Egyptian Journal of Psychiatry

Vol. 44, No. 2, 2023
ISSN: 1110-1105 (print)
ISSN: 2090-2425 (online)
DOI: 10.21608/EJPSY.2024.340967

REVIEW ARTICLE

Cerebral perfusion changes specific to auditory verbal hallucination in schizophrenia: an arterial spin labeling MRI study

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Background

Auditory verbal hallucinations (AVH) are considered a significant diagnostic positive symptom that is experienced by ~70% of schizophrenia spectrum disorders. Up to 25% of AVHs are resistant to treatment; also, depression and suicide are common with auditory hallucinations. Therefore, future research should be done to clarify the pathology of these hallucinations to help in more effective treatment. Recent perfusion studies have investigated regional cerebral blood flow (rCBF) in brain areas, especially those generating AVH. The study aims to evaluate CBF alterations of brain regions in schizophrenic patients with AVH and without AVH compared with healthy control individuals using MRI using the pseudocontinuous arterial spin labeling technique. This study highlights that there is statistically significant higher rCBF in schizophrenic patients in the AVH group) compared with the schizophrenic non-AVH group in the following areas: right parietal, right superior temporal gyrus, left caudate, right lateral prefrontal, right insular cortex, right putamen, right temporal, and left temporal. However, there is statistically significant lower regional CBF in schizophrenic patients in (AVH) group in comparison with schizophrenic non-AVH group in the left parietal, left lateral prefrontal, right caudate, and left midcingulate cortex. Also, there is statistically significant higher regional CBF in the schizophrenic patients in the AVH group compared with the control group in the following areas: right parietal, right superior temporal gyrus, right caudate, right lateral prefrontal, right putamen, right temporal, and left midcingulate cortex. However, there is statistically significant lower regional CBF in schizophrenic patients in the AVH group in comparison with the control group in the following areas: bilateral occipital, left parietal, left lateral prefrontal, left caudate, bilateral insular, right anterior cingulate cortex, left putamen, and left temporal. There are significant changes in rCBF, which discriminate schizophrenic patients in the AVH group from other groups schizophrenic patients without AVH group and control group. Potential implications: exploring the path physiology of the brain underlying auditory hallucinations will open new horizons for treating auditory hallucinations in different approaches such as neurosurgery and transcranial magnetic stimulation to achieve a new perspective for the diagnosis and treatment of psychotic disorders.).

Keywords

Arterial spin labeling, Auditory verbal hallucinations, Cerebral perfusion.

Egyptian Journal of Psychiatry 2023,
44:65–74

INTRODUCTION

Hallucination can be defined as a ‘mental impression of sensory vividness without the presence of a real external stimulus of the relevant sensory organ, over which the subject has no direct or voluntary control’ (David, 2004).

Auditory verbal hallucinations (AVH) are considered a significant diagnostic positive symptom, which is experienced by ~70% of schizophrenia spectrum disorders (McCarthy-Jones *et al.,* 2017).

Up to 25% of AVHs are resistant to treatment and are associated with higher relapse rates, resulting in social and occupational dysfunction. Postpsychotic depression and increased risk of suicide are common with auditory hallucinations (Fujita *et al.,* 2015).

Therefore, future research should be done to clarify the underlying pathology of these hallucinations to help in more effective treatment.

Brain imaging has offered a wealth of knowledge to help better understand the occurrence of hallucinations in schizophrenic patients and also the further developed risk stratification criteria for the occurrence of hallucinations in schizophrenia, dementia, and Parkinsonism (Ffytche and Wible, 2014; Cui *et al.,* 2017). Recent perfusion studies have investigated regional CBF in different brain areas, especially those involved in the generation of AVH (Ford *et al.,* 2019).

Arterial spin labeling (ASL) is an MRI perfusion study used as an indirect tool to evaluate brain metabolism (Borogovac and Asllani, 2012). It has been validated as a sensitive, exclusively noninvasive imaging modality to quantify cerebral blood flow (CBF) without administering an exogenous tracer and using blood water as an endogenous tracer; it also can be accomplished with routine MRI protocol. Moreover, it provides quantitative maps with improved spatial and temporal resolution than other perfusion imaging modalities. ASL has been extensively utilized to measure cerebral perfusion in healthy individuals and various neuro/psychiatric disorders, for example, dementia, schizophrenia, and Alzheimer's disease (Du *et al.,* 2006; Guimarães *et al.,* 2016).

Principle of ASL: in the ASL technique, water protons are labeled by radiofrequency pulse and allowed to migrate through the arterial system as free diffusible tracers and pass to the extravascular compartment. Then imaging is acquired rapidly. Perfusion maps are generated by subtraction labeled and control acquisitions to extinguish the stationary tissue signal. CBF is the main physiological parameter calculated by ASL as the volume of blood per volume of tissue per minute (100 g−1 min^{-1}). CBF is considered a biomarker of brain function reflecting brain metabolism (Detre *et al.,* 2009; Ferré *et al.,* 2013). ASL in schizophrenia; multiple research studies have investigated rCBF alterations using ASL in different brain regions in schizophrenic patients. These studies have shown a statistically significant difference in regional CBF between schizophrenic patients and healthy controls. Areas of decreased rCBF in schizophrenic patients were the anterior cingulate cortex (ACC), frontal lobe, and the parietal lobe and increased regional CBF in putamen (Scheef *et al.,* 2010; Pinkham *et al.,* 2011; Ota *et al.,* 2014; Guimarães *et al.,* 2016; Jing *et al.,* 2017).

Few studies have addressed their concern about regional CBF alteration in schizophrenic patients with AVH; they found alterations in CBF in different brain regions (Stegmayer *et al.,* 2017; Zhuo *et al.,* 2017, 2021).

The study aims to evaluate CBF alterations of different brain regions in schizophrenic patients with AVH and without AVH compared with healthy control individuals using MRI using the pseudocontinuous ASL technique.

METHODS

This case–control study was applied in the Psychiatry and Radiology Departments, Mansoura University Hospitals from November 2020 to October 2021. The aim of the study was clarified to all participants in this study or their guardians, and they were given a choice to participate or not or to leave the research at any time, without penalty. All participants' data are confidential, and written informed consent was taken.

Patients group

Inclusion criteria

Both sexes, right-handed, age (20–40 years); the brain is supposed to be less affected by the aging process. Diagnosed as patients with schizophrenia according to the diagnostic criteria of the fourth edition (DSM-IV) with its Arabic version (Omar *et al.,* 2019) of the Structured Clinical Interview (SCID-1) (American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR, 2001; Furnham *et al.,* 2001). According to if they had AVHs, patients with schizophrenia were subdivided into two subgroups: the AVH group (n= 22), which included patients who had AVHs at least once daily. Moreover, the non-AVH group (n= 11) included patients who never had AVHs or had no AVHs within the last 12 months before MRI). Their PANSS-P3 hallucinatory behavior score= 1.

Exclusion criteria

Age less than 20 years, more than 40 years old, patients with cerebrovascular diseases, and left-handed, other types of psychotic disorders, history of head trauma, history of drug or alcohol misuse (except for nicotine), cardiovascular disease or neurological disorders, pregnancy, and intellectual disability.

Control group

Inclusion criteria

Both sexes, right-handed, age 20–40 years, absence of the diagnostic criteria for schizophrenia according to DSM-IV.

Exclusion criteria

Age less than 20 years, more than 40 years old, left-handed, presence of previous psychiatric history, presence of first-degree relatives with a history of psychiatric illness, history of head trauma, and .drug or alcohol misuse (except

for nicotine), cardiovascular disease or neurological disorder, pregnancy, and intellectual disability.

Sample size calculation

It depends on the mean difference of MRI changes in cases with auditory and visual hallucination retrieved from previous research (Orlov *et al.,* 2018). Using G power program, version 3.1.9.4, to calculate sample size based on effect size= 1.32 (mean1 and mean 2= 20.4 and 13.5 and SD1= 5.5, SD2= 4.9), using two-tailed test, α error= 0.05, and power= 90.0%, the total sample size will be 14 in each group.

Finally, 22 (Orlov *et al.,* 2018) cases of schizophrenia with AVH, 11 (Ferré *et al.,* 2013) cases of schizophrenia without AVH, and 22 (Orlov *et al.,* 2018) healthy controls participated in this study. Antipsychotic dosages used in the last month before MRI was reported as chlorpromazine equivalents.

The psychometric assessment of the patient's group was done using the following:

The Positive and Negative Syndrome Scale (PANSS) (Kay *et al.,* 1987):

Arabic version (Amro *et al.,* 2019) was used for the assessment of schizophrenia clinical symptoms through three subscales (positive symptoms, general psychopathology, negative symptoms) items rated from 1 (absence) to 7 (extreme). The PANSS has one specific item for hallucinations.

The Auditory Vocal Hallucination Rating Scale (AVHRS) (Bartels-Velthuis *et al.,* 2012):

This scale was used to assess the severity AVHs on 16 characteristics: the total score is indicative of the severity of AVHs.

The radiological assessment of all participants was done using the following:

MRI data acquisition: MRI data acquisition was conducted for all participants upon a 1.5-T MR system (Siemens Magnetom, Aera, Germany) and 16-element head coil. Tight cozy foam pads were fitted around the head to minimize head movement and earplugs to minimize noise.

A pseudocontinuous ASL sequence did the resting-state perfusion imaging with a 3D fast spin-echo acquisition and background suppression repetition time (TR)= 4600ms, echo time (TE)= 23ms, postlabel delay 1.5 s, spiral in a readout of eight arms with 512 sample points, flip angle 111°, field of view= 224×224mm, reconstruction matrix 128×128, slice thickness 3 mm, no gap, 40 axial slices, the number of excitations 3, and 1.9×1.9mm in-plane resolution. The total acquisition time was 4min. All examined groups were asked to close their eyes, stay awake, relax, think of nothing in particular, and avoid motion during scanning. All images were reviewed to exclude images with visible artifacts from subsequent analyses.

Postprocessing of data:

Perfusion-weighted images are produced automatically by subtracting ASL-labeled images from control coregistered T1W images. The mean regional resting-state CBF was calculated by voxels. Then quantification models are applied to generate CBF calculation maps (Fig. 1a,b).

Cerebral blood flow measurements

Regions of interest of the same size were placed in different brain regions bilaterally three times, and mean values of three readings representing regional CBF were recorded. Measurements are obtained from different brain regions involving language, hearing, and hallucinations) [occipital lobes, parietal lobes, temporal lobes, superior temporal gyrus (STG), caudate nucleus, lateral prefrontal cortex, insular cortex, ACC, middle cingulate cortex, putamen, and thalamus]. Fig. 2 shows region of interest placement in the left middle cingulate cortex to measure regional CBF.

Image analysis was performed by one neuroradiologist with 17 years of experience who was blinded to the clinical data of the participants.

A urine drug screen for drug abuse was done for all participants.

All female patients were checked by a blood pregnancy test the day before MRI.

Statistical Analysis

Data were introduced and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0. (IBM Corp., Armonk, New York, USA). Qualitative data were described using numbers and percentages. χ^2 test for comparison of two or more groups. Quantitative data were described using mean and SD for parametric data after testing normality using the Kolmogorov–Smirnov test. Student's t test was used to compare two independent groups. The significance of the obtained results was judged at the 0.05 level.

RESULTS

The AVH group was statistically significant females (59.1%), single (63.6%), and nonworking (100%) (Table 1).

Table 2 shows the psychometric characteristics of patient groups; the AVH group had statistically significant higher scores in the PANSS positive ($P< 0.001$).

Table 3 highlights the differences in rCBF between the cases group ($n= 33$) and the control group ($n= 22$). There is a statistically significant increase in regional CBF in the cases group (patients with schizophrenia) in comparison to the control group in the following areas: right parietal, right STG, right caudate, right lateral prefrontal, right putamen, right thalamus, right temporal, right midcingulate cortex (MCC), and left MCC.

While, there is a statistically significant reduction in rCBF in the cases group (patients with schizophrenia) compared to the control group in the following areas: bilateral occipital, left parietal, left prefrontal, right insular, left insular, right ACC, left putamen and left temporal regions (Table 4).

Schizophrenic patients experiencing auditory verbal hallucination compared with the non-auditory verbal hallucination group

There is a statistically significant higher rCBF in schizophrenic patients in the AVH group compared with the schizophrenic non-AVH group in the following areas: right parietal, right STG, left caudate, right lateral prefrontal, right insular cortex, right putamen, right temporal, and left temporal.

However, there is statistically significant lower rCBF in schizophrenic patients with AVH group in comparison to schizophrenic non-AVH group in left parietal, right caudate, and left MCC.

Schizophrenic patients experiencing auditory verbal hallucination compared with the control group

There is a statistically significant higher rCBF in schizophrenic patients in the AVH group in comparison to the control group in the following areas: right parietal, right STG, right caudate, right lateral prefrontal, right putamen, right temporal, and left MCC.

However, there is statistically significant lower rCBF in schizophrenic patients with AVH group in comparison to the control group in the following areas: bilateral occipital, left parietal, left lateral prefrontal, left caudate, bilateral insular, right ACC, left putamen, and left temporal.

Schizophrenic patients non-auditory verbal hallucination compared with the control group

There is statistically significant higher rCBF in schizophrenic patients non-AVH group compared with the control group in the following areas: right putamen, right temporal, and left MCC.

However, there is statistically significant lower rCBF in schizophrenic patients non-AVH group in comparison to the control group in the following areas: bilateral occipital, bilateral insular, right ACC, left putamen, left thalamus, and left temporal.

DISCUSSION

This study aimed to evaluate CBF alterations of different brain regions in schizophrenic patients with AVH and without AVH compared with healthy control individuals using MRI using the pseudocontinuous ASL technique.

In the current study, sociodemographic characteristics of the studied groups revealed that the AVH group was statistically significant females (59.1%), single (63.6%), and nonworking (100%).

The presence of auditory hallucinations is a core feature, considering its distracting and annoying nature, which affects their functions. It is known that schizophrenia is associated with social and occupational dysfunction. The current results agreed with those of several recent studies (Abd El-Hay *et al.,* 2017; El-Azzab, 2018; Abd Elmonem *et al.,* 2021).

An important finding in this study is the presence of rCBF changes in schizophrenic patients compared with the control group detected using ASL.

There is a statistically significant increase in rCBF in the cases group compared with the control group in the following areas: right parietal, right STG, right caudate, right lateral prefrontal, right putamen, right thalamus, right temporal, correct MCC, and left MCC.

However, there is statistically significant reduction in rCBF in the cases group compared with the control group in the following areas: bilateral occipital, left parietal, left prefrontal, right insular, left insular, suitable ACC, left putamen, and left temporal regions.

Table 1: Sociodemographic characteristics of the studied groups:

	AVH group (*N*=22)	Non-AVH group (*N*=11)	Control group (*N*=22)	Test of significance
Age (years)	29.14±11.35	33.09±3.62	31.2±4.91	*t*= 1.12 *P*= 0.271
Sex [*n* (%)]				
Male	9(40.9)	11(100)	12(54.5)	$\hat{e}^2$= 10.73
Female	13(59.1)	0	10(45.4)	*P*= 0.001*
Marital status [*n* (%)]				
Single	14(63.6)	2(18.2)	5(22.7)	$\hat{e}^2$= 6.07
Married	8(36.4)	9(81.8)	17(77.2)	*P*= 0.014*
Occupation (nonworking) (working) [*n* (%)]				
	22(100)	11(100)	0	*P*< 0.001*
	0	0	22(100)	

$\hat{e}^2$, $\hat{e}^2$ test AVH, auditory verbal hallucination; *t*, Student *t* test. *Statistically significant if *P* value less than 0.0.

Table 2: The psychometric characteristics of patient groups:

	AVH group (*N*=22)	Non-AVH group (*N*=11)	Test of significance
PANSS +ve	25.64±7.71	15.90±3.27	*t*= 3.98 *P*< 0.001*
PANTS –ve	21.09±7.65	22.91±6.04	*t*= 0.687 *P*= 0.497
PANSS general	46.36±10.99	41.36±5.85	*t*= 1.40 *P*= 0.17
AHRS total	43.36±5.73	Non-AVH	

AVH, auditory verbal hallucination; AVHRS, the Auditory Vocal Hallucination Rating Scale; PANSS, Positive and Negative Syndrome Scale; *t*, Student's *t* test. *Statistically significant if *P* value less than 0.05.

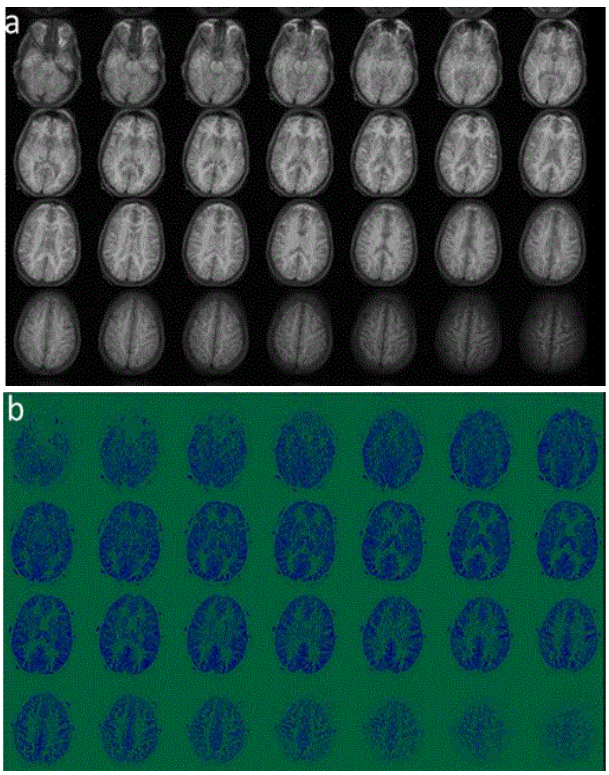

Figure 1a, b: Perfusion Quantification model (a) p-ASL model for generation of CBF colored quantitative maps.

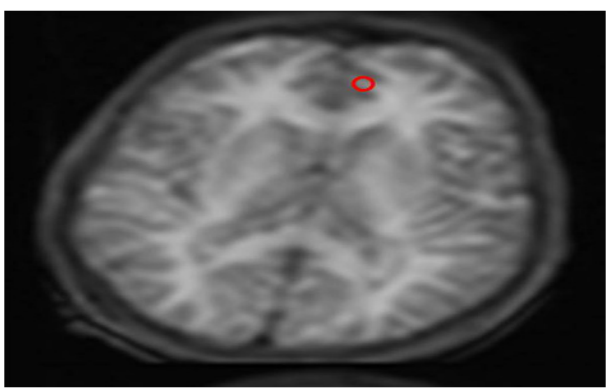

Figure 2: Place ROI (region of interest) in the left middle cingulate cortex to measure r CBF.

The detected variations in the regional CBF of these regions can be attributed to the pathophysiology of schizophrenia regardless of the occurrence of auditory hallucinations. Similar results were reported by recent studies (Cronenwett and Csernansky, 2010; Marenco *et al.,* 2012; Homan *et al.,* 2013).

The main finding in this study is the difference in rCBF between schizophrenic patients experiencing AVH and schizophrenic patients without AVH. There is a statistically significant higher rCBF in schizophrenic patients AVH group compared with the schizophrenic non-AVH group in the following areas: right parietal, right STG, left caudate, right lateral prefrontal, right insular cortex, right putamen, right temporal, and left temporal, while there is statistically significant lower rCBF in schizophrenic AVH group compared with the schizophrenic non-AVH group in left parietal, left lateral prefrontal, right caudate, and left MCC.

This study revealed the presence of significant changes in rCBF, which discriminate schizophrenic patients with AVH group from other groups (schizophrenic patients without AVH group and control group).

There is statistically significant higher rCBF in schizophrenic patients AVH group in the following areas: right parietal, right STG, right lateral prefrontal, right putamen, and right temporal, while there is statistically significant lower rCBF in schizophrenic patients with AVH group in left parietal and left lateral prefrontal.

These data are supported by previous research by Zhuo *et al.,* (2017) and Zhuo *et al.,* (2017) but inconsistent with the results of Homan *et al.,* (2013). This variation in findings may be due to different treatment durations with antipsychotic drugs and sample sizes.

The results of some recent studies have agreed with the theory that auditory hallucinations result from dysfunctions in sensory processing areas such as the primary auditory cortex (Dierks *et al.,* 1999; van de Ven *et al.,* 2005) or Broca's area (McGuire *et al.,* 1993). At the same time, other studies, such as Copolov *et al.,* (2003), have reported that the activity of the hippocampus and parahippocampal gyrus during AVHs supporting the role of memory processes in the hallucinatory experience. Others, such as the study by for example, Shergill *et al.,* (2000), highlighted the role of cortical and subcortical regions.

Although several types of research with different radiological techniques were done to accurately identify the areas of the brain responsible for auditory hallucinations, there is still a lack of consensus about the mechanism of occurrence of such hallucinations.

From the practical side, it is difficult to examine the patient with neuroimaging during the actual occurrence of auditory hallucinations.

The possibility of more than one type of hallucination in the same patient necessitates the existence of comparative studies to determine the responsibility of different areas of

Table 3: Regional cerebral blood flow with significant differences between cases group and control group:

	N	Mean	SD	Test of significance	Regional CBF in cases group
Right occipital					
Cases	33	46.1182	4.93555	*t*= 17.11	Reduced
Control	22	68.2727	4.32503	*P*< 0.001*	
Left occipital					
Cases	33	44.0818	4.04092	*t*= 21.23	Reduced
Control	22	67.9227	4.13854	*P*< 0.001*	
Right parietal					
Cases	33	69.1182	3.11513	*t*= 2.06	Increased
Control	22	67.2864	3.40032	*P*= 0.04*	
Left parietal					
Cases	33	70.3152	101.49529	*Z*= 4.37	Reduced
Control	22	93.8182	120.38307	*P*< 0.001*	
Right STG					
Cases	33	77.6909	8.08240	*t*= 5.69	Increased
Control	22	67.2864	3.40032	*P*< 0.001*	
Right caudate					
Cases	33	100.3939	96.29468	*Z*= 4.33	Increased
Control	22	67.2864	3.40032	*P*< 0.001*	
Left caudate					
Cases	33	69.5303	3.03444	*Z*= 1.46	Reduced
Control	22	93.8182	120.38307	*P*= 0.144	
Right prefrontal					
Cases	33	69.8030	3.69285	*t*= 2.55	Increased
Control	22	67.2864	3.40032	*P*= 0.014*	
Left prefrontal					
Cases	33	46.4061	4.38277	*Z*= 6.24	Reduced
Control	22	93.8182	120.38307	*P*< 0.001*	
Right insular					
Cases	33	52.7455	7.59626	*t*= 8.41	Reduced
Control	22	67.2864	3.40032	*P*< 0.001*	
Left insular					
Cases	33	46.4636	4.73345	*Z*= 6.24	Reduced
Control	22	93.8182	120.38307	*P*< 0.001*	
Right ACC					
Cases	33	46.2576	4.30255	*t*= 19.25	Reduced
Control	22	67.2864	3.40032	*P*< 0.001*	
Right putamen					
Cases	33	86.3364	5.94721	*t*= 13.59	Increased
Control	22	67.2864	3.40032	*P*< 0.001*	
Left putamen					
Cases	33	84.8545	4.45906	*Z*= 5.67	Reduced
Control	22	93.8182	120.38307	*P*< 0.001*	
Right thalamus					
Cases	33	87.2515	5.39248	*t*= 15.42	Increased
Control	22	67.2864	3.40032	*P*< 0.001*	
Right temporal					
Cases	33	86.4818	5.85195	*t*= 13.88	Increased
Control	22	67.2864	3.40032	*P*< 0.001*	
Left temporal					
Cases	33	86.4818	5.85195	*Z*= 5.67	Reduced
Control	22	93.8182	120.38307	*P*< 0.001*	
Right MCC					
Cases	33	83.1727	98.74323	*Z*= 5.04	Increased
Control	22	67.2864	3.40032	*P*< 0.001*	
Left MCC					
Cases	33	76.5667	5.58249	*t*= 6.19	Increased
Control	22	67.9545	4.13127	*P*< 0.001*	

CBF, cerebral blood flow; MCC, midcingulate cortex; STG, superior temporal gyrus; *t*, Student's *t* test; Z, Mann–Whitney *U* test. *Statistically significant if *P* value less than 0.05.

Table 4: Regional cerebral blood flow with significant differences among schizophrenic patients with auditory verbal hallucination group, schizophrenic patients without auditory verbal hallucination group, and control group:

	N	Mean	SD	Test of significance	Within group significance	Regional CBF
Right occipital						
AVH	22	46.3955	6.04810	*F*, *P*< 0.001*	*P*1= 0.636	
Non-AVH	11	45.5636	.79155		*P*2< 0.001*	Reduced
Control	22	68.2727	4.32503		*P*3< 0.001*	Reduced
Total	55	54.9800	11.90332			
Left occipital						
AVH	22	43.5227	4.85876	*F*, *P*< 0.001*	*P*1= 0.270	
Non-AVH	11	45.2000	0.78358		*P*2< 0.001*	Reduced
Control	22	67.9227	4.13854		*P*3< 0.001*	Reduced
Total	55	53.6182	12.46101			
Right parietal						
AVH	22	70.1136	2.46486	*F*, *P*= 0.005*	*P*1= 0.01*	Increased
Non-AVH	11	67.1273	3.42844		*P*2= 0.003*	Increased
Control	22	67.2864	3.40032		*P*3= 0.889	
Total	55	68.3855	3.32674			
Left parietal						
AVH	22	46.3955	6.04810	KW, *P*< 0.001*	*P*1< 0.001*	Reduced
Non-AVH	11	118.1545	170.61982		*P*2< 0.001*	Reduced
Control	22	93.8182	120.38307		*P*3= 0.665	
Total	55	79.7164	108.97390			
Right STG						
AVH	22	82.8136	3.33599	<0.0001*	*P*1< 0.001*	Increased
Non-AVH	11	67.4455	3.53139		*P*2< 0.001*	Increased
Control	22	67.2864	3.40032		*P*3= 0.002	
Total	55	73.5291	8.34685			
Left STG						
AVH	22	70.4909	2.21185	KW, *P*= 0.057	*P*1= 0.194	
Non-AVH	11	69.4818	4.39109		*P*2= .017*	Reduced
Control	22	93.8182	120.38307		*P*3= 0.646	
Total	55	79.6200	76.01515			
Right caudate						
AVH	22	91.5136	4.41505	KW *P*< 0.001*	*P*1< 0.001*	Reduced
Non-AVH	11	118.1545	170.61982		*P*2< 0.001*	Increased
Control	22	67.2864	3.40032		*P*3= 0.702	
Total	55	87.1509	75.94306			
Left caudate						
AVH	22	70.5727	2.16271	KW, *P*= 0.003*	*P*1= 0.001*	Increased
Non-AVH	11	67.4455	3.53139		*P*2= 0.015*	Reduced
Control	22	93.8182	120.38307		*P*3= 0.486	
Total	55	79.2455	76.06224			
Right prefrontal						
AVH	22	71.1409	3.09156	*F*, *P*< 0.001*	*P*1= 0.002*	Increased
Non-AVH	11	67.1273	3.42844		*P*2< 0.001*	Increased
Control	22	67.2864	3.40032		*P*3= 0.896	
Total	55	68.7964	3.75845			
Left prefrontal						
AVH	22	45.8318	3.37376	*F*, *P*= 0.089	*P*1= 0.952	
Non-AVH	11	47.5545	5.94884		*P*2= 0.043*	Reduced
Control	22	93.8182	120.38307		*P*3= 0.108	
Total	55	65.3709	78.71900			
Right insular						
AVH	22	56.5000	5.03038	*F*, *P*< 0.001*	*P*1< 0.001*	Increased
Non-AVH	11	45.2364	6.20262		*P*2< 0.001*	Reduced
Control	22	67.2864	3.40032		*P*3< 0.001*	Reduced
Total	55	58.5618	9.50662			
Left insular						
AVH	22	47.0773	3.82597	KW *P*< 0.001*	*P*1= 0.411	
Non-AVH	11	45.2364	6.20262		*P*2< 0.001*	Reduced

Table 4: (Continued)

	N	Mean	SD	Test of significance	Within group significance	Regional CBF
Control	22	93.8182	120.38307		*P*3< 0.001*	Reduced
Total	55	65.4055	78.72257			
Right ACC						
AVH	22	45.6091	3.16783	*F*, *P*< 0.001*	*P*1= 0.187	
Non-AVH	11	47.5545	5.94884		*P*2< 0.001*	Reduced
Control	22	67.2864	3.40032		*P*3< 0.001*	Reduced
Total	55	54.6691	11.11585			
Right putamen						
AVH	22	88.1318	6.14750	*F*, *P*< 0.001*	*P*1= 0.003*	Increased
Non-AVH	11	82.7455	3.54157		*P*2< 0.001*	Increased
Control	22	67.2864	3.40032		*P*3< 0.001*	Increased
Total	55	78.7164	10.68482			
Left putamen						
AVH	22	85.8409	4.69991	KW, *P*< 0.001*	*P*1= 0.069	
Non-AVH	11	82.8818	3.28902		*P*2< 0.001*	Reduced
Control	22	93.8182	120.38307		*P*3< 0.001*	Reduced
Total	55	88.4400	75.28103			
Left thalamus						
AVH	22	65.6818	5.79200	KW, *P*= 0.214	*P*1= 0.401	
Non-AVH	11	67.1273	3.42844		*P*2= 0.103	
Control	22	93.8182	120.38307		*P*3< 0.001*	Reduced
Total	55	77.2255	76.40852			
Right temporal						
AVH	22	88.2818	6.07035	*F*, *P*< 0.001*	*P*1= 0.003*	Increased
Non-AVH	11	82.8818	3.28902		*P*2< 0.001*	Increased
Control	22	67.2864	3.40032		*P*3< 0.001*	Increased
Total	55	78.8036	10.71724			
Left temporal						
AVH	22	88.2818	6.07035	KW, *P*< 0.001*	*P*1= 0.007*	Increased
Non-AVH	11	82.8818	3.28902		*P*2< 0.001*	Reduced
Control	22	93.8182	120.38307		*P*3< 0.001*	Reduced
Total	55	89.4164	75.29449			
Left MCC						
AVH	22	73.4091	3.31690	*F*, *P*< 0.001*	*P*1< 0.001*	Reduced
Non-AVH	11	82.8818	3.28902		*P*2< 0.001*	Increased
Control	22	67.9545	4.13127		*P*3< 0.001*	Increased
Total	55	73.1218	6.57534			

AVH, auditory verbal hallucination; *F*, one way analysis of variance test; KW, Kruskal–Wallis test; MCC, midcingulate cortex; STG, superior temporal gyrus. *P1*: difference between AVH and non-AVH. *P2*: difference between AVH and control group. *P3*: the difference between control and non-AVH. *Statistically significant if *P* value less than 0.05.

the brain for each type of hallucination and the small size of the samples.

Before conclusion, various limitations of this study should be mentioned; the study's small sample size and the radiological assessment could not be done during the actual occurrence of auditory hallucinations. The possibility of more than one type of hallucination in the same patient necessitates the existence of comparative studies to determine the responsibility of different areas of the brain for each type of hallucination.

CONCLUSION

This study revealed the presence of significant changes in rCBF, which discriminate schizophrenic patients with AVH group from other groups (schizophrenic patients without AVH group and control group); there is a statistically significant higher rCBF in schizophrenic patients in the AVH group in the following areas: right parietal, right STG, right lateral prefrontal, right putamen, and right temporal. However, there is statistically significant lower rCBF in schizophrenic patients with AVH group in left parietal and left lateral prefrontal.

Potential implications: this study has important clinical implications.

This study highlighted significant changes in rCBF that discriminate schizophrenic patients with AVH group from other groups (schizophrenic patients without AVH group and control group).

Exploring the path physiology of the brain underlying auditory hallucinations has considerable benefits, especially

with using updated radiological techniques. It will open new horizons for treating auditory hallucinations in different approaches such as neurosurgery and transcranial magnetic stimulation. In addition, research can be applied to delusions to achieve a new perspective for the diagnosis and treatment of psychotic disorders.

ACKNOWLEDGEMENTS

The authors thank all the participants for their time and effort.

Authors' contributions: Y.S: prepared the study design, psychiatric evaluation , analysis and interpretation of data, manuscript drafting and revising. G.A.A: supervising MRI acquisition, carrying out postprocessing and interpretation of ASL results, calculating rCBF on different locations ,helping in data analysis, and conducting medical assessment. Both authors have read and approved the final manuscript. I.H.R.E: prepared the study design, psychiatric evaluation, analysis and interpretation of data, manuscript drafting, and revising.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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