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Associations of resting-state perfusion and auditory verbal hallucinations with and without emotional content in schizophrenia

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ABSTRACT

Auditory Verbal Hallucinations (AVH) are highly prevalent in patients with schizophrenia. AVH with high emotional content lead to particularly poor functional outcome. Increasing evidence shows that AVH are associated with alterations in structure and function in language and memory related brain regions. However, neural correlates of AVH with emotional content remain unclear. In our study (n = 91), we related resting-state cerebral perfusion to AVH and emotional content, comparing four groups: patients with AVH with emotional content (n = 13), without emotional content (n = 14), without hallucinations (n = 20) and healthy controls (n = 44). Patients with AVH and emotional content presented with increased perfusion within the amygdala and the ventromedial and dorsomedial prefrontal cortex (vmPFC/ dmPFC) compared to patients with AVH without emotional content. In addition, patients with any AVH showed hyperperfusion within the anterior cingulate gyrus, the vmPFC/dmPFC, the right hippocampus, and the left pre- and postcentral gyrus compared to patients without AVH. Our results indicate metabolic alterations in brain areas critical for the processing of emotions as key for the pathophysiology of AVH with emotional content. Particularly, hyperperfusion of the amygdala may reflect and even trigger emotional content of AVH, while hyperperfusion of the vmPFC/dmPFC cluster may indicate insufficient top-down amygdala regulation in patients with schizophrenia.

1. Introduction

Auditory Verbal Hallucinations (AVH) are a key symptom of schizophrenia. AVH occur in approximately 60–80 % of patients (Andreasen and Flaum, 1991; Chaudhury, 2010; Maranhão, 2013; Sartorius et al., 1986; Sommer et al., 2012), and are associated with a particularly poor functional outcome and low quality of life (Copolov et al., 2004; Maranhão, 2013; Shergill et al., 1998; Sommer et al., 2012). While several effective treatments are available, such as antipsychotic medication, brain stimulation and cognitive behavioral therapy, up to 30 % of patients with AVH do not respond to antipsychotic medication (Nathou et al., 2019), or to add-on treatments, such as low-frequency repetitive transcranial magnetic stimulation (rTMS; Guttesen et al., 2021). Neuroimaging studies have shown that AVH are linked to a variety of alterations in brain structure and function. However, there is considerable heterogeneity, and the precise associations of AVH and brain function remain equivocal. Yet, a thorough understanding of neurobiological underpinnings of AVH would not only provide insights for explaining AVH, but could also lead to new insights into the pathophysiology associated with treatment resistance in some patients.

Several studies detected key brain areas hypothesized to be relevant for AVH development. Five meta-analyses summarized functional neuroimaging findings, identifying language- and memory-related brain regions most consistently implicated in AVH (Jardri et al., 2011; Kompus et al., 2011; Kühn and Gallinat, 2012; van Lutterveld et al., 2013; Zmigrod et al., 2016). The same holds true for patients in their first episode (Curtis et al., 2021; Mulert et al., 2012; Salisbury et al., 2021). In detail, patients with hallucinations show hyperactivity of the inferior frontal gyri (IFG), including Broca's area, the temporal lobe (Wernicke's area, MTG and STG), the hippocampi and the insula. Thus, mostly task-based imaging studies detected hyperactivation of key primary language and memory areas in patients with schizophrenia and AVH (Jardri et al.,

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2011; Kompus et al., 2011; Kühn and Gallinat, 2012; van Lutterveld et al., 2013; Zmigrod et al., 2016). Structural neuroimaging studies found parallel alterations in AVH. For instance, two meta-analyses reported reduced grey matter volume of the superior temporal gyrus, the insula, and frontal regions associated with AVH (Modinos et al., 2013; Palaniyappan et al., 2012). Furthermore, three studies suggest increased white matter microstructure within the arcuate fasciculus connecting Broca's and Wernicke's area (Hubl et al., 2004; Salisbury et al., 2021; Shergill et al., 2007). However, while alterations in language- and memory-related brain areas are most likely central to AVH, structural and functional anomalies are not limited to these regions. For instance, studies report hyperactivation of the amygdala (Dierks et al., 1999; Escartí et al., 2010; Horga et al., 2014; Vercammen et al., 2010), cingulate gyrus (Copolov et al., 2003; Hoffman et al., 2008; Lennox et al., 2000; Raij et al., 2009; Silbersweig et al., 1995; Sommer et al., 2008), ventral striatum (Raij et al., 2009), nucleus accumbens (Raij et al., 2009), thalamus (Lennox et al., 2000; Shergill et al., 2000; Silbersweig et al., 1995; Zmigrod et al., 2016), putamen (Salisbury et al., 2022; Silbersweig et al., 1995), globus pallidus (Jardri et al., 2011), and cerebellum (Diederen et al., 2010; Lennox et al., 2000; Sommer et al., 2008) in patients who experience AVH. Thus, while numerous reports point to and hypothesize that alterations in language- and memory related brain areas contribute to the development of hallucinations in schizophrenia, results are heterogeneous, and the pathophysiology of AVH is still unclear.

One important aspect regarding the phenomenological diversity of AVH is the emotional content of AVH. AVH with high emotional content are mostly characterized by degrading or threatening messages, and are associated with anxiety, distress, functional impairment, need for care and an overall lower quality of life (de Boer et al., 2022; Larøi et al., 2019). Additionally, emotional content was proposed as a mediator between AVH and suicidality (Kjelby et al., 2015; Larøi et al., 2019). Yet, neural correlates of AVH with emotional content are unclear. Single studies suggest that the amygdala may play a central role in processing emotional content of AVH (Dierks et al., 1999, Escartí et al., 2010, Horga et al., 2014). In accordance with these findings from functional imaging, structural imaging evidence suggests altered connectivity between the amygdala and language areas (i.e. the uncinated fasciculus) in patients with schizophrenia and adolescence at risk to develop schizophrenia with AVH (Ćurčić-Blake et al., 2015; O'Hanlon et al., 2015). In contrast, severity of negative emotional content of AVH was associated with right Broca's homologue activity during a verbal fluency task in schizophrenia patients (Sommer et al., 2008).

While first evidence points to the amygdala and the Broca's homologue to be related to emotional content in hallucinations, the precise association with brain function remains unclear. Importantly, no study compared neural activity in patients with AVH and emotional content, to patients with AVH without emotional content. In the current study, we thus aim to compare resting cerebral blood flow (rCBF) between patients with hallucinations with emotional content and without emotional content. Especially, rCBF measures with arterial spin labelling (ASL) allow an absolute quantification of rCBF at high spatial and temporal resolution, representing a crucial correlate of brain function and resting metabolism (Borogovac and Asllani, 2012). We hypothesize that patients with hallucinations with emotional content will show a hyperperfusion of the amygdala and additional limbic brain areas compared to patients with hallucinations without emotional content, patients without hallucinations and healthy controls. In addition, we suggest that patients with hallucinations, independent of the voice content, will present increased perfusion of key language and memory related areas, e.g., the temporal lobe, IFG and the hippocampi.

2. Material and methods

2.1. Participants

In total, 47 patients diagnosed with a schizophrenia spectrum disorder according to DSM-5, and 44 healthy controls participated in this study. We recruited patients at the in- and outpatient facilities of the University Hospital of Psychiatry and Psychotherapy in Bern. Healthy controls were recruited via advertisement and among staff. To be included, participants needed to be between 18 and 65 years of age and right-handed (according to the Edinburgh handedness inventory; Oldfield, 1971). Participants were excluded if they presented with a severe medical condition, a history of electroconvulsive treatment, head trauma with loss of consciousness, substance abuse or dependence (apart from nicotine). Furthermore, healthy controls were excluded if they had a psychiatric diagnosis or a first-degree relative with a schizophrenia spectrum disorder. We assessed current symptom severity with the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), the Comprehensive Assessment of Symptoms and History (CASH; Andreasen, 1992), and the Psychotic Symptom Rating Scale (PSYRATS; Haddock et al., 1999). Additionally, we completed the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) with healthy controls, to screen for the presence of any psychiatric disorder. We assessed antipsychotic medication and calculated chlorpromazine equivalents (CPZEs) in accordance to Woods (Woods, 2003). The study protocol was approved by the cantonal ethics committee (Kantonale Ethikkommission Bern: KEK-BE 025/13) and all participants provided written informed consent before participation. Psychopathological assessments were conducted by a psychiatric resident (KS) within 48 h of the MRI scan.

2.2. Hallucination assessments

To assess the presence and characteristics of auditory verbal hallucinations (AVH), we conducted semi-structured interviews guided by the hallucination scale of the PSYRATS. In detail, this scale includes 11 dimensions, which are rated on five-point ordinal scales. The dimensions acquire detailed information on the physical characteristics of the voices (frequency, duration, location and loudness), emotional characteristics of the voices (amount of negative content, degree of negative content, amount of distress and intensity of distress), as well as cognitive interpretation of the experience (conviction in beliefs about origin, disruption and controllability). In addition, we studied patients' case files, to fill in potential gaps of information.

2.3. Neuroimaging

We acquired a 3D-T1-weighted structural image (Modified Driven Equilibrium Fourier Transform Pulse [MDEFT] sequence; Deichmann et al., 2004) and 110 functional images (pseudo continuous arterial spin labeling [pCASL] sequence) on a 3-T Siemens Magnetom TrioTim Scanner System, equipped with a standard 12-channel radio frequency head coil for signal reception (Siemens Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany). The structural image consisted of 176 sagittal slices, with 256 × 256 matrix points and a non-cubic field of view (FOV) of 256 mm, which yielded a nominal isotopic resolution of 1x1x1 mm. Additional parameters included a repetition time (TR) of 7.92 ms, an echo time (TE) of 2.48 ms, and a flip angle (FA) of 16°. The functional images consisted of 20 slices, with 64 × 64 matrix points, and a non-cubic field of view (FOV) of 230 mm, which yielded a nominal isotopic resolution of 3.6 × 3.6 × 6 mm. Additional parameters included a repetition time (TR) of 4000 ms, an echo time (TE) of 18 ms, and a flip angle (FA) of 25°. Slices of the functional images were acquired in ascending order. We processed all images with SPM12 for MATLAB (Wellcome Trust Centre for NeuroImaging, University College London; http://www.fil.ion.ucl.ac.uk/spm) and with an in-house custom-written

MATLAB program toolbox, designed for ASL-image-analyses (Cantisani, König, et al., 2016; Cantisani, Stegmayer, et al., 2016; Cantisani et al., 2018; Federspiel et al., 2006; Jann et al., 2013; Kindler et al., 2015; Kübel et al., 2018; Maderthaner et al., 2023; Stegmayer et al., 2017; Walther et al., 2011; Walther et al., 2017). We first segmented the T1-3D scans into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Then, we realigned the perfusion images to correct for motion, calculated the mean regional resting-state cerebral blood flow (CBF, ml/100 g/min) voxelwise and stored the resulting CBF maps. Finally, we co-registered the mean CBF maps to the corresponding structural images, normalized, modulated and smoothed them with an 8-mm-full-width at half-maximum (FWHM) Gaussian kernel.

2.4. Statistical analyses

We analyzed demographic and clinical data with SPSS 27.0 (SPSS Inc., Chicago, IL, USA) and performed neuroimaging analyses with SPM12, applying a general linear model (GLM). We used univariate analyses, two-sample *t*-tests, chi-square tests (χ^2), and multiple regression analyses, where appropriate.

The primary aim was to test the effect of emotional content on whole-brain rCBF in patients with AVH. We thus stratified patients into three groups: (1) The emotional content group included patients who currently experience AVH with emotional content, (2) the non-emotional content group included AVH-patients with no or very rarely emotional content, and (3) the no-auditory verbal hallucinations group (noAVH) included patients who did not experience AVH. Groups with and without emotional content were defined according to PSYRATS ratings item 6 (amount of emotional content). Patients with $>$ 10 % of emotional content were defined as with emotional content, $<$ 10 % as without emotional content respectively. We provide additional results with the alternative grouping of $>$ 50 % of amount of emotional content defined as with emotional content (n = 11), and $<$ 10 % as defined as without emotional content in the supplementary material (Table S1).

We performed a one-way analysis of covariation (ANCOVA, *F*-test) between four groups (i.e. AVH with emotional content, AVH with non-emotional content, noAVH and healthy controls). Next, to separately examine the effect of emotional content on whole-brain perfusion within patients with AVH status, we conducted a two-sample *t*-test between patients with and without emotional content within the ANCOVA. Finally, we assessed AVH effects on brain perfusion independent of emotional content. We therefore performed two-sample *t*-tests within the ANCOVA, comparing mean perfusion values of patients with any type of AVH and patients without hallucinations and healthy controls, respectively.

We included mean motion parameters ($x, y, z, \alpha, \beta, \gamma$), age, and antipsychotic medication dosage (CPZEs) as covariates of no interest in all analyses. Furthermore, we provide results with sex as additional covariate in the supplementary material (Table S2). We report clusters at a statistical threshold of p <.001, uncorrected, with a minimum cluster size of 50 voxels and indicate results corrected for multiple comparison. This threshold was set to report both results at a reasonable uncorrected threshold (Lindquist and Mejia, 2015) and corrected results. Importantly, our main results remain significant after correction for multiple comparison at familywise error at peak level: $FWE_{corr} < 0.05$. For illustration purposes, we extracted mean perfusion values from all significant clusters.

3. Results

3.1. Clinical characteristics

Patient groups and healthy controls did not differ regarding age, sex, and education. Furthermore, illness duration and medication did not differ between the three patient groups. As expected, patients with AVH had significantly more positive symptoms (PANSS positive) compared to patients without AVH. However, patient groups did not differ in negative symptoms (PANSS negative) and overall symptom severity (PANSS total). An overview of all demographic and clinical variables is presented in Table 1a. All patients of the AVH group reported AVH for at least two weeks prior to the scanning. In contrast, none of the noAVH group reported AVH within the last two years according to the CASH interview. When comparing PSYRATS ratings, patients with emotional content and patients without emotional content of AVH did not differ in regard to the physical characteristics of their AVH (i.e. 'frequency', 'duration', 'location', or 'loudness') and their cognitive interpretation of the 'amount of disruption' and 'feelings of control'. Patients with AVH and emotional content, however, were more likely to believe in external (alien, outside the head) than internal (inside the head) origin of AVH. Additionally, as expected, patients with AVH and emotional content presented with significantly higher scores on the 'emotional content'

Table 1
Demographics and Clinical Variables.

(a) Demographics	**Con** n = 44	**noAVH** n = 20	**AVH-nEC** n = 14	**AVH-EC** n = 13	$F/t/X^2$	p
Age (yrs)	38.8 (13.6)	40.8 (12.1)	36.9 (11.4)	35.5 (10.2)	0.538	0.658
Sex (f %)	18 (41 %)	10 (50 %)	3 (21 %)	4 (31 %)	3.277	0.351
Education (yrs)	14.1 (2.7)	13.8 (2.9)	13.0 (2.7)	13.3 (3.8)	0.721	0.542
Illness duration		15.6 (13.2)	12.5 (11.6)	7.1 (9.9)	2.018	0.145
CPZE		432.2 (376.3)	371.4 (347.5)	362.7 (318.4)	0.197	0.822
PANSS pos.		15.6 (4.9)	19.1 (7.7)	21.2 (5.9)	3.584	0.036
PANSS neg.		18.0 (6.0)	18.4 (4.6)	18.8 (4.3)	0.090	0.914
PANSS tot.		67.9 (18.2)	73.8 (13.7)	78.6 (17.5)	1.645	0.205
(b) PSYRATS						
Physical			8.36 (2.50)	9.33 (1.97)	1.04	0.311
Frequency			2.27 (0.91)	2.42 (0.90)	0.382	0.706
Duration			2.00 (0.89)	2.25 (1.06)	0.610	0.548
Location[1]			2.18 (1.08)	2.33 (1.23)	0.313	0.758
Loudness			1.91 (1.04)	2.33 (0.89)	1.05	0.304
Cognitive			5.27 (2.53)	7.08 (2.31)	1.79	0.088
Origin Beliefs[2]			1.18 (0.60)	2.58 (1.38)	3.20	0.006
Disruption			1.91 (1.14)	2.25 (1.14)	0.718	0.481
Control[1]			2.18 (1.40)	2.25 (1.29)	0.122	0.904
Emotional Content			2.18 (2.56)	10.92 (2.39)	8.45	<0.001
Amount			0.27 (0.47)	3.08 (0.67)	11.58	<0.001
Degree			0.45 (0.69)	2.67 (0.78)	7.20	<0.001
Amount Distress			0.64 (1.03)	2.83 (0.94)	5.37	<0.001
Intensity Distress			0.82 (0.87)	2.33 (1.16)	3.52	0.002
Total Score			15.82 (2.56)	27.33 (4.92)	6.94	<0.001

Abb.: Con = Controls, noAVH = no auditory verbal hallucinations, nEC = non-emotional content, EC = emotional content, CPZE = chlorpromazine equivalent dosage, PANSS = Positive and Negative Syndrome Scale, pos. = positive, neg. = negative, tot. = total, PSYRATS = Psychotic Symptom Rating Scale; [1] missing value for one patient, [2] missing values for three patients.

items of the PSYRATS (i.e. 'amount of negative content', 'degree of negative content', 'amount of distress', and 'intensity of distress'), which also led to an overall higher PSYRATS total score in the patient group (Table 1b).

3.2. Whole-brain cerebral perfusion associated with AVH with and without EC

Group comparisons between patients without AVH, patients with AVH and emotional content, patients with AVH and non-emotional content, and healthy controls revealed significant differences in cerebral perfusion in several clusters, including the left amygdala, the right ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), dorsolateral prefrontal cortex (dlPFC), and the anterior cingulate cortex (ACC) (see Fig. 1 and Table 2a). Patients with AVH and emotional content had higher perfusion than patients with AVH and non-emotional content within the left amygdala (*FWE*-corr. at $p = .022$) and the right vmPFC / dmPFC cortex (FWE-corr. at $p = .005$) (Fig. 2 and Table 2b).

3.3. Whole-brain cerebral perfusion associated with AVH independent of emotional content

Comparing patients with AVH and patients without AVH revealed a hyperperfusion within the ACC, the vmPFC, the dmPFC, the right hippocampus, the left precentral gyrus and the left postcentral gyrus in patients with AVH (see Table 3a, and Fig. 3). Finally, comparing patients with any type of AVH and healthy controls yielded no rCBF differences.

Re-analyzing our data with sex as additional covariate yielded substantially the same results. The same holds true for the alternative grouping of patients with emotional content (see supplementary material (Tables S1 and S2).

Table 2
Regions with differences in cerebral perfusion.

	MNI Coordinates				
(a) *F*-test: AVH-EC, AVH-nEC, noAVH, Con	x	y	z	*k*	*F* (3, 80)
L/R ACC, vmPFC	6	64	24	316	11.37
R vmPFC/dmPFC	32	54	30	159	11.27
L Amygdala	−30	2	−18	64	9.29
R vmPFC/dmPFC	44	44	20	78	8.47
R dlPFC	34	32	48	118	8.16
(b) *t*-test: AVH-EC > AVH-nEC	x	y	z	*k*	*t* (79)
R vmPFC/dmPFC	30	56	28	290	5.56
L Amygdala	–32	2	−18	149	5.11
(c) *t*-test: AVH-nEC > AVH-EC	x	y	z	*k*	*t* (79)
No significant clusters					

Abb.: AVH = auditory verbal hallucinations, EC = emotional content, nEC = non-emotional content, noAVH = no auditory verbal hallucinations, Con = controls, ACC = Anterior Cingulate Cortex, vmPFC = ventromedial prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, L = left, R = right; threshold was set at $p < .001$, uncorrected, $k > 50$ voxels; covariates of no interest: mean motion parameters, age, and medication.

4. Discussion and conclusion

Here we investigated the impact of emotional content on resting-state cerebral blood-flow (rCBF) in patients with schizophrenia and auditory verbal hallucinations (AVH). In line with our hypothesis,

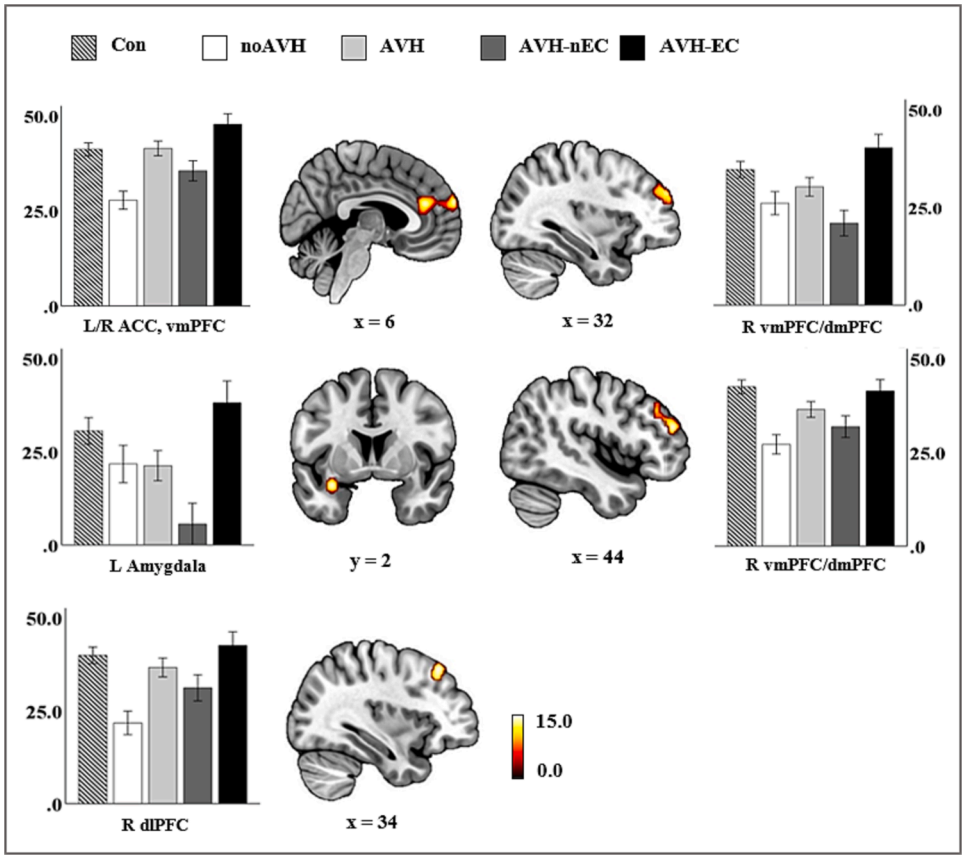

Fig. 1. Differences in perfusion between AVH-EC-patients, AVH-nEC-patients, noAVH-patients and Controls; *Abb.*: AVH = Auditory Verbal Hallucinations, EC = emotional content, nEC = non-emotional content, noAVH = no auditory verbal hallucinations, ACC = anterior cingulate cortex, vmPFC = ventromedial prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex; threshold was set at $p < .001$, uncorrected; minimum cluster size: $k > 50$ voxels; Covariates of no interest: mean motion parameters, age, and medication; L = left, R = right.

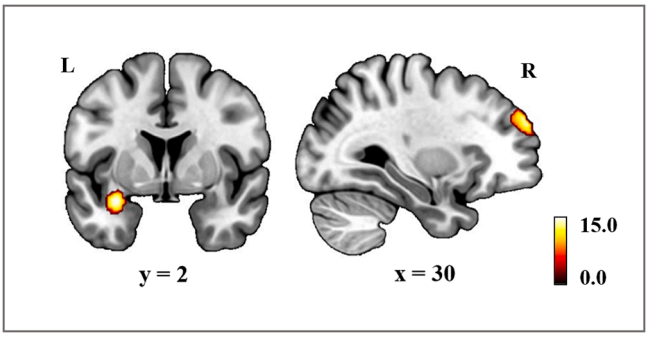

Fig. 2. Amygdala and vmPFC/dmPFC hyperperfusion in patients with AVH-EC, compared to patients with AVH-nEC; *Abb.*: AVH = auditory verbal hallucinations, EC = emotional content, nEC = non-emotional content, L = left, R = right; for illustration purposes, the threshold was set at $p < .001$, uncorrected; minimum cluster size: k > 50 voxels; covariates of no interest: mean motion parameters, age, and medication.

Table 3
Regions with differences in perfusion between AVH-patients, noAVH-patients, and Controls.

(a) *t*-test: AVH > noAVH	x	y	z	*k*	*t* (79)
L/R ACC, vmPFC/dmPFC	6	34	20	148	4.58
R dmPFC	6	64	26	63	4.34
L ACC	−10	30	18	108	4.19
R Hippocampus	28	−20	−12	58	4.01
L PrCG, L PoCG	−54	−10	34	51	3.84
L PrCG, L dlPFC	−48	6	34	55	3.77
R dlPFC	34	30	48	59	3.66
(b) *t*-test: noAVH > AVH	x	y	z	*k*	*t* (79)
No significant clusters					
(c) *t*-test: AVH > Con	x	y	z	*k*	*t* (79)
No significant clusters					
(d) *t*-test: Con > AVH	x	y	z	*k*	*t* (79)
R Entorhinal area, fusiform gyrus	32	−2	32	57	3.68
(e) *t*-test: SZ > Con	x	y	z	*k*	*t* (79)
No significant clusters					
(f) *t*-test: Con > SZ	x	y	z	*k*	*t* (79)
R dlPFC	44	36	28	63	3.69

Abb.: AVH = auditory verbal hallucinations, noAVH = no auditory verbal hallucinations, SZ = schizophrenia, Con = controls, ACC = anterior cingulate cortex, vmPFC = ventromedial prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, PrCG = precentral gyrus, PoCG = postcentral gyrus, IFG = inferior frontal gyrus; L = left, R = right; threshold was set at $p < .001$, uncorrected; minimum cluster size: $k > 50$ voxels; Covariates of no interest: mean motion parameters, age, and medication.

patients with hallucinations with emotional content showed a hyperperfusion within the left amygdala, a key region for emotion processing. In addition, we detected hyperperfusion within the vmPFC and dmPFC, among other functions important brain regions for emotion regulation. Finally, patients with any type of AVH showed a hyperperfusion within the ACC, the vmPFC/dmPFC, the right hippocampus and the left pre- and postcentral gyrus compared to patients without AVH. Our results suggest major metabolic alterations in brain areas that are central for the processing of emotions, in patients experiencing AVH with emotional content. In fact, hyperperfusion of the amygdala may critically contribute to emotional content of AVH, and hyperperfusion of the vmPFC/dmPFC cluster may reflect insufficient regulation of this hyperperfusion in patients with schizophrenia.

Our main results show a hyperperfusion within the amygdala, and the vmPFC/dmPFC in patients with AVH and emotional content. We investigated the impact of emotional content on resting-state cerebral perfusion as a marker of tonic activity in patients with AVH. Collectively, our results nicely fit to recently proposed models of AVH with emotional content, and previous reports of task-based peak activation. For instance, one review advocates dysfunctions in amygdala as well as Broca's area as possible neurophysiological explanations of emotional content of AVH (Larøi et al., 2019). Furthermore, one study found task based activation within the amygdalae in three patients with chronic AVH with emotional content (Dierks et al., 1999). Likewise, two task-based fMRI studies provide indirect evidence for amygdala hyperactivity in patients with AVH and emotional content. In particular, the authors detected increased amygdala activation in response to aversive verbal stimuli, suggested to mimic negative emotional content in patients with AVH (Escartí et al., 2010; Horga et al., 2014). Contrary, Sommer and colleagues advocated a relation of the right Broca's homologue to negative content of AVH during a verbal fluency task (Sommer et al., 2008). The amygdala may thus be essential in the development of emotional content of AVH. In fact, the fundamental role of the amygdala in emotion processing and affective responses is widely accepted (Adolphs et al., 1995; Damasio, 1998; Damasio et al., 2000; Dolan and Vuilleumier, 2003; Janak and Tye, 2015; LeDoux, 2000; Palomero-Gallagher and Amunts, 2021; Pessoa, 2008; Stegmayer et al., 2018; K. Stegmayer et al., 2017; Walther et al., 2021). As a main hub, the amygdala has functional connections with important language-related brain regions (Roy et al., 2009). Importantly, the amygdala is thought to be responsible for the integration of emotional information with linguistic meaning (Liebenthal et al., 2016), for instance in the recognition and interpretation of emotionally salient words and sentences (Adolphs et al., 1999) or while reading or hearing emotionally charged words (Herbert et al., 2009). Interestingly the here detected tonic amygdala hyperactivity was shown on the left side. Theories suggest specific affective information-processing roles for the left and the right amygdala (Baas et al., 2004; Zald, 2003). Functional imaging studies in healthy controls point to lateralization differences of amygdala activity, with especially the left amygdala implicated in negative affect (Baas et al., 2004) and to be more involved in specific, sustained stimulus evaluation (Gläscher and Adolphs, 2003; Wright et al., 2001). Most importantly our results fit to the suggested general left-hemispheric dominance for language-related functions in the brain, in particular for emotional information conveyed through language (Funayama et al., 2001; Markowitsch, 1998; Morris et al., 1998; Olsson and Phelps, 2004; Phelps et al., 2001; Costafreda et al., 2008). Thus, our results greatly support concepts and first evidence, suggesting the amygdala as crucial for the emotional content of AVH in schizophrenia, and beyond that provide first evidence for tonic hyperactivity at rest, perhaps contributing to the emotional valence of AVH or possibly even as a trigger of AVH. On the other hand, the detected hyperperfusion within the amygdala could also be a consequence of AVH with emotional content. However, contrary to our hypothesis the difference between AVH-EC patients and healthy controls was smaller than the difference between AVH-EC and AVH-nEC patients. We may speculate that reduced amygdala activity in patients with AVH and no emotional content may prevent AVH-nEC patients from having distressing emotional content. On the other hand, we must bear in mind some methodological aspects of rCBF measures: While rCBF is closely correlated with neuronal metabolic measures and correlates with regional brain activity measures using other techniques (e.g. BOLD), changes in rCBF may not have the same origin as brain activation. Several other mechanisms may play a role in altered perfusion. For example, molecular mechanisms at the receptor level, including distribution or up- and down-regulation are relevant in determining regional perfusion patterns. Thus, there are several parallel processes we need to consider. Conclusively, future studies are warranted to employ multiple methodologies, including positron emission tomography (PET) or MR spectroscopy as well as different study designs (cross-sectional versus longitudinal) to clarify the causes of the detected altered perfusion in the amygdala in AVH-EC patients.

In addition to amygdala hyperperfusion, we detected hyperperfusion within the vmPFC/dmPFC to be associated with emotional content in

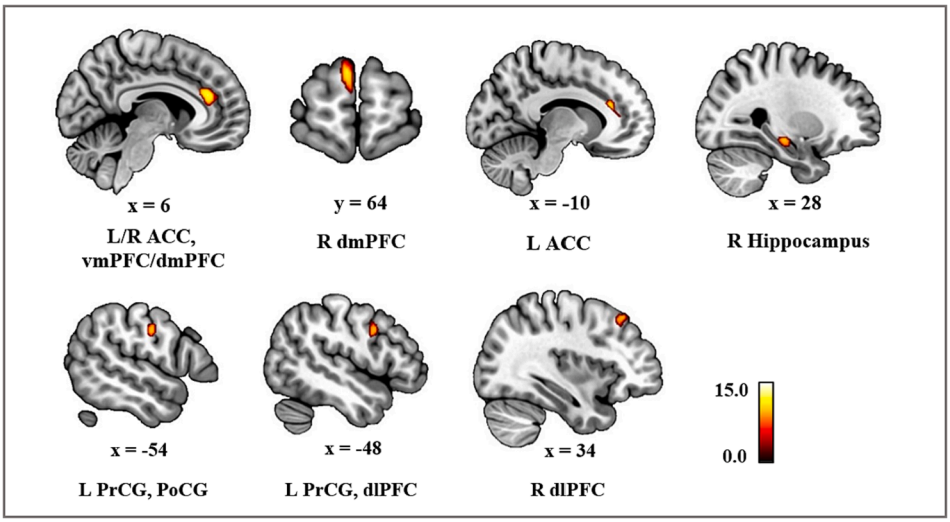

Fig. 3. Hyperperfusion in AVH-patients, compared to noAVH-patients (*t*-test); *Abb.*: AVH = auditory verbal hallucinations, noAVH = no auditory verbal hallucinations, ACC = Anterior Cingulate Cortex, vmPFC = ventromedial prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, PrCG = Precentral Gyrus, PoCG = postcentral gyrus, L = left, R = right; threshold was set at $p < .001$, uncorrected, $k > 50$ voxels; covariates of no interest: mean motion parameters, age and medication.

patients with AVH. Both, the vmPFC and the dmPFC are assumed to play a crucial role in emotion regulation (Helion et al., 2019; Hiser and Koenigs, 2018). Rodent studies (Morgan et al., 1993; Quirk et al., 2000; Milad and Quirk, 2002; Quirk et al., 2003; Rosenkranz et al., 2003; Likhtik et al., 2005), anatomical tracing studies (Ghashghaei and Barbas, 2002; Mcdonald et al., 1996) and human functional imaging studies (Delgado et al., 2008; Fullana et al., 2016; Kalisch et al., 2006; Motzkin et al., 2015; Phelps et al., 2004; Urry et al., 2006) support the notion that the vmPFC suppresses amygdala activity, particularly when processing negative emotional content (Likhtik et al., 2005; Quirk et al., 2003; Rosenkranz et al., 2003). Likewise, growing evidence suggests that the dmPFC suppresses amygdala activity during emotion regulation (Herwig et al., 2019; Koush et al., 2017; Seo et al., 2014; Wheelock et al., 2014). This appears to be specifically reflected in the high functional connectivity between the dmPFC and the amygdala during emotion regulation tasks (Banks et al., 2007; Berboth and Morawetz, 2021; Buhle et al., 2014; Herwig et al., 2019; Sripada et al., 2014). Interestingly the vmPFC seems to not only suppress amygdala activity, which arises in response to negative stimuli, but also suppresses spontaneous amygdala activity, which occurs without the influence of external stimuli ("spontaneous postsynaptic potentials (PSPs)"; Rosenkranz et al., 2003). Thus, the detected vmPFC/dmPFC hyperperfusion reflects perhaps the insufficient attempt to suppress spontaneous amygdala activity in patients with AVH, leading to high negative emotional content of AVH. However, the connections between the amygdala and the vmPFC have been found to be bidirectional (Ghashghaei and Barbas, 2002). Therefore, alternatively vmPFC hyperperfusion may not be the consequence of altered amygdala perfusion, but could also be the cause of the detected amygdala hyperperfusion. Conversely, patients with AVH are thought to engage in more maladaptive cognitive emotion regulation strategies (Liu et al., 2020) In fact, severity of AVH (frequency, loudness, duration) was related to the use of maladaptive emotion regulation strategies (Badcock et al., 2011) and techniques to learn adaptive emotion regulation strategies are consequently used as a therapeutic strategy in patients with AVH (Lincoln and Peters, 2019). In schizophrenia, altered top-down (cognitive) emotion control was associated with altered PFC and amygdala activity (Goldin et al., 2008; Morris et al., 2012; Ohira et al., 2006; van der Meer et al., 2014). In addition, previous fMRI task-based studies on AVH report altered activity within the PFC in schizophrenia (Diederen et al., 2010; Lennox et al., 2000; Shergill et al., 2000; Sommer et al., 2008). However, as far as we know, studies particularly focused on the association of emotion control and brain imaging in the context of AVH are missing. Thus, whether the detected vmPFC/dmPFC hyperactivity causes the amygdala hyperactivity, leading to emotional content of AVH or reflects an insufficient attempt to suppress altered amygdala remains speculative.

When looking at brain perfusion in patients with AVH independent of the voice content we hypothesized increased perfusion of key language and memory related areas. In line with this hypothesis, we found hyperperfusion in patients with AVH in a key memory area, the right hippocampus. In addition, we detected hyperperfusion within the ACC, the vmPFC/ dmPFC and the left pre- and postcentral gyrus compared to patients without AVH. However, contrary to previous reports and our hypotheses, we failed to detect hyperperfusion within the temporal lobe and the IFG in our patients with AVH. Likewise, no effect was shown comparing all patients with AVH to healthy controls. One reason why our results do not support our hypothesis might be relevant methodological differences compared to previous reports. In particular, the majority of the previous studies examined differences in the blood-oxygen-level-dependent (BOLD) signal on and off hallucinations. Here, we examined whole-brain absolute activity at rest using ASL. While BOLD-contrast primarily detects changes that indirectly reflect changes in CBF, ASL perfusion techniques directly quantify CBF, and are believed to be directly linked to neuronal activity rather than BOLD-changes (Liu and Brown, 2007). Therefore, ASL measures may detect direct neuronal activity associated with hallucinations in contrast to BOLD-activation or -connectivity. Still, our findings are partly in line with the previous literature (Homan et al., 2013). Comprehensively, functional neuroimaging studies have consistently linked AVH to hyperactivation within the hippocampus (Jardri et al., 2011; van Lutterveld et al., 2013; Zmigrod et al., 2016), the superior frontal gyrus (Kompus et al., 2011), the precentral gyrus (Jardri et al., 2011; van Lutterveld et al., 2013; Zmigrod et al., 2016), and the anterior cingulate gyrus (Lennox et al., 2000; Raij et al., 2009; Shergill et al., 2000; Silbersweig et al., 1995; Sommer et al., 2008).

The findings of the present study should be interpreted in the light of some limitations. First, we cannot rule out the effect of medication. In the present study, all but four patients received antipsychotic medication at the time of testing. Studies assessing the impact of antipsychotic medication on rCBF yielded conflicting results, showing no effect of medication on rCBF (Gur et al., 1985; Mathew et al., 1982; Paulman et al., 1990), rCBF reduction (Goldstein et al., 1990; Jibiki et al., 1990),

regional different effects on rCBF (Handley et al., 2013; Lahti et al., 2009) or substance-specific effects on rCBF (Lahti et al., 2005). In our study patient groups did not differ in mean CPZE values (see Table 1). To minimize, however, the impact of medication we added chlorpromazine equivalent dosages (CPZE; Woods, 2003) as covariate of no interest to all neuroimaging analyses. Second, we cannot exclude that childhood trauma may impact our results as childhood trauma has been found to influence amygdala function (Dannlowski et al., 2012), and may be associated with emotional content of AVH (Misiak et al., 2016). We cannot state on this aspect as we did not assess childhood trauma in our sample. However, childhood trauma was previously also associated with AVH independent of emotional content (Daalman et al., 2012; Fowler et al., 2007). Third, including mean motion parameters, age, sex, and medication as covariates of no interest we did not observe differences in brain perfusion comparing schizophrenia patients and healthy controls independent of hallucination status which may limit the interpretation of our results. Fourth, we did not assess whether patients were hearing voices during the scanning. In fact, this might be one reason why we did not detect the hypothesized hyperperfusion within the temporal lobe and the IFG in patients with AVH. In addition, in four subjects we had missing information of single items of the PSYRATS physical and cognitive dimensions. However, PSYRATS rating for the emotional content dimension were complete. Finally, we included a relatively small number of carefully characterized patients. However, this is the largest study comparing patients with AVH with and without emotional content ever investigated with brain imaging.

To conclude, our results suggest the amygdala and the vm/dmPFC to be essential in the pathophysiology of AVH with emotional content. Particularly, hyperperfusion of the key emotion processing area, amygdala, may critically contribute to the development of emotional content of AVH. In addition, hyperperfusion of the vmPFC/dmPFC may reflect insufficient regulation of the detected amygdala hyperperfusion in patients with AVH and emotional content. Thus, thorough investigation of neurobiological underpinnings of AVH with emotional content provides new insights for explaining the heterogeneous pathophysiology of AVH.

Author contributions

SW designed the study, wrote the protocol, acquired funding, supervised the data acquisition, and edited the manuscript. KS acquired funding, performed data acquisition, analyzed data, and edited the manuscript. FC analyzed data and wrote the first draft of the manuscript. All authors discussed findings and edited the final manuscript.

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Declaration of competing interest

SW received honoraria from Lundbeck, Mepha and Neurolite. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The statistical maps that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103527.

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