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Do patients with hallucinations imagine speech right?

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ABSTRACT

A direct relationship between auditory verbal hallucinations (AVHs) and decreased left-hemispheric lateralization in speech perception has been often described, although it has not been conclusively proven. The specific lateralization of AVHs has been poorly explored. However, patients with verbal hallucinations show a weak Right Ear Advantage (REA) in verbal perception compared to non AVHs listeners suggesting that left-hemispheric language area are involved in AVHs. In the present study, 29 schizophrenia patients with AVHs, 31 patients with psychotic bipolar disorder who experienced frequent AVHs, 27 patients with schizophrenia who had never experienced AVHs and 57 healthy controls were required to imagine hearing a voice in one ear alone. In line with previous evidence healthy controls confirmed the expected REA for auditory imagery, and the same REA was also found in non-hallucinator patients. However, in line with our hypothesis, patients with schizophrenia and psychotic bipolar disorder with AVHs showed no lateral bias. Results extend the relationship between abnormal asymmetry for verbal stimuli and AVHs to verbal imagery, suggesting that atypical verbal imagery may reflect a disruption of inter-hemispheric connectivity between areas implicated in the generation and monitoring of verbal imagery and may be predictive of a predisposition for AVHs. Results also indicate that the relationship between AVHs and hemispheric lateralization for auditory verbal imagery is not specific to schizophrenia but may extend to other disorders as well.

1. Introduction

Auditory verbal hallucinations (AVHs), also known as 'hearing voices', are psychotic symptoms common to a variety of psychiatric disorders including schizophrenia (Aleman and Laroi, 2008; Hugdahl, 2003) and bipolar disorder (BD) (Toh et al., 2015). Approximately 70–80% of people with schizophrenia (Aleman and Laroi, 2008) and 11–63% of people with BD (Toh et al., 2015) experience AVHs. Moreover, since AVHs occur in the context of language, it has been hypothesized that such sensory experiences might be associated with dysfunction of the left, rather than the right hemisphere, since the left hemisphere is dominant for language-related processing in a large majority of individuals (see e.g., David, 1999; van der Gaag, 2006).

More specifically, abnormal lateralization of brain regions involved in speech perception, localized to the temporal lobes, has been proposed as an underlying mechanism of AVHs (Bruder et al., 1995; Wexler and Heninger, 1979; 1991; Stephane et al., 2001; Hugdal et al., 2008a). The auditory pathways from sensory organs to processing areas are mainly contralateral rather than ipsilateral, and speech processing for most individuals is lateralized to the left temporal lobe more than to the right temporal lobe (Kimura, 1967). These findings suggest that AVHs might reflect a distinguishing brain functional asymmetry that favors right over left temporal activation (Pollmann et al., 2002; Brancucci et al., 2004). In line with this, several structural neuroimaging studies in schizophrenia have reported significant correlations between AVHs and reduced size of the left temporal lobe regions (Barta et al., 1990; Flaum et al., 1995; Levitan et al., 1999; Hugdal et al., 2008a) or abnormal connectivity within auditory brain networks (Allen et al., 2012; Ćurčić-Blake et al., 2017). Nonetheless, experimental evidence for this hypothesis remains inconclusive.

A possible empirical test to investigate a potential association between AVHs and abnormal lateralization of speech perception is the dichotic listening task (DLT) (Green et al., 1994; Hugdahl et al., 2009; Løberg et al., 2004). During a standard dichotic listening test a

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participant is simultaneously presented with two different auditory stimuli (usually speech), one in each ear, and required to report the content of the message they were asked to attend to. The resulting Right Ear Advantage (REA) found by means of this paradigm in healthy individuals is considered a behavioral evidence of the left-hemispheric superiority for language processing (for a review see Hugdahl and Westerhausen, 2016), as also confirmed by electrical brain stimulation techniques (e.g., Prete et al., 2017). Furthermore, many previous behavioral studies demonstrated a reduced REA in schizophrenia during standard dichotic listening tests (e.g., Wale and Carr, 1988; Green et al., 1994; Conn and Posey, 2000; Hugdahl et al., 2009, 2008; Pollmann et al., 2002; Løberg et al., 2004; Rossell and Boundy, 2005). Results have been interpreted as indicating a reduced left-hemispheric lateralization for speech perception associated with auditory hallucinations.

However, the question of the REA as a simple measure of laterality during a dichotic listening task has been questioned when the individuals who are tested may have disrupted speech perception (David et al., 1966; Woodruff et al., 1995; McKay et al., 2000). Particularly, it has been hypothesized that AVHs might "compete" with external speech within the temporal cortex by eliciting neuronal activation in the left temporal lobe that blocks reception of speech stimuli when presented e.g., in a dichotic mode (Hubl et al., 2007; Hugdahl et al., 2009). Further, fMRI studies have found contradicting results showing that externally presented speech stimuli can be associated with both increased and decreased activation in left temporal lobe areas in hallucinating patients (see for review, Hugdahl et al., 2009; Woodruff et al., 1997; Lennox et al., 2000; Shergill et al., 2004; Zhang et al., 2008). In particular, some researchers using a speech listening paradigm reported no correlation between abnormal functional lateralization of language related areas, comprising the left temporal gyrus (i.e., increased right hemispheric activation), and severity of positive symptoms in schizophrenia, suggesting that the decrease in functional asymmetry might be a characteristic of psychosis but not necessarily the source of AVHs (Dollfus et al., 2005; Alary et al., 2013). Therefore, while a direct relationship between AVHs and decreased language perception lateralization has been hypothesized, the presence of such a relationship must still be established.

An alternative method for assessing hemispheric lateralization for language-related processing including speech perception in healthy and in clinical population is to use auditory imagery paradigms (McGuire et al., 1996a; Prete et al., 2016, 2018, 2019). Recently, Prete et al. (2016) investigated hemispheric lateralization for verbal auditory imagery in healthy individuals. The authors found that participants asked to imagine hearing a voice or a sound unilaterally showed a strong preference to localize the self-generated auditory image at their right ear suggesting that verbal imagery are lateralized to the left hemisphere. In a different study, a dichotic listening task was used by presenting either a voice with different intensity levels and a white noise stream in the two ears, or white noise in both ears: when asked to localize the voice, participants revealed the REA, even when no verbal stimuli were presented, suggesting that the REA effect extends beyond the domain of auditory perception to that of auditory imagery (Prete et al., 2018). These findings suggest that auditory imagery paradigms could be useful in the investigation of hemispheric imbalance in the production of auditory verbal imagery.

Cognitive models of AVHs propose that internally generated speech or verbal imagery are perceived as auditory hallucinations due to abnormal lateralization of speech processing and a failure of frontal executive functions which may subserve the sense of ownership of one's own imagery (Allen et al., 2007; Heinks-Maldonado et al., 2007; Mammarella et al., 2010; Fairfield et al., 2016). Numerous studies have shown that AVHs and verbal imagery are associated with overlapping neural networks, including temporal and frontal areas in the left hemisphere and their contralateral homologues (McGuire et al., 1996b; Allen et al. 2007; Raij and Riekki, 2012; Linden et al., 2011). Therefore, if the neuronal origin of verbal imagery implicates the same areas as AVHs, auditory imagery paradigms could be valid tools for studying cerebral asymmetries associated with AVHs. Indeed, McGuire et al. (1996a) found that when schizophrenia patients with AHVs imagine hearing a person speaking to them, a kind of 'external' stimulus, although internally generated, they showed reduced activation in the left temporal regions compared to both healthy controls and schizophrenic patients with no history of hallucinations. In a survey on the phenomenological features of AVHs, McCarthy-Jones et al. (2014) found that among psychiatric patients who reported their hallucinations as originated "outside the head", 38% localized the voices "outside all around", 29% "outside left", and 22% "outside right". Still, the laterality of auditory imagery in patients with AHVs has not been examined despite its potential relevance for understanding auditory hallucinations in clinical populations.

Accordingly, in this study we aimed to directly investigate lateralization for auditory imagery in a group of schizophrenia patients to further investigate the nature of language lateralization in verbal hallucinations. We hypothesized that patients with AVHs would show reduced lateralization for auditory verbal imagery. Moreover, to investigate if such differences are specifically related to a vulnerability to hallucinations, as opposed to the illness of schizophrenia, we compared hallucinators with schizophrenic patients without a history of hallucinations (non-hallucinators). Moreover, to investigate whether the possible decreased hemispheric lateralization for auditory imagery is a specific characteristic of schizophrenic patients opposed to patients with other psychiatric disorders with a strong predisposition to experience hallucinations, we compared schizophrenia patients with psychotic bipolar disorder patients. Finally, the three group of patients (schizophrenia with AVHs, schizophrenia without AVHs, bipolar with AVHs) were compared to a group of healthy participants. We expected to confirm the REA by means of the imagery paradigm in the healthy sample and in schizophrenia patients without history of AVHs, and we hypothesized that lateralization for auditory imagery would be decreased in hallucinators regardless of diagnosis (schizophrenia and bipolar disorder).

2. Material and methods

2.1. Participants

A total sample of 144 participants took part in the study, including 87 psychiatric patients and 57 healthy controls. The study included 29 patients with schizophrenia with a history of AVHs (hallucinators), 27 patients with schizophrenia who had never experienced AVHs (non-hallucinators) and 31 patients with psychotic bipolar disorder who experienced frequent AVHs. Among the schizophrenia group with a history of hallucinations, three were diagnosed as schizoaffective. Of the 31 individuals with psychotic bipolar disorder, 23 were manic and 8 were depressed. Patients were recruited from consecutively admissions to an acute psychiatric unit. Patients from all diagnostic categories were in partial remission. The patient groups were matched for age, gender, age of onset and duration of illness and general psychopathology. Patients and healthy controls were matched for age and gender (Table 1). Exclusion criteria for all participants included report of a history of severe head trauma, stroke, neurological disease, severe medical illness, or alcohol or substance abuse in the past 6 months.

The study was approved by the local Institutional Review Board. In accordance with the Declaration of Helsinki, all participants gave written informed consent prior to inclusion in the study.

2.1.1. Diagnosis and assessment

Diagnoses were made according to the DSM-5 criteria, as determined by the structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-5) (SCID-5-CV) by a board-certified attending research team of psychiatrists (First et al., 2015). Psychotic symptoms were rated in all patient groups with the

Table 1
Presents demographic and clinical characteristics of the study sample.

	Schizophrenia (hallucinators)	Schizophrenia (non-hallucinators)	Bipolar Disorder with psychosis	Controls
N	29	27	31	57
Age	38.8 (11.9)	41.4 (10.2)	40.1 (11.7)	38.7 (10.6)
Gender F/M	13/16	12/15	17/14	28/29
Education (years completed)	12.2 (3.5)	9.7 (3.2)	12.6 (4.1)	16.1 (2.1)
EHI	78.7 (27.8)	75.3 (15.0)	71.1 (43.2)	81.3 (9.0)
Age of onset (y)	23.6 (2.9)	24.1 (2.4)	22.8 (4.0)	
Duration of illness (y)	15.2 (10.6)	17.2 (9.0)	16.3 (12.0)	
PANSS (total score)	64.8 (16.1)	63.7 (13.0)	54.5 (8.7)	
PANSS (negative score)	15.7 (5.4)	15.5 (5.4)	8.9 (6.4)	
PANSS (positive score)	14.5 (5.9)	13.8 (3.4)	10.4 (5.0)	
PANSS (general score)	35.1 (8.7)	34.3 (8.4)	35.2 (6.2)	
HAM-D	7.0 (3.0)	6.4 (3.1)	10.0 (5.4)	
YMRS	7.1 (2.8)	7.3 (2.4)	14.6 (6.9)	

Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987). Symptoms of mania and depression were quantified in the patient group with bipolar disorder using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Hamilton Depression Rating Scale (HAM-D (17); Hamilton, 1960), respectively. We recruited patients who, over the course of their illness, had consistently experienced prominent and frequent auditory verbal hallucinations during exacerbations. Information about individual's hallucinations was collected from their medical record and anamnesis data collected before beginning the experimental session (Mcguire et al., 1996). The presence of auditory hallucinations was defined as a PANSS P3 hallucination score of 4 or higher with validation of the auditory nature of the hallucinations during the SCID interview. To further compare the severity of the AVHs the clinical sample (patients with schizophrenia and patients with psychotic bipolar disorder) was also administered the Cardiff Anomalous Perceptions Scale (CAPS) (Bell et al., 2006, 2011). The 32-item CAPS is a reliable, self-report scale, that includes subscale measuring distress, intrusiveness, and frequency of anomalous experiences. The sum of the scores of selected CAPS items (11, 13, 28) was used as a measure of verbal hallucination severity (i.e., distress, intrusiveness, frequency) in hallucinators. This score reflects severity of all hallucinations experienced, not just AVHs (Badcock et al., 2015). Three principal components which included "clinical psychosis", "temporal lobe disturbance" and chemiosensation (i.e., largely olfactory and gustatory) were used. Handedness was assessed by the Edinburgh Handedness Inventory Questionnaire (EHI) (Oldfield, 1971). This questionnaire is composed of 20 items describing different motor activities. On the response sheet, each item is followed by two columns labelled left and right. Participants are instructed to mark a "+" in the appropriate column if the activity was preferentially carried out using one hand/foot/eye/ear, a " + +" if the other hand/foot/eye/ear would never be used unless in a forced situation, and a "+" in both columns in case of real indifference on which side to use. In addition, participants are asked whether they had any first-degree (father, mother, grandparents, uncle, aunt, cousins) left-handed relatives and whether they had ever experienced any tendency toward the use of the left-hand and whether this tendency had been corrected. The overall laterality index is calculated using all the items according to the formula [(Right preference – Left preference)/(-Right preference + Left preference) x 100].

2.2. Stimuli and procedure

To investigate lateralization of verbal auditory imagery, we adopted a two-phase procedure as done in previous studies (Prete et al., 2016, 2019). During the first phase, we asked each participant to sit without crossing their legs, feet or arms, to place their hands on their knees and then to close their eyes and relax. After, the participant put on a pair of sound-attenuating headphones and was verbally instructed to imagine hearing a lateralized auditory input. Participants were explicitly invited to imagine hearing a voice in one ear alone. The instructions did not contain specific references as to what was to be imagined. After a brief interval, the experimenter asked the participant whether they had formed a vivid image. If the participant confirmed having a clear image in mind, the experimenter asked in which ear the content had been heard, otherwise the instructions were repeated. Finally, the participant was instructed to briefly describe the content of the imagery, confirming that the required task had been carried out (i.e. that the voice had been imagined). In the second phase, participants completed the Edinburgh Handedness Inventory (Oldfield, 1971). The test was administered at the end of the procedure, to avoid any influence of the test on the lateralized response of participants.

2.3. Statistical analysis

In a first analysis, group differences were analyzed with a one-way analysis of variance (ANOVA). For all analyses, Scheffé post-hoc analyses were computed to identify the sources of eventual differences. Chi-square analyses were used for categorical variables. In the second analysis aimed to investigate the possible presence of a lateral preferences in imagining a voice, the frequency of Left Ear (LE) and Right Ear (RE) responses were compared in each group (three groups of patients and healthy controls). Finally, to test for possible group differences, $\chi 2$ tests were used to compare the proportion of REA in the different groups.

3. Results

Groups did not differ for age ($F(3,140) = 0.20$, $p = 0.8$), sex distribution (all $\chi 2$, $p > 0.05$) and EHI laterality quotients ($F(3,140) = 1.20$, $p = 0.3$). There was a significant effect of group for years of education ($F(3,140) = 19.9$, $p = 0.001$). However, the ANOVA showed that the schizophrenia and bipolar disorder groups were comparable for education ($F(2,84) = 0.56$, $p = 0.5$). We also examined differences between the patient groups for clinical data. There were no significant differences between the three groups of patients in age of onset, $F(2,84) = 1.09$, $p = 0.3$, and duration of psychosis, $F(2,84) = 0.2$, $p = 0.7$. All participants had a measure of PANSS P3 hallucination. An ANOVA revealed a significant effect of groups on PANSS P3 hallucination severity ($F(2,84) = 64.5$, $p < 0.001$). There was no significant difference between the schizophrenia with AVH (mean = 4.62, SD = 0.67) and bipolar disorder with psychosis (mean = 4.12, DS = 0.34), ($p = 0.1$). There was a significant difference between both hallucinators (schizophrenia with AVH, bipolar disorder with psychosis) and non-hallucinators (mean = 0.24, DS = 0.43) ($p < 0.05$). Participants with schizophrenia (hallucinators) experienced significantly higher frequency, but not distress and intrusiveness associated with their hallucinations (CAPS items 11, 13, 28) compared to participants with bipolar with psychosis ($F(1,58) = 4.13$, $p = 0.04$). Comparison on PANSS scores, excluding the PANSS hallucination item, indicated a main effect of group on positive, $F(2,84) = 7.6$, $p < 0.001$, negative, $F(2,84) = 14.5$, $p < 0.001$, and total scores $F(2,84) = 5.9$, $p = 0.003$. Post-hoc analyses revealed that schizophrenia patients had a higher PANSS total score, and more positive and negative symptoms than bipolar patients (all, $p < 0.05$). There were no differences between the two schizophrenia groups (all p values > 0.05). There was a significant effect of groups on HAM-D, $F(2,84) = 6.8$, $p = 0.001$, and YMRS, $F(2,84) = 25.0$, $p < 0.001$. As expected, post-hoc analyses revealed that bipolar patients had more mood symptoms than schizophrenia patients (all p values < 0.05). All patients were receiving antipsychotic medication at the time of the study (37 on risperidone, 25 on olanzapine, 18 on quetiapine, 11 on aripiprazole). Four patients were taking more than one antipsychotic. All patients with bipolar disorder and ten participants with schizophrenia were taking mood stabilizer medications. Six patients with bipolar disorder were receiving antidepressant medication. There were no group differences in the proportion of antipsychotics being currently taken (all $\chi 2$, $p > 0.05$) There was, however, a significant group difference in the proportion of participants taking mood stabilizers, with a significantly greater proportion of participants with bipolar disorder with psychosis taking these medications compared to participants with schizophrenia, $\chi 2\,(1) = 5.89$, $p = 0.001$.

Comparisons between LE and RE responses in each group revealed that schizophrenic participants with AVHs imagined the voice in the LE 62.1% ($N = 18$) of the time, whereas they imagined the voice in the RE 37.9% ($N = 11$) of the time. The asymmetry was not statistically significant ($\chi 2\,(1) = 1.13$, $p = 0.2$). Participants with psychotic bipolar disorder imagined the voice in the LE 51.6% ($N = 16$) of the time and 48.4% ($N = 15$) of the time in the RE The asymmetry was not statistically significant ($\chi 2\,(1) = 0.02$, $p = 0.8$). On the contrary, 71.9% ($N = 41$) of the healthy controls and 74.1% ($N = 20$) of the schizophrenic participants without AVHs imagined the voice in the RE while 28.1% ($N = 16$) of healthy controls and 25.9% ($N = 7$) of schizophrenic participants without AVHs imagined the voice in the LE. The asymmetry was statistically significant in both cases, $\chi 2\,(1) = 7.47$ $p = 0.006$ and $\chi 2\,(1) = 4.28$ $p = 0.03$, respectively (Fig. 1).

In the chi-square tests, no significant differences emerged between schizophrenia patients with AVHs and patients with psychotic bipolar disorder (with AVHs) in the proportion of LE and RE ($p > 0.05$). Similarly, the non-hallucinating schizophrenia patients showed a RE comparable to normal controls ($p > 0.05$). We performed logistic regression analyses to assess the association between individual differences in symptom severity (PANSS, HAMD and YRMS scores) and lateral preferences in imagining voice ("LE" or "RE"). We found no association between the variables (all $p > 0.05$).

The mean CAPS scores for clinical groups with AVHs are provided in Table 2. Group differences on frequency, duration, distress, and intensity of AVHs were non-significant (all p values were greater than 0.1). As expected, schizophrenia patients had a higher CAPS score of the clinical psychosis factor than bipolar patients ($t = 2.0$, $df = 28$, $p = 0.02$). Based on these findings, in order to address whether there were differences between LE and RE participants in the CAPS scores, we combined results across diagnostic groups (schizophrenia and bipolar disorder with AVHs) to increase power. Independent t-tests revealed that LE participants compared to RE participants exhibited significantly higher scores of temporal lobe ($t = 1.1$, $df = 25$, $p = 0.05$) and chemosensation ($t = 2.4$, $df = 25$, $p = 0.01$) factors. There was no significant difference for any other subscale score.

4. Discussion

In line with the neurodevelopmental hypothesis of schizophrenia, the existence of decreased brain asymmetry has long been thought to underlie much of the behaviour and cognition of these patients. It has been proposed that laterality and schizophrenia may have a common genetic basis and that schizophrenia might even be the consequence of a failure in brain lateralization (Crow, 1997; Shenton et al., 2001; Oertel et al., 2010; Altamura et al., 2012; Alary et al., 2013). Ear preference for auditory language processing has been extensively used as an easy-to-measure proxy of brain asymmetry since it has been considered as a manifestation of cerebral dominance and thus is closely correlated with anatomical asymmetry. However, contradicting results have been reported from studies that have used externally presented speech stimuli (e.g., DL) to establish a direct relationship between AVHs and abnormal hemispheric lateralization for speech perception. The present study investigated the lateralization for subjective imagery of auditory content in patients with schizophrenia with ongoing AVHs. These patients were compared to patients with psychotic bipolar disorder, non-hallucinating patients with schizophrenia and healthy individuals using a paradigm requiring pure mental imagery. Only a few studies have examined brain asymmetry involved in auditory imagery (McGuire et al., 1995, 1996a; Shergill et al., 2004). To our knowledge, the current study is the first investigation concerning prevalence of ear preference for auditory verbal imagery in schizophrenia that involves standardized procedures and a validated scale (CAPS) for dimensional measurement (frequency, being distressing, intrusiveness) of hallucinations. Our main finding was a clear right ear preference for auditory imagery in both healthy controls and schizophrenia patients without AVHs while patients with schizophrenia and psychotic bipolar disorder with AVHs showed no lateral bias. These findings concur with the results by Prete et al. (2016, 2018) showing a REA for hearing imagined voices in healthy individuals, suggesting - at behavioral level - a left hemispheric dominance for auditory imagery. The higher prevalence of non-right advantage for auditory imagery in patients with AVHs, compared to both controls and

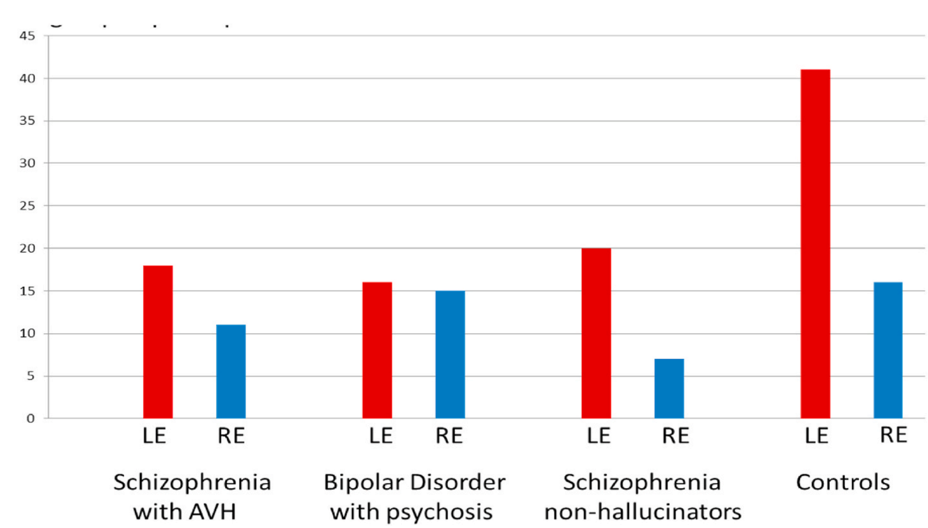

Fig. 1. Lateral preference in imaging voce (left ear = LE; right ear = RE) in each group of participants.

Table 2
Descriptive statistic for CAPS in Schizophrenia and Bipolar Disorder samples.

	Schizophrenia (hallucinators)	SCZ (LE)	SCZ (RE)	Bipolar Disorder with psychosis	BD (LE)	BD (RE)
CAPS-Total	11.6 (7.9)	12.9 (8.1)	9.4 (7.5)	10 (8.0)	9.0 (8.6)	9.7 (5.9)
Verbal Hallucinations*	1.7 (0.7)	2 (0.7)	1.7 (0.8)	1.5 (0.7)	1.3 (0.8)	1.6 (0.7)
Perceptual anomalies	8.4 (6.3)	11.2 (8.0)	7.6 (6.7)	8.4 (7.5)	7.6 (7.9)	9.4 (7.1)
CAPS frequency*	6.0 (4.7)	6.6 (4.7)	5.9 (4.7)	3.9 (3.3)	4.0 (3.9)	3.8 (2.6)
CAPS intrusiveness*	6.4 (4.8)	6.9 (5.2)	6.0 (4.2)	4.3 (3.9)	4.4 (4.6)	4.3 (3.1)
CAPS distress*	6.5 (4.8)	6.9 (5.1)	5.1 (4.5)	4.5 (4.0)	4.1 (4.1)	4.9 (3.8)
CP	21.5 (16.3)	24.6 (18.4)	16.5 (11.3)	13.2 (14.3)	12.5 (13.3)	10.7 (9.6)
TLD	35.9 (36.3)	44.5 (41.5)	21.9 (20.3)	35.9 (40.7)	31.1 (38.7)	32.2 (27.9)
C	19.3 (23.4)	26.3 (27.0)	18.0 (8.5)	19.1 (26.3)	11.6 (17.8)	21.5 (24.3)

CAPS-Total = Cardiff Anomalous Perceptions Scale, total number of items endorsed. *CAPS verbal hallucinations (items 11, 13, 28); CAPS perceptual anomalies (all remaining CAPS items); CP = Clinical Psychosis; TLD = Temporal Lobe Disturbance; C = Chemosensation. Mean (SD).

non-hallucinating patients in our study, supports previous evidence suggesting that AVHs are associated with abnormal brain lateralization of the temporal lobes involved in auditory imagery. In this frame, we must highlight that a direct comparison among patients with and without AVHs and healthy controls in a more conventional paradigm, such as DL, would be useful to confirm this conclusion. In line with the present behavioral results, however, earlier neuroimaging studies of auditory verbal imagery have shown that patients with schizophrenia with AVHs exhibit reduced left temporal lobe functional asymmetry during auditory verbal imagery as compared to normal controls (McGuire et al., 1995; Shergill et al., 2004). Particularly, our results are consistent with the results from a PET study in schizophrenia patients done by McGuire et al. (1996) who instructed their patients to imagine hearing a person speaking to them. They found that hallucinators displayed reduced left and increased right temporal cortical response during auditory verbal imagery compared to both controls and non-hallucinator schizophrenia patients. This abnormal activity in the left and right temporal regions when hallucinators imagined speech, suggests, in accordance with our behavioral findings, a reduced leftward asymmetry in brain areas thought to be implicated in perceiving inner speech and auditory verbal imagery. It is possible that patients with schizophrenia may fail to inhibit the ipsilateral auditory cortical response during DL through transcallosal pathways (Brancucci et al., 2004). Since in our study schizophrenia patients with and without AVHs were matched for age of onset and duration of illness and general psychopathology, the absence of a right ear bias in auditory imagery for voices may be attributed to their predisposition to AVHs as opposed to psychosis in general. Patients with schizophrenia and bipolar disorder with AVHs exhibit similarities regarding non-right bias for auditory imagery which implies that decreased imagery lateralization may not be specifically related to schizophrenia. This is consistent with the results described in previous studies using the DL procedure, showing that - compared to normal controls - psychotic bipolar patients failed to show the normal right-ear (left-hemisphere) advantage (Bruder et al., 1995; Kaprinis et al., 1995; Najt and Hausmann, 2014). This reduction in right-ear advantage in bipolar patients has been related to left temporal lobe dysfunction associated with psychotic symptoms such as auditory hallucinations as opposed to the affective manifestations of mania (Kaprinis et al., 1995; Sommer, 2007; Bozikas et al., 2008). Current literature suggests that AVHs may reflect a disruption of cortico-cortical connectivity between areas concerned with normal speech perception. In particular, several studies evidenced altered microstructure of the interhemispheric auditory pathways which significantly contribute to abnormal asymmetry of speech perception and the emergence of AVHs (Gavrilescu et al., 2010; Mulert et al., 2012; Wigand et al., 2015; Leroux et al., 2017; Steinmann et al., 2014, 2019). Since auditory verbal imagery has its neuronal origin in the same brain regions and networks that underlie speech perception, it can be assumed that our results might reflect similar brain functional asymmetry that favors right over left temporal activation in patients with AVHs. The finding that higher scores in the temporal lobe component of the CAPS is associated with abnormal asymmetry for verbal imagery could also be interpreted as support to the arguments that temporal lobe disturbance represent a potential shared mechanism underlying the symptom of AVHs. Our results are also in line with converging evidence that indicates that inter-hemispheric dysconnectivity associated with psychotic symptoms are common to both schizophrenia and bipolar disorder (see for review, O'Donoghue et al., 2017). Therefore, a predisposition for AVHs might be associated, regardless of diagnosis, with abnormal organization of temporal language-related areas and a failure to activate areas implicated in verbal imagery. This pattern of results is even more powerful considering the fact that all the subsamples described in this study did not differ in the laterality index, as measured by means of the EHI, meaning that the absence of the REA in patients with AVHs cannot be ascribed to a possible less extreme lateralization (i.e., right-handedness), often described in schizophrenia (Sommer et al., 2001) and in bipolar disorder (Klar, 1999).

Last, our study was limited by several factors that merit consideration. First, hallucinations as well as lateralization of verbal imagery were identified by self-report. There is no objective way of verifying these experiences as described by the individual. It must be noticed, however, that a similar paradigm has already been used (Prete et al., 2016, 2019), and the results found here with healthy participants confirm those previously described, showing the expected REA. Second, verbal imagery lateralization is probably not a categorical function. To reduce any systematic bias in arbitrarily assigning non-left-hemispheric lateralization, future studies examining quantitative data of verbal imagery are clearly needed, but also in this case we should highlight that a parametric analysis of the heard/imagined verbal stimuli presented by means of a DL paradigm revealed a positive correlation between the perceptual REA and the imagery REA in healthy participants (Prete et al., 2018). Finally, ear bias is simply an indirect and developmentally labile proxy of anatomical asymmetry. Nonetheless, our findings are in line with many previously published work suggesting that non-right bias for auditory imagery might be associated with brain asymmetry in the temporal areas (e.g., Ocklenburg et al., 2014).

In conclusion the present results indicate a strong relationship between abnormal asymmetry for verbal imagery and hallucinations. This raises the possibility that atypical verbal imagery could be predictive of a disposition to auditory verbal hallucinations. To the extent that schizophrenia can be differentiated pathophysiologically from other disorders that have been associated with aberrant lateralization of language function such as BD, our data indicate that non-left-hemispheric lateralization for auditory verbal imagery is not associated with schizophrenia per se. This latter speculation is reinforced by the fact that the laterality preference did not differ among the subsamples tested here, suggesting that the commonly measured laterality quotient (i.e., EHI) is not a valid instrument to detect the possible predisposition for an abnormal brain lateralization for verbal stimuli. Nevertheless, the present study supports the view that the auditory imagery paradigm may be a useful tool to characterize hemispheric imbalance as a risk factor for hallucinatory experiences in various neuropsychiatric disorders.

Considering that the imagery paradigm, as used here, is a easy-to-use instrument and it can be administered very rapidly, we suggest that it could be inserted in a fast screening protocol aimed to detect people potentially at risk of AVHs, who should be then tested in more depth. The results found in the present study, in fact, reveal a clear cut evidence, with the expected REA for verbal contents in both healthy individuals and in patients suffering from psychiatric conditions but not from AVHs, and with a non-significant lateralization in auditory imagery in hallucinated patients, independently of their specific diagnosis (schizophrenia and bipolar disorder). Indeed, we suggest that the imagery paradigm may be a potential tool that can be used to rapidly detect potential risks of AVHs.

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Declaration of competing interest

The authors disclose no conflicts of interest.

CRediT authorship contribution statement

Mario Altamura: Supervision, Writing - original draft, Writing - review & editing. **Giulia Prete:** Methodology, Writing - original draft, Writing - review & editing, Formal analysis. **Antonella Elia:** Investigation, Data curation. **Eleonora Angelini:** Investigation, Data curation. **Flavia A Padalino:** Investigation. **Antonello Bellomo:** Supervision. **Luca Tommasi:** Conceptualization. **Beth Fairfield:** Conceptualization, Supervision, Investigation, Resources, Writing - original draft, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2020.107567.

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