Schizophrenia Research xxx (2017) xxx–xxx

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 xxxx

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.

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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
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Please cite this article as: Aguilar, E.J., et al., Emotional fMR auditory paradigm demonstrates normalization of limbic hyperactivity after cognitive behavior therapy for auditory h..., Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.07.024

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	

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