22, R [15] and the beeswarm package.

RESULTS

Patients did not show differences to HCs in general neuropsychological testing except in the Benton Visual Retention Test (see Table 1). Since auditory stimuli were used, this difference should not have an effect on our results. As expected by preselection criteria, lesion maps of patients showed predominantly right and left hemispheric insular damage (see Figure S2). Patients did not report lower numbers of chills compared to HCs ($F(1, 30) = 1.167$, $p = 0.289$). Generally, harsh sounds led to a higher number of chills per minute than the music excerpts ($F(1, 30) = 21.358$, $p < 0.001$). No interaction between Group and Valence was found ($F(1, 30) = 1.430$, $p = 0.241$). However, stroke patients showed lower SCRs compared to HCs ($F(1, 40) = 4.963$, $p = 0.032$; see Figure 1, upper row). Harsh sounds evoked a stronger SCR than the music passages ($F(1, 40) = 30.893$, $p < 0.001$). Lowered SCR in the patients compared to HCs was especially observable during harsh sounds which was reflected by an interaction between Group and Valence ($F(1, 40) = 4.671$, $p = 0.037$). For both conditions

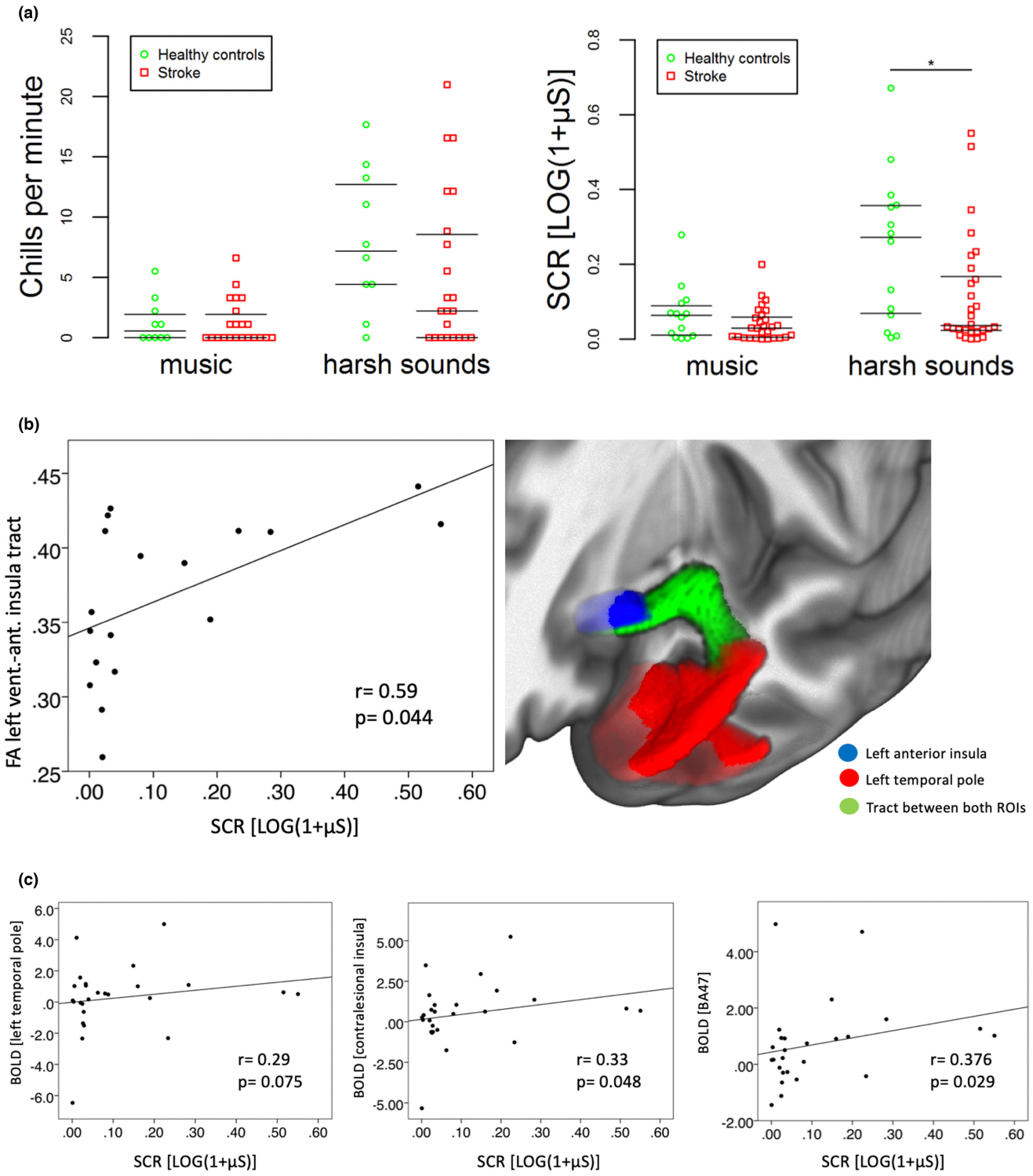

FIGURE 1 Swarm plots showing individual chills per minute values and mean SCR towards chill stimuli of both valences for HCs and stroke patients (a). Horizontal lines represent quartiles. The asterisk indicates a significant difference between groups (one-sided *t* test with Bonferroni–Holm correction). Correlation plots showing associations of SCR during harsh sounds with DTI (b) and the corresponding fMRI quantification (c) for the stroke group. The rendered brain shows the insula (blue), the tract associated with SCR (green) and the temporal pole predominantly targeted by the tract (red). [Colour figure can be viewed at wileyonlinelibrary.com]

no significant associations between lesioned voxels and SCR were found. Generally, patients showed decreased FA ($F(1, 30) = 8.82$, $p = 0.006$) with neither differences between sides ($F(1, 30) = 0.889$, $p = 0.353$) nor interaction between Side and Group ($F(1, 30) = 1.031$, $p = 0.318$). When testing specifically, the left inferior posterior tract was relevantly decreased in FA compared

to HCs ($t(30) = 3.524$, $p = 0.004$), whilst all other tracts showed no significant decrease. Only FA of the left anterior inferior insula tract interconnecting to the temporal pole was significantly related to SCR ($r = 0.59$, $p = 0.044$; see Figure 1, middle row) during harsh sounds. When testing for higher BOLD response in the insula, BA47 and left temporal pole, no significant differences between HCs and our stroke patients were found ($F(1, 38) = 0.260$, $p = 0.613$) whilst also no significant interaction between Group and ROI was present ($F(3, 114) = 0.546$, $p = 0.652$). SCR correlated significantly with BOLD magnitude in the contralesional insula ($r = 0.333$, $p = 0.049$) and in the BA47 ($r = 0.376$, $p = 0.030$) whilst a trend for a correlation was found with BOLD magnitude in the left temporal pole ($r = 0.291$, $p = 0.075$), however, these p values were not corrected for multiple comparisons (see Figure 1, lower row).

DISCUSSION

In a sample of predominantly insula damaged stroke patients, evidence is provided for impairments in bodily response (i.e., lowered SCR) to chill-provoking stimuli whilst subjective chill experiences of both valences remain unaffected. Hence, our work corroborates findings from a case report previously reported from our group [4]. The finding of significantly lowered SCR especially during harsh sounds could be attributable to a generally more pronounced response towards such stimuli compared to music resulting in more variance as shown here but also previously [2,16].

The extent of SCR was not associated with specific brain sites (VLSM analyses) but with integrity of the structural connectivity of the anterior inferior insula. These structures target the temporal pole which showed relevant modulation in fMRI response to chill stimuli in association with SCR. It is therefore concluded that the impaired bodily response in our group of patients was related to an impaired interaction of the left anterior insula and the temporal pole.

Interoceptive processes accompanying bodily reactions associated with chills [3] have various representations in the human cortex but are predominantly associated with the anterior insula [1]. Hence, it is not surprising that insula activity was found during music-induced feelings [17] and that musicians show increased insular connectivity compared to non-musicians [18]. Monitoring and processing body signals influence further decision making, attention to other stimuli and their emotional appraisal [19]. The IC interferes not only in processing one's own emotions [1] but also in recognizing the emotional state of another person (e.g., feeling empathy) [20]. Such processes are essential for everyday social interaction and disturbances can have dramatic negative consequences [21]. Interestingly, chill experiences of both valences have been suggested to be highly relevant for social behavior [7]. Hence, the here shown reduced bodily arousal during chill evoking stimuli might not only reflect post-stroke musical anhedonia [22] but also refer to impaired social cognition frequently found in stroke patients [23].

This group study therefore adds further data on a major function of the IC for bodily reaction to emotionally evocative stimuli associated with chills. More interestingly, the connection to and the activation of the left temporal pole seems to have an influence on the bodily response. The temporal pole has been described to process autobiographical emotional memory retrieval [24]. Reduced activation in relation to bodily response might therefore also indicate a decoupling of retrieval of emotional memories which has been suggested to be relevant for chill responses especially towards positively valenced stimuli like music [25].

Bodily reactions seem to be uncoupled from subjective chill experiences after damage of the insula or their anterior inferior connections. A similar dissociation between intact subjective experience and reduced bodily arousal after brain damage in general has been previously reported [26]. Interestingly, the administration of the opioid antagonist naltrexone was recently shown to have a similar effect in HCs with temporarily reduced bodily arousal but preserved subjective pleasure during music listening [27] which is in line with our findings since it is plausible that the blockade of opioid receptors especially in the insula is crucial. In fact, reduced opioid receptor availability in the insula was linked to depressive states [28] which in turn are characterized by lowered bodily arousal [29].

It may well be, however, that chronic stroke patients have developed strategies to compensate for the lack of interoceptive responses. If that was the case here it was not associated with relevant fMRI activation increase in regions hypothesized to represent these compensations (contralesional IC, BA47). However, our finding in the correlation of BOLD magnitude and SCR could be seen as a compensation mechanism. One limitation of our work could be that analyses focused on predefined music passages, in order to allow for group comparisons and to avoid different data sources between groups. For the same reason, analyses (SCR, fMRI) were run irrespective of actual chill reports which, however, might have prevented us from finding relevant fMRI activation in areas possibly compensating for the lack of bodily response.

As far as is known this is the first study to test the impact of IC lesions on the capability of experiencing strong emotional responses (i.e., chills) using also structural connectivity and event-related functional imaging data. Relevance for intact structural connectivity for bodily responses towards chill evoking stimuli is shown which might be closely related to adequate social functioning.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data can be downloaded on https://github.com/martinlotze/insula_chill.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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