Schizophrenia Research 193 (2018) 304–312

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Emotional fMR auditory paradigm demonstrates normalization of limbic hyperactivity after cognitive behavior therapy for auditory hallucinations

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ARTICLE INFO

Article history:
Received 30 January 2017
Received in revised form 8 July 2017
Accepted 9 July 2017
Available online 15 July 2017

Keywords:
Schizophrenia
Neuroimaging
Cognitive behavior therapy
Emotional response
Functional magnetic resonance
Psychosis

ABSTRACT

To date, no study has evaluated the effects on brain function of cognitive behavior therapy (CBT) for persistent auditory hallucinations. This study explored the changes in brain activation associated with an emotional auditory paradigm when patients with schizophrenia and auditory hallucinations were treated with CBT. Functional magnetic resonance (fMR) imaging data were obtained from 55 subjects (17 patients with schizophrenia in the therapy group, 24 patients with schizophrenia in the control patient group, and 14 healthy control subjects). The patients in the experimental group were treated with 16–20 bi-weekly sessions of CBT, whereas the patients in the control group received treatment as usual. fMR images were obtained at baseline, 9 and 14 months after enrollment. Patients who received CBT showed significant decrease in brain activation in right and left amygdalae, and the left middle temporal gyrus, compared to both control groups. Significantly reductions in the brain activation of therapy patients were found in both amygdalae, but also in the left superior temporal gyrus and the right superior frontal gyrus at 14-month follow-up. Significant and stable reductions in the abnormal activation of key limbic regions appear to be attributable to the CBT during an emotional auditory paradigm in patients with schizophrenia and persistent auditory hallucinations. These results point to the availability of a biological imaging biomarker for CBT effects in patients with persistent auditory hallucinations.

1. Introduction

Although auditory hallucinations (AH) are present in some medical illnesses and in the general population, hearing voices remains the key characteristic of psychotic patients and is known to occur in approximately 70% of patients with schizophrenia. AH may become totally or partially resistant in approximately 25–50% of patients despite adequate pharmacological treatment (González et al., 2006). This pervasive phenomenon is clinically relevant because AH are usually experienced as distressing, having severe clinical implications, such as depressive symptoms, suicide and violent behavior (Braham et al., 2004). Cognitive behavior therapy (CBT) effectively modifies persistent positive symptoms as an adjunct to antipsychotic drugs (Pfammatter et al., 2006; Turkington et al., 2006; Wykes et al., 2008). Based on this evidence, the National Institute for Health and Clinical Excellence (NICE) recommends offering CBT to all subjects suffering from schizophrenia (NICE, 2010).

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http://dx.doi.org/10.1016/j.schres.2017.07.024
0920-9964/

Table 1
Sociodemographical characteristics of subjects.

	CBT patients ($N = 17$)	TAU patients ($N = 23$)	Healthy controls ($N = 14$)
Age	35·4 ± 3·9	37·5 ± 8·9	35·28 ± 9·9
Sex	10 M/7 F	15 M/8 F	10 M/4 F
Marital status	Single = 13	Single = 20	Single = 7
	Married = 1	Married = 1	Married = 7
	Divorced = 1	Divorced = 1	Divorced = 0
	Cohabitation >6 m = 2	Cohabitation >6 m = 1	
Education level	Primary = 7	Primary = 6	Primary = 1
	Secondary = 2	Secondary = 6	Secondary = 1
	High School = 4	High school = 8	High school = 8
	University = 4	University = 3	University = 4
Work status	Active = 4	Active = 1	Active = 6
	Unemployed = 5	Unemployed = 4	Unemployed = 4
	Disabled = 6	Disabled = 13	Disabled = 0
	Student = 2	Student = 5	Student = 3
			Lost Data = 1

Hallucinatory experiences are associated with dysfunctions of the secondary and primary sensory areas, the prefrontal cortex, the cingulate, subcortical and cerebellar areas (Allen et al., 2008). Brain activation has been associated with the improvement in AH after treatment. Liddle et al. (2000) showed specific activation patterns with a single dose of risperidone that were correlated with the improvement of AH. However, there is a lack of longitudinal studies investigating the brain's responses to the therapeutic approaches that target AH.

There appear to be different mechanisms for the clinical effects of pharmacotherapy and psychotherapy (Linden, 2008). Most neuroimaging research correlates of the psychotherapeutic effects have been conducted in obsessive compulsive disorder, anxiety disorders, and depression. It has been shown that CBT produces changes in brain activation profiles related to symptom improvement (Roffman et al., 2005; Linden, 2006; Linden, 2008). Few studies have used neuroimaging procedures before and after psychotherapeutic interventions in patients with schizophrenia and related psychoses, and none of these studies have focused on AH (Wykes, 1998; Wexler et al., 2000; Penadés et al., 2000, 2002, 2013; Wykes et al., 2002; Kumari et al., 2009, 2011; Eack et al., 2010; Premkumar et al., 2009, 2015). Most studies used neurocognitive interventions, such as memory tasks or cognitive remediation (Wykes, 1998; Wexler et al., 2000; Penadés et al., 2000, 2002, 2013; Wykes et al., 2002; Eack et al., 2010).

Interestingly, CBT has also been used to improve psychotic symptoms. Premkumar et al. (2009, 2015) used structural magnetic resonance (MR) imaging to predict the response of psychotic symptoms to CBT in two studies. The same group used functional MR (fMR) imaging to predict the response to CBT through brain activation patterns in the presence of a working memory task (Kumari et al., 2009). These authors demonstrated that CBT attenuated the brain's psychotic responses to fearful and angry expressions. The decreased activation responses correlated with symptom improvement (Kumari et al., 2011). To date, no neuroimaging study has evaluated the brain's response to a psychotherapeutic approach focused on AH. Therefore, the neurobiological underpinnings of the efficacy of CBT on AH are still not completely understood, which limits our ability to predict which patients would benefit from CBT and undermines our efforts to develop new treatment strategies.

Although cognitive and visual emotional paradigms are frequently used in fMR neuroimaging research on the therapeutic approaches for schizophrenia, an auditory emotional paradigm appears to be a more consistent approach to study AH. In psychotic patients, emotional paradigms have frequently used stimuli other than auditory stimuli, mainly demonstrating brain under activation (Taylor et al., 2012). This meta-analysis concluded that in some conditions, patients with schizophrenia exhibit increased activation in areas not expected to be associated with emotion, including the left temporal lobe.

Increased activity has been shown in higher cortical areas, such as the bilateral inferior frontal cortex, during audio-visual stimulation

Table 2
Clinical characteristics of subjects.

	CBT patients ($N = 17$)	TAU patients ($N = 23$)	*P* values *t*-tests
GAS at baseline	48·29 ± 9·19	46·57 ± 13·87	0·64
BPRS at baseline	50·94 ± 11·22	55·26 ± 11·14	0·24
PANSS positive at baseline	17·94 ± 5·0	19·70 ± 7·02	0·36
PANSS negative at baseline	19·12 ± 6·51	20·26 ± 6·64	0·59
PSYRATS total hallucinations at baseline	27·18 ± 4·29	24·57 ± 8·04	0·19
GAS at 9 months	50·94 ± 13·30	45·09 ± 10·94	0·15
BPRS at 9 months	46·81 ± 8·93	49·55 ± 9·95	0·38
PANSS positive at 9 months	16·47 ± 6·54	18·26 ± 6·87	0·41
PANSS negative at 9 months	16·35 ± 6·53	20·04 ± 6·86	0·09
PSYRATS total hallucinations at 9 months	24·06 ± 6·75	23·09 ± 7·84	0·80
GAS at 6 months post-therapy	51·43 ± 10·46	47·96 ± 14·95	0·41
BPRS at 6 months post-therapy	43·06 ± 6·46	48·09 ± 12·79	0·12
PANSS positive at 6 months post-therapy	14·69 ± 3·18	16·61 ± 5·47	0·17
PANSS negative at 6 months post-therapy	14·81 ± 4·97	19·22 ± 8·61	0·05
PSYRATS total hallucinations at 6 months post-therapy	24·13 ± 6·0	23·28 ± 7·81	0·43
	1st G APS = 4	1st G APS = 6	N.S.
Medication	2nd G APS = 8	2nd G APS = 11	
	Mixed = 5	Mixed = 6	

compared with visual stimulation. This aspect may be considered a cognitive effort that compensates for perception deficits in the emotion domain (mood induction) of patients with schizophrenia (Dyck et al., 2014). Sanjuan et al. (2007) also found an overactivation in the frontal and limbic areas using an auditory emotional paradigm designed to reproduce hallucinatory experiences.

Some therapeutic approaches have shown significant changes in brain activation patterns in patients with schizophrenia. Hyperactivity in key cerebral areas, such as the primary auditory cortex, the left Broca's area, and the cingulate gyrus, has been associated with AH. These changes are reversible as symptoms improved after treatment with transcranial magnetic stimulation (Kindler et al., 2013).

Considering that CBT, to some extent, dampen the salience of AH, it appears reasonable to ascertain that this emotional paradigm might be used in a fMR study investigating changes in brain activation patterns associated with reductions in the severity of AH after CBT. The aim of this study was to evaluate these changes attributable to CBT for persistent AH and to explore the potentiality of a fMR auditory emotional paradigm as an imaging biomarker of the effectiveness of a psychotherapeutic intervention focused on AH.

2. Material and methods

2.1. Participants

Patients were recruited from a two-centre research study (Clinical University Hospital, Valencia, Spain; and Santa Creu i Sant Pau Hospital, Barcelona, Spain). Our sample consisted of 54 adult subjects (17 patients with DSM-IV-TR schizophrenia in the CBT therapy group, 23 patients with DSM-IV-TR schizophrenia in the non-CBT patient group, and 14 healthy subjects). Thirty-two subjects were studied in Valencia and 22 in Barcelona. All patients experienced persistent AH and were randomly assigned to the therapy or control patient groups. A random series of 0 (TAU) and 1 (Therapy) values was generated for each one of the two hospitals and followed until completing the corresponding samples. All patients and control subjects provided written informed consent according to the Local Ethical Committee, and were older than 18 years old. The patients were recruited from the outpatient clinics of both hospitals, and were under treatment with stable doses of antipsychotic medication. The patients in the therapy group underwent 16–20 sessions of CBT (initially weekly and mostly bi-weekly afterwards), whereas the patients in the control group received treatment as usual. A total number of 96 patients entered the clinical study. Nine patients abandoned it during the intervention phase and 5 of them dropped out of the study during the follow-up phase. Fifty-three patients specifically gave informed consent for the MR study and were evaluated at baseline and after therapy but 15 of them (28%) did not complete the three MR examinations.

The persistence of hallucinations was defined as: (a) voices were not modified in any way by treatment over the course of 1 year; (b) present at least one time per day; and (c) utilized at least two antipsychotics in doses equivalent to 600 mg of chlorpromazine.

Healthy subjects were excluded if they (a) suffered from a medical illness that potentially affected cerebral function or (b) met present or past criteria for psychoactive drug abuse or dependence (except for tobacco). The sociodemographic characteristics are depicted in Table 1. The clinical characteristics at baseline and follow-up are shown in Table 2.

2.2. MR scanning protocol

Three MR imaging examinations were obtained, at baseline, at 6–9 months follow-up, and at 14 months follow-up. Subjects were scanned at both institutions with Philips 3T magnets (Achieva, Philips Medical Systems, Best, The Netherlands). Subjects used earphones connected by a pair of air tubes to an external audio player. The acquisition was performed with 32-channel head coil, and the same protocol was used at both institutions. A dynamic echo planar imaging (EPI) T2* weighted MR sequence (repetition time = 2000 msec; echo time = 30 msec; section thickness = 3·50 mm with no interslice gap; flip angle 90; matrix 128 × 128; pixel size 1·80 × 1·80 mm) was obtained, and each dynamic acquisition was composed of 40 contiguous slices covering the whole brain. The total duration of the fMR sequence was 160 s.

The procedures at both locations were equal, including the training and the reliability testing for the technicians and the equipment. Parametric fMR imaging maps were obtained for each participant. Anatomical labeling of the activated areas was obtained by using a normalized atlas.

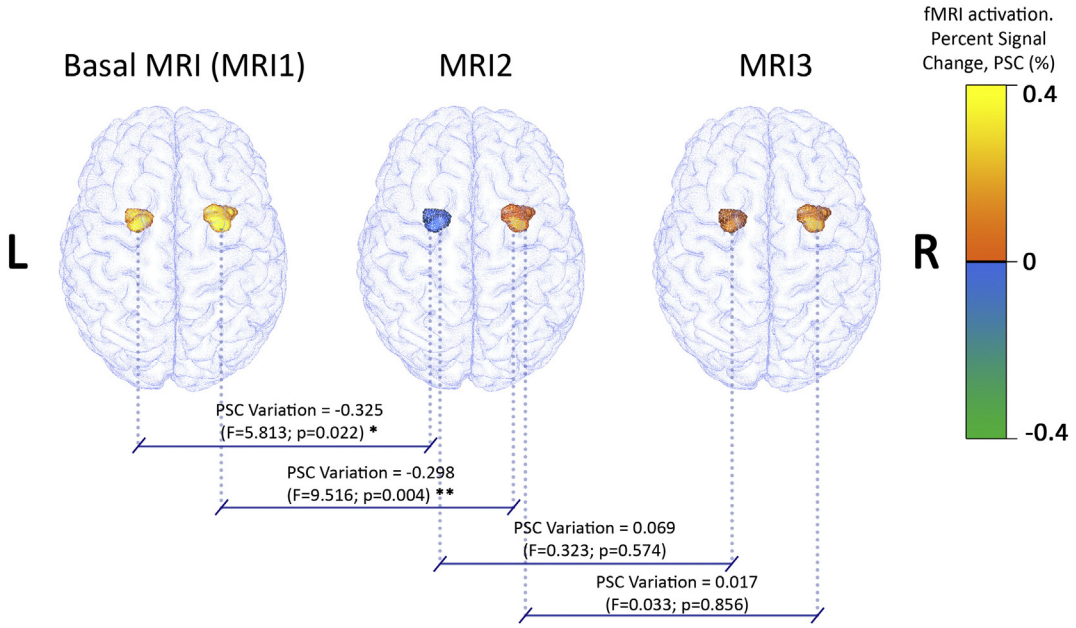

Fig. 1. fMRI PSC amygdalae activation in therapy group.

Table 3
Results for ANOVA test when comparing PSC differences between timeline in each clinical group.

Region	Patient therapy group					Patient control group					Healthy control group				
	ANOVA F	ANOVA *p*-value	Post-hoc	[a]PSC difference	Post-hoc *p*-value	ANOVA F	ANOVA *p*-value	Post-hoc	[a]PSC difference	Post-hoc *p*-value	ANOVA F	ANOVA *p*-value	Post-hoc	[a]PSC difference	Post-hoc *p*-value
Superior Temporal Gyrus R	0,992	0,379	MRI1 vs MRI2	+0.091	0,473	0,050	0,952	MRI1 vs MRI2	+0.019	0,978	1024	0,370	MRI1 vs MRI2	−0.177	0,484
			MRI1 vs MRI3	−0.010	0,992			MRI1 vs MRI3	−0.014	0,991			MRI1 vs MRI3	−0.219	0,418
			MRI2 vs MRI3	−0.101	0,436			MRI2 vs MRI3	−0.032	0,950			MRI2 vs MRI3	−0.042	0,967
Superior Temporal Gyrus L	**3305**	**0,046***	MRI1 vs MRI2	−0.236	0,080	1650	0,201	MRI1 vs MRI2	−0.145	0,180	0,384	0,684	MRI1 vs MRI2	−0.087	0,829
			MRI1 vs MRI3	−0.248	0,081			MRI1 vs MRI3	−0.096	0,551			MRI1 vs MRI3	−0.142	0,675
			MRI2 vs MRI3	−0.012	0,994			MRI2 vs MRI3	+0.049	0,858			MRI2 vs MRI3	−0.055	0,940
Middle Temporal Gyrus R	0,939	0,398	MRI1 vs MRI2	+0.057	0,633	0,019	0,981	MRI1 vs MRI2	−0.015	0,980	1293	0,288	MRI1 vs MRI2	−0.145	0,311
			MRI1 vs MRI3	−0.030	0,889			MRI1 vs MRI3	−0.006	0,998			MRI1 vs MRI3	−0.135	0,444
			MRI2 vs MRI3	−0.088	0,385			MRI2 vs MRI3	+0.010	0,994			MRI2 vs MRI3	+0.010	0,996
Middle Temporal Gyrus L	2460	0,097	MRI1 vs MRI2	+0.131	0,089	0,066	0,936	MRI1 vs MRI2	−0.018	0,951	1250	0,300	MRI1 vs MRI2	−0.130	0,416
			MRI1 vs MRI3	+0.037	0,828			MRI1 vs MRI3	+0.004	0,999			MRI1 vs MRI3	−0.162	0,346
			MRI2 vs MRI3	−0.094	0,316			MRI2 vs MRI3	+0.022	0,947			MRI2 vs MRI3	−0.032	0,958
Hippocampus R	1170	0,320	MRI1 vs MRI2	+0.007	0,979	0,417	0,661	MRI1 vs MRI2	+0.059	0,749	**3321**	**0,049***	MRI1 vs MRI2	**−0.158**	**0,041***
			MRI1 vs MRI3	−0.047	0,436			MRI1 vs MRI3	+0.076	0,694			MRI1 vs MRI3	−0.055	0,714
			MRI2 vs MRI3	−0.054	0,335			MRI2 vs MRI3	+0.017	0,982			MRI2 vs MRI3	+0.103	0,308
Hippocampus L	0,371	0,692	MRI1 vs MRI2	+0.038	0,758	0,275	0,761	MRI1 vs MRI2	+0.044	0,761	2568	0,092	MRI1 vs MRI2	−0.110	0,098
			MRI1 vs MRI3	−0.005	0,996			MRI1 vs MRI3	+0.037	0,865			MRI1 vs MRI3	−0.018	0,949
			MRI2 vs MRI3	−0.043	0,726			MRI2 vs MRI3	−0.008	0,994			MRI2 vs MRI3	+0.092	0,255
Amygdala R	**3920**	**0,027***	MRI1 vs MRI2	**−0.325**	**0,027***	0,833	0,440	MRI1 vs MRI2	−0.101	0,412	0,791	0,462	MRI1 vs MRI2	−0.095	0,488
			MRI1 vs MRI3	−0.255	0,125			MRI1 vs MRI3	−0.037	0,911			MRI1 vs MRI3	−0.090	0,598
			MRI2 vs MRI3	+0.070	0,849			MRI2 vs MRI3	+0.064	0,758			MRI2 vs MRI3	+0.005	0,998
Amygdala L	**6984**	**0,002****	MRI1 vs MRI2	**−0.298**	**0,004****	0,770	0,468	MRI1 vs MRI2	−0.080	0,583	2232	0,123	MRI1 vs MRI2	−0.159	0,103
			MRI1 vs MRI3	**−0.281**	**0,011***			MRI1 vs MRI3	−0.101	0,516			MRI1 vs MRI3	−0.089	0,550
			MRI2 vs MRI3	+0.017	0,982			MRI2 vs MRI3	−0.021	0,971			MRI2 vs MRI3	+0.070	0,684
Anterior Cingulated Gyrus R	0,090	0,914	MRI1 vs MRI2	−0.016	0,945	1059	0,353	MRI1 vs MRI2	−0.054	0,576	**3467**	**0,043***	MRI1 vs MRI2	**−0.133**	**0,039***
			MRI1 vs MRI3	−0.021	0,917			MRI1 vs MRI3	−0.084	0,354			MRI1 vs MRI3	−0.037	0,804
			MRI2 vs MRI3	−0.005	0,995			MRI2 vs MRI3	−0.031	0,869			MRI2 vs MRI3	+0.096	0,233
Anterior Cingulated Gyrus L	0,384	0,683	MRI1 vs MRI2	−0.002	1000	1459	0,241	MRI1 vs MRI2	−0.066	0,562	**3638**	**0,037***	MRI1 vs MRI2	**−0.154**	**0,029***
			MRI1 vs MRI3	−0.050	0,714			MRI1 vs MRI3	−0.122	0,222			MRI1 vs MRI3	−0.079	0,445
			MRI2 vs MRI3	−0.049	0,731			MRI2 vs MRI3	−0.057	0,720			MRI2 vs MRI3	+0.075	0,470
Inferior Frontal Gyrus R	0,125	0,883	MRI1 vs MRI2	+0.024	0,892	0,657	0,522	MRI1 vs MRI2	−0.067	0,552	2086	0,140	MRI1 vs MRI2	−0.119	0,244
			MRI1 vs MRI3	+0.022	0,918			MRI1 vs MRI3	−0.065	0,654			MRI1 vs MRI3	−0.150	0,173
			MRI2 vs MRI3	−0.002	0,999			MRI2 vs MRI3	+0.003	0,999			MRI2 vs MRI3	−0.031	0,921
Inferior Frontal Gyrus L	0,495	0,613	MRI1 vs MRI2	+0.055	0,598	0,273	0,762	MRI1 vs MRI2	−0.022	0,919	0,896	0,418	MRI1 vs MRI2	−0.068	0,606
			MRI1 vs MRI3	+0.016	0,960			MRI1 vs MRI3	−0.046	0,744			MRI1 vs MRI3	−0.101	0,422
			MRI2 vs MRI3	−0.039	0,793			MRI2 vs MRI3	−0.025	0,919			MRI2 vs MRI3	−0.033	0,907

(continued on next page)

Table 3 (*continued*)

Region	Patient therapy group					Patient control group					Healthy control group				
	ANOVA F	ANOVA *p*-value	Post-hoc	[a]PSC difference	Post-hoc *p*-value	ANOVA F	ANOVA *p*-value	Post-hoc	[a]PSC difference	Post-hoc *p*-value	ANOVA F	ANOVA *p*-value	Post-hoc	[a]PSC difference	Post-hoc *p*-value
Middle Frontal Gyrus R	0,768	0,470	MRI1 vs MRI2	−0.050	0,564	0,716	0,493	MRI1 vs MRI2	−0.015	0,949	2190	0,128	MRI1 vs MRI2	−0.136	0,107
			MRI1 vs MRI3	−0.057	0,521			MRI1 vs MRI3	+0.050	0,640			MRI1 vs MRI3	−0.075	0,569
			MRI2 vs MRI3	−0.006	0,992			MRI2 vs MRI3	+0.066	0,473			MRI2 vs MRI3	+0.061	0,676
Middle Frontal Gyrus L	0,900	0,414	MRI1 vs MRI2	+0.026	0,891	0,837	0,438	MRI1 vs MRI2	−0.056	0,616	1168	0,323	MRI1 vs MRI2	−0.014	0,968
			MRI1 vs MRI3	−0.054	0,648			MRI1 vs MRI3	−0.082	0,452			MRI1 vs MRI3	+0.078	0,446
			MRI2 vs MRI3	−0.080	0,388			MRI2 vs MRI3	−0.026	0,922			MRI2 vs MRI3	+0.092	0,320
Superior Frontal Gyrus R	**9076**	<**0.000**[**]	MRI1 vs MRI2	**−0.273**	**0,001**[**]	1632	0,204	MRI1 vs MRI2	−0.079	0,222	0,650	0,528	MRI1 vs MRI2	−0.037	0,778
			MRI1 vs MRI3	**−0.216**	**0,010**[*]			MRI1 vs MRI3	−0.007	0,990			MRI1 vs MRI3	+0.031	0,871
			MRI2 vs MRI3	+0.057	0,700			MRI2 vs MRI3	+0.072	0,380			MRI2 vs MRI3	+0.068	0,508
Superior Frontal Gyrus L	0,959	0,391	MRI1 vs MRI2	+0.034	0,810	2330	0,106	MRI1 vs MRI2	−0.057	0,414	1418	0,257	MRI1 vs MRI2	−0.018	0,926
			MRI1 vs MRI3	−0.045	0,708			MRI1 vs MRI3	−0.109	0,093			MRI1 vs MRI3	+0.070	0,413
			MRI2 vs MRI3	−0.079	0,358			MRI2 vs MRI3	−0.052	0,576			MRI2 vs MRI3	+0.088	0,243
Orbitomedial Frontal Gyrus R	0,017	0,984	MRI1 vs MRI2	+0.014	0,982	1304	0,279	MRI1 vs MRI2	−0.014	0,967	1860	0,172	MRI1 vs MRI2	−0.057	0,634
			MRI1 vs MRI3	+0.007	0,995			MRI1 vs MRI3	+0.083	0,387			MRI1 vs MRI3	+0.076	0,530
			MRI2 vs MRI3	−0.006	0,996			MRI2 vs MRI3	+0.096	0,278			MRI2 vs MRI3	+0.134	0,147
Orbitomedial Frontal Gyrus L	**4670**	**0,014**[*]	MRI1 vs MRI2	**−0.220**	**0,016**[*]	2541	0,087	MRI1 vs MRI2	−0.131	0,092	0,144	0,866	MRI1 vs MRI2	−0.005	0,996
			MRI1 vs MRI3	−0.183	0,070			MRI1 vs MRI3	−0.112	0,257			MRI1 vs MRI3	+0.031	0,901
			MRI2 vs MRI3	+0.037	0,889			MRI2 vs MRI3	+0.019	0,959			MRI2 vs MRI3	+0.037	0,865

Abbreviations: MRI (magnetic resonance imaging), PSC (Percent Signal Change).

[a] Positive PSC differences between group MRIx vs MRIy indicates increases of fMRI activation in group MRIy vs MRIx, whereas negative PSC values represents a decrease of activation in group MRIy vs MRIx.

[*] $p < 0.05$.

[**] $p < 0.005$.

2.3. Experimental paradigm

All cases were evaluated at fMR with an auditory emotional response paradigm that was designed and has been applied in several studies to replicate the emotions related to hallucinatory experiences in psychotic patients (Sanjuán et al., 2005; Sanjuan et al., 2007; Martí-Bonmatí et al., 2007; Escartí et al., 2010). In particular, a clear enhanced activity of the frontal lobe, temporal cortex, insula, cingulate, and amygdala in patients when hearing emotional words in comparison with controls has been previously demonstrated (Sanjuan et al., 2007). Hippocampus was the only region not included in any of our previous results that was added to the study's hypotheses. This brain region is a key structure in the pathophysiology of hallucinations through its prominent role in episodic memory (Behrendt, 2016) and connectivity dynamic models (Li et al., 2017). At least some auditory hallucinations, particularly those related to previous trauma, rely on memory processes (Jones, 2010). A therapeutical work on hallucinations will plausibly have an impact on relational memory processing and may therefore provoke changes on hippocampal activation patterns. Thirteen emotional Spanish words were selected according to their frequency of presentation in the patient's hallucinations. Neutral words were obtained from a linguistic database (Algarabel, 1996). A professional actor, pronouncing both emotional and neutral words with negative and neutral tones while maintaining constant voice intensity, recorded a compact disc.

The subjects were binaurally stimulated during two different sessions with the same fMR image acquisition procedure. During the functional sessions the stimulation was presented using a block-design approach consisting of 4 blocks with 20 s of word stimulation mixed with 4 blocks with 20 s of rest. This blocked-designed paradigm included a first session that consisted of four activation blocks of 13 consecutive neutral words followed by four rest blocks with no words. The second session involved a similar procedure (activation-rest blocks) involving words with high emotional content. Before the procedure, all patients were informed about the test characteristics and were asked to focus their attention on the words they were about to hear. fMR experiments were performed three times for all subjects: at baseline (RM1), after therapy (9 months) or at similar time points in the control groups (RM2), and at 14 months in order to assess durability of effects (RM3).

2.4. Therapeutic procedures

Patients in the CBT therapy group had 16–20 planned CBT 1-hour sessions over 6–9 months with trained therapists. The therapist followed a manual supervision by international experts (Drs. Douglas Turkington and Alison Brabban) and was based on expert recommendations (Turkington et al., 2006). The specific training consisted of three workshops with these experts and regular fortnightly Skype supervisions. Following a period of engagement and assessment, the patients

were given an explanation of how CBT might be of benefit for AH by changing the appraisal of the experience and reducing the distressing affect and dysfunctional safety behaviors, such as avoidance, rumination, and thought suppression. A normalizing explanation was given to reduce stigma and illustrate successful coping styles. Distressing appraisals, such as 'it's the voice of the devil', were questioned, and alternatives were generated. CBT was used to improve sleep hygiene and reduce the voice worsening affects, such as anger, anxiety, and shame. Each patient was then taught a tailored coping strategy, which involved distraction, focusing, or metacognitive components. This was followed by sessions of reality testing the voice hearing experience and experimenting with strategies to gain increased control and reduce emotional distress. Social rank theory-based approaches and exposure-based approaches were used for troublesome command hallucinations. Metacognitive approaches, such as prescribing voice postponement with voice listening periods and detached mindfulness, were used if needed. Voices that echoed core beliefs about the self (such as 'I am bad') were tackled using schema focused techniques. CBT ended by establishing a relapse prevention plan to attempt to prevent or delay relapse.

Patient control group: The patients followed treatment as usual (TAU) by their regular psychiatrists. These patients were chosen as the comparison group to identify the potential modifications in the activation patterns in these persistently hallucinating patients. The patients were expected to show similar levels of AH scores at baseline and follow-up. This comparison group was used to demonstrate the activation pattern stability when no therapeutic intervention was performed.

Healthy control group: The healthy volunteer subjects were recruited by our healthy volunteer database, advertisements, and individuals related to the staff involved in the study.

2.5. Clinical measurements

All patients were assessed with the Global Assessment Scale (GAS) (Endicott et al., 1976) and the 24-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). AH were assessed by the Psychotic Symptoms Rating Scale (PSYRATS) (Haddock et al., 1999) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The assessments were conducted at baseline and two follow-up evaluations by interviewers who were blind to the treatment condition.

2.6. Analyses

The post-processing of the acquired images was done using the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). These steps included both spatial (realignment) and temporal (slice timing) corrections to minimize movement effects and to adjust for the temporal delay between the first and the last slice of each dynamic acquisition. Images were then normalized to a standard template (MNI350, Montreal Neurological Institute) and smoothed with a $6 \times 6 \times 6$ mm Gaussian smoothing kernel. For each participant a first-level statistical model was designed and adjusted. fMR imaging activation was measured during emotional words in all patients in areas related to AH, specifically, the superior temporal gyrus, the middle temporal gyrus, the hippocampus, the amygdala, the anterior cingulate, the inferior frontal gyrus, the middle frontal gyrus, the superior frontal gyrus, and the orbitomedial frontal gyrus. For each subject the Percent Signal Change (PSC), calculated as the % signal difference between the signal-averaged in the rest period and the signal-averaged in the active period was measured in each region of interest (ROI). The calculation of PSC values by comparing active versus rest activation was preferred instead of using a subtraction contrast to directly compare emotional versus neutral word processing in order to reduce the high level of variability that patients with schizophrenia reach when processing neutral stimuli (Potvin et al., 2016). To avoid spurious values, the mean, median, deviation, kurtosis and skewness of the data were obtained from each region. All values were recalculated in a 'robust' way, discarding outliers (values 2 times above or below the standard deviation). Basal fMR signals were compared with the follow-up signals, and the percentages of change were analyzed. A voxel-by-voxel computation of the PSC in each ROI and participant was calculated and stored in a multidimensional database. A Bonferroni correction was applied to control for multiple comparisons.

ANOVA tests were applied to identify the differences among the three groups between baseline and both follow-up evaluations. Tukey's test was used for post-hoc comparisons among the three time periods.

3. Results

Age did not show significant differences between the clinical groups ($F = 0.307$, $p = 0{,}737$). None of the clinical variables showed significant differences between both groups at baseline and follow-up assessments (Table 2). Negative symptoms showed a non-significant trend favoring therapy group in 9- & 14-week evaluations.

3.1. Repeated-measures ANOVA: effect over time for each clinical group

Significant changes of fMR response were found in different brain areas when evaluating the PSC with each MR evaluation over time. The patient therapy group showed significant reductions in fMR activation in the follow-up examinations mainly in the right superior frontal gyrus ($F = 9.076$, $p < 0.000$), left ($F = 6.986$, $p = 0.002$) and right ($F = 3.920$, $p = 0.027$) amygdalae (Fig. 1) and left superior temporal gyrus ($F = 3.305$, $p = 0.046$).

On the contrary, the patient control group did not show any significant functional PSC difference over time for any ROI.

The healthy control group showed PSC significant reductions for the right ($F = 3.467$, $p = 0.043$) and left ($F = 3.638$, $p = 0.037$) anterior cingulated gyri and right hippocampus ($F = 3.321$, $p = 0.049$).

Table 3 shows the detailed results for the ANOVA testing for the considered ROIS as well as Tukey's post-hoc comparisons for each MR evaluation over time.

3.2. Repeated-measures ANOVA: effect over clinical groups for each MR examination

Several areas appeared as statistically significant when evaluated functional PSC between the clinical groups. The baseline (MRI1) showed a significant reduction of fMR activation in the patient therapy and patient control groups when compared with healthy controls. These findings were mainly located at the frontal lobe, including the left orbitomedial frontal gyrus ($F = 16.824$, $p < 0.000$), right ($F = 12.381$, $p < 0.000$) and left ($F = 9.278$, $p < 0.000$) superior frontal gyrus and left middle frontal gyrus ($F = 7.748$, $p = 0.001$).

The MR examination post-CBT (MRI2) showed various significant PSC changes between clinical groups (see Table 4). Interestingly, the left amygdala appeared as the most significant region, showing an increase of activity in the patient control group versus the patient therapy group in this MR evaluation ($F = 9.771$, $p < 0.000$). This trend was maintained in the 6 months MR examination after the end of the CBT.

Since findings on both amygdalae were of special interest. Fig. 2 shows a summary of these findings for the three groups of subjects over time.

4. Discussion

This report shows differences in brain activation during an emotional auditory paradigm in a sample of patients with schizophrenia and persistent AH, attributable to the effects of CBT. The patients who received CBT showed significantly greater decreases of activation compared with the patient control subjects in the right and left amygdalae, and the left middle temporal gyrus while listening to emotional words. Several significant differences were also found when

Table 4
Results for ANOVA test when comparing PSC differences between clinical groups at each MRI evaluation.

Region	Basal MRI (MRI1)					MRI2					MRI3				
	ANOVA F	ANOVA *p*-value	Post-hoc	[a]PSC difference	Post-hoc *p*-value	ANOVAF	ANOVA *p*-value	Post-hoc	[a]PSC difference	Post-hoc *p*-value	ANOVA F	ANOVA *p*-value	Post-hoc	[a]PSC difference	Post-hoc *p*-value
Superior Temporal Gyrus L	1390	0,258	PT vs PC	+0.108	0,537	1596	0,213	PT vs PC	+0.199	0,193	**4198**	**0,023***	PT vs PC	**+0.259**	**0,026***
			PT vs HC	−0.066	0,838			PT vs HC	+0.083	0,796			PT vs HC	+0.039	0,931
			PC vs HC	−0.174	0,259			PC vs HC	−0.116	0,601			PC vs HC	−0.220	0,117
Superior Temporal Gyrus R	0,935	0,399	PT vs PC	−0.071	0,775	1579	0,216	PT vs PC	−0.143	0,329	0,548	0,583	PT vs PC	−0.075	0,772
			PT vs HC	+0.083	0,776			PT vs HC	−0.186	0,240			PT vs HC	−0.127	0,573
			PC vs HC	+0.154	0,372			PC vs HC	−0.042	0,916			PC vs HC	−0.052	0,907
Middle Temporal Gyrus R	0,397	0,674	PT vs PC	−0.077	0,678	**6379**	**0,003****	PT vs PC	−0.150	0,079	1966	0,155	PT vs PC	−0.053	0,779
			PT vs HC	−0.072	0,780			PT vs HC	**−0.274**	**0,002****			PT vs HC	−0.176	0,135
			PC vs HC	+0.006	0,998			PC vs HC	−0.124	0,208			PC vs HC	−0.124	0,352
Middle Temporal Gyrus L	0,069	0,934	PT vs PC	−0.024	0,937	**7303**	**0,002****	PT vs PC	**−0.174**	**0,032***	3146	0,055	PT vs PC	−0.058	0,741
			PT vs HC	−0.024	0,954			PT vs HC	**−0.286**	**0,001****			PT vs HC	**−0.223**	**0,047***
			PC vs HC	+0.000	1000			PC vs HC	−0.112	0,269			PC vs HC	−0.165	0,167
Hippocampus R	0,599	0,553	PT vs PC	−0.096	0,577	**8508**	**0,001****	PT vs PC	−0.043	0,521	0,357	0,702	PT vs PC	+0.027	0,869
			PT vs HC	−0.015	0,990			PT vs HC	**−0.180**	**0,001****			PT vs HC	−0.023	0,925
			PC vs HC	+0.081	0,715			PC vs HC	**−0.136**	**0,006***			PC vs HC	−0.050	0,689
Hippocampus L	0,355	0,703	PT vs PC	−0.060	0,682	**7154**	**0,002****	PT vs PC	−0.053	0,468	0,329	0,722	PT vs PC	−0.018	0,948
			PT vs HC	−0.041	0,873			PT vs HC	**−0.190**	**0,002****			PT vs HC	−0.054	0,700
			PC vs HC	+0.019	0,969			PC vs HC	**−0.136**	**0,017***			PC vs HC	−0.036	0,849
Amygdala R	1918	0,157	PT vs PC	+0.022	0,978	**4925**	**0,011***	PT vs PC	**+0.246**	**0,017***	**5574**	**0,008***	PT vs PC	**+0.240**	**0,021***
			PT vs HC	−0.198	0,263			PT vs HC	+0.032	0,943			PT vs HC	−0.033	0,940
			PC vs HC	−0.220	0,156			PC vs HC	−0.214	0,060			PC vs HC	**−0.273**	**0,021***
Amygdala L	4631	0,014*	PT vs PC	+0.029	0,942	**9771**	**<0.000****	PT vs PC	**+0.248**	**0,011***	**6238**	**0,005***	PT vs PC	**+0.210**	**0,023***
			PT vs HC	**−0.252**	**0,046***			PT vs HC	−0.112	0,455			PT vs HC	−0.060	0,770
			PC vs HC	**−0.281**	**0,014***			PC vs HC	**−0.360**	**<0.000****			PC vs HC	**−0.269**	**0,009***
Anterior Cingulated Gyrus R	0,549	0,581	PT vs PC	+0.026	0,905	**6540**	**0,003****	PT vs PC	−0.011	0,965	0,574	0,568	PT vs PC	−0.037	0,749
			PT vs HC	−0.044	0,814			PT vs HC	**−0.161**	**0,006***			PT vs HC	−0.060	0,563
			PC vs HC	−0.071	0,551			PC vs HC	**−0.150**	**0,006***			PC vs HC	−0.023	0,915
Anterior Cingulated Gyrus L	0,756	0,475	PT vs PC	+0.021	0,954	**6479**	**0,003****	PT vs PC	−0.043	0,735	1179	0,319	PT vs PC	−0.051	0,650
			PT vs HC	−0.072	0,653			PT vs HC	**−0.225**	**0,004****			PT vs HC	−0.101	0,295
			PC vs HC	−0.093	0,450			PC vs HC	**−0.181**	**0,013***			PC vs HC	−0.050	0,733
Inferior Frontal Gyrus R	0,173	0,841	PT vs PC	+0.030	0,902	2369	0,104	PT vs PC	−0.062	0,579	**3640**	**0,037***	PT vs PC	−0.057	0,600
			PT vs HC	−0.010	0,991			PT vs HC	−0.153	0,086			PT vs HC	**−0.182**	**0,029***
			PC vs HC	−0.040	0,855			PC vs HC	−0.091	0,355			PC vs HC	−0.125	0,164
Inferior Frontal Gyrus L	0,966	0,388	PT vs PC	−0.017	0,958	**5661**	**0,006***	PT vs PC	−0.094	0,231	**4527**	**0,018***	PT vs PC	−0.080	0,402
			PT vs HC	−0.094	0,393			PT vs HC	**−0.218**	**0,004****			PT vs HC	**−0.212**	**0,013***
			PC vs HC	−0.077	0,487			PC vs HC	−0.124	0,111			PC vs HC	−0.132	0,154
Middle Frontal Gyrus R	1882	0,163	PT vs PC	−0.089	0,152	**3278**	**0,046***	PT vs PC	−0.054	0,592	1434	0,252	PT vs PC	+0.018	0,951
			PT vs HC	−0.074	0,382			PT vs HC	**−0.159**	**0,038***			PT vs HC	−0.092	0,377
			PC vs HC	+0.016	0,949			PC vs HC	−0.105	0,182			PC vs HC	−0.109	0,244
Middle Frontal Gyrus L	**7748**	**0,001****	PT vs PC	+0.007	0,990	**5222**	**0,009***	PT vs PC	−0.075	0,465	0,273	0,763	PT vs PC	−0.021	0,948
			PT vs HC	**−0.190**	**0,005***			PT vs HC	**−0.230**	**0,007***			PT vs HC	−0.058	0,743
			PC vs HC	**−0.197**	**0,002****			PC vs HC	−0.155	0,064			PC vs HC	−0.037	0,884
Superior Frontal Gyrus R	**12,381**	**<0.000****	PT vs PC	−0.070	0,453	**6377**	**0,003****	PT vs PC	+0.124	0,085	**8109**	**0,001****	PT vs PC	**+0.139**	**0,021***
			PT vs HC	**−0.321**	**<0.000****			PT vs HC	−0.085	0,396			PT vs HC	−0.074	0,404
			PC vs HC	**−0.251**	**0,001****			PC vs HC	**−0.209**	**0,003****			PC vs HC	**−0.212**	**0,002****
Superior Frontal Gyrus L	**9278**	**<0.000****	PT vs PC	+0.025	0,805	**5977**	**0,005***	PT vs PC	−0.066	0,444	0,311	0,735	PT vs PC	−0.038	0,770
			PT vs HC	**−0.157**	**0,004****			PT vs HC	**−0.208**	**0,004****			PT vs HC	−0.042	0,794
			PC vs HC	**−0.182**	**<0.000****			PC vs HC	**−0.142**	**0,041***			PC vs HC	−0.003	0,999
Orbitomedial Frontal Gyrus R	2149	0,127	PT vs PC	−0.117	0,139	**4025**	**0,024***	PT vs PC	−0.144	0,063	0,216	0,807	PT vs PC	−0.041	0,832
			PT vs HC	−0.113	0,248			PT vs HC	**−0.184**	**0,032***			PT vs HC	−0.044	0,853
			PC vs HC	+0.004	0,998			PC vs HC	−0.040	0,815			PC vs HC	−0.003	0,999
Orbitomedial Frontal Gyrus L	**16,824**	**<0.000****	PT vs PC	−0.013	0,975	**4694**	**0,013***	PT vs PC	+0.077	0,492	2309	0,114	PT vs PC	+0.059	0,759
			PT vs HC	**−0.356**	**<0.000****			PT vs HC	−0.141	0,163			PT vs HC	−0.142	0,307
			PC vs HC	**−0.343**	**<0.000****			PC vs HC	**−0.218**	**0,010***			PC vs HC	−0.200	0,097

Abbreviations: MRI (magnetic resonance imaging), PSC (Percent Signal Change), PT (Patient Therapy Group), PC (Patient Control Group), HC (Healthy Control Group).

[a] Positive PSC differences between group A vs B indicates increases of fMRI activation in group B vs A, whereas negative PSC values represents a decrease of activation in group B vs A.

* $p < 0.05$.

** $p < 0.005$.

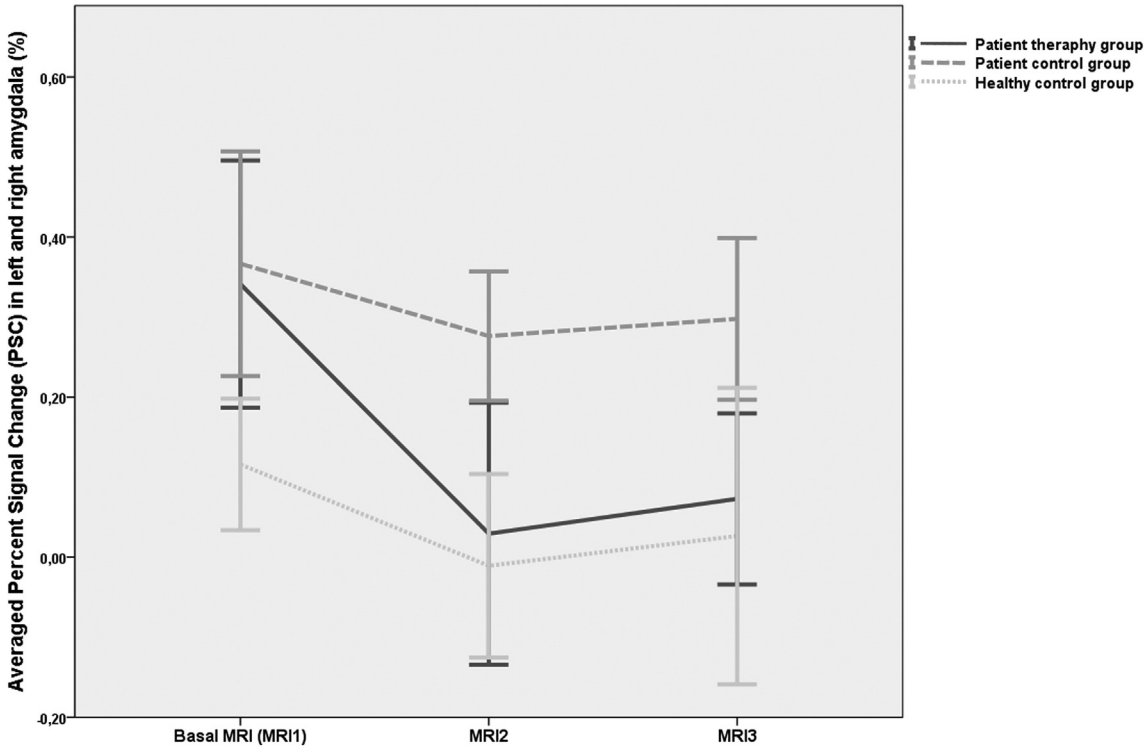

Fig. 2. Averaged PSC in both amygdalae for every group.

comparing healthy control subjects with both groups of patients. Even more interestingly, these results were partially maintained at 14-month follow-up. Thus, patients that received therapy showed significantly greater decreases in the activation of the right superior frontal gyrus, the right and left amygdalae, and the left superior temporal gyrus.

Our results can be understood in light of the aberrant salience model for the pathogenesis of positive symptoms in schizophrenia (Kapur, 2003). The patients in the experimental therapy group showed marked reductions in key abnormally activated regions while patients following treatment as usual did not. A plausible explanation implies a reduction of aberrant salience along with a reduction of abnormal overactivation in specific limbic and auditory cortexes. A detailed explanation of each region can help shed light on this reasoning.

It has been established that the amygdala is a key area for the recognition of threatening stimuli. Its activation is related to affective judgments and emotional intensity (Phan et al., 2004). It therefore appears to sustain the underpinnings to process the emotional salience associated with the stimuli. More specifically, persistently hallucinatory patients also showed an increase of activity in the parahippocampal gyrus and the amygdala during passive listening of emotional words (auditory emotional paradigm) in a fMR study (Escartí et al., 2010). Horga et al. (2014) used a similar auditory paradigm with aversive stimuli mimicking the content of AH in patients with schizophrenia to show an exaggerated response to these stimuli in several regions including the left amygdala. Our data on the reduction of brain activation in amygdalae could reflect an improved response to the adverse auditory stimuli after a psychotherapeutic intervention.

Taylor et al. (2012) concluded in their meta-analysis that in some conditions, patients with schizophrenia exhibit increased activation in areas not expected to be associated with emotion, including the left temporal lobe. Normalization of this abnormal activation in a key area for the pathogenesis of AH is particularly interesting and concordant with our expectations when we designed the auditory emotional paradigm used in this study.

Stable changes after therapy merit further attention. Auditory hallucinations' postulated underpinnings include superior temporal gyrus hyper-activation, not controlled because of frontal lobe hypo-activation. Their negative emotional tone would be mediated by the amygdala (Hugdahl, 2015). Our results show a pattern of normalization in these brain areas in the follow-up evaluations. If confirmed these results could help to understand the biological mechanisms associated with the therapeutical effects of CBT for voices in the patients with schizophrenia.

Penadés et al. (2013) using Cognitive Remediation Therapy (CRT) with 30 schizophrenia outpatients and 15 healthy volunteers, found an increase in inter hemispheric information transfer in the CRT group compared with the control group. We can speculate that different psychotherapeutical strategies may have different brain effects. CBT focused in the emotional response to positive symptoms might be based on decreasing brain activity in limbic and temporal areas, while CRT focused in cognitive deficits and negative symptoms might be based on increasing brain activity in the prefrontal cortex.

In regard with the absence of clinical significant findings attributable to the therapy, a Type-2 error should not be discarded. A larger sample also including an analysis of emotion-driven Psyrats items will surely yield significant results. In spite of this and, according to our data, functional neuroimaging seems to have a higher sensitivity to changes. Somehow surprisingly, negative symptoms showed promising almost significant results that would be maintained in a long term. Although the role of negative symptoms is still unclear, they seem to be a predictor of CBT inefficacy when assessed as independent variables. Many studies omit them as outcome variables (Pontillo et al., 2016) and some that have indeed included them in CBT for auditory hallucinations studies also show an improvement in negative symptoms after therapy (Mortan et al., 2011). The most plausible explanation for this improvement is to consider a global effect on hallucinations leading to an improvement in secondary negative symptoms.

This study has some limitations. Although the results are very consistent, a larger sample is always desirable. Second, a ROI based approach has been considered to reduce the type I error rate and to help to specifically test the initial hypothesis and assumptions. However, a

whole brain voxel-by-voxel analysis of the fMRI signal across subjects would help to minimize the presence of false negatives (type II errors). Third, the usage of different antipsychotic treatments may have influenced the results, but both groups of patients were under similar treatment conditions. Fourth, although blind raters (ignoring group assignation processes) were used for symptom assessments, true blindness is more an aim than a reality and it certainly is a limitation of this kind of evaluations. From this assumption, we made sure they were blind to study hypotheses and did not participate in research group reunions. On the other hand, fully blind processes were guaranteed in neuroimaging analyses. Finally, the results are only generalizable to patients with schizophrenia and persistent AH and not to all patients diagnosed with schizophrenia.

In conclusion, we have shown striking findings in a sample of patients with schizophrenia who showed significant reductions in the activation of key brain areas after CBT. The potential of psychotherapy to normalize limbic abnormalities in front of negative stimuli in a persistent way improves our knowledge on how psychotherapy may help our patients. If the results are confirmed by further studies, our knowledge of the biological foundations of AH and the therapeutic approaches will increase.

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