Schizophrenia Research 145 (2013) 27–32

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

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

The influence of stimulus detection on activation patterns during auditory hallucinations

Remko van Lutterveld [a,b,*,1], Kelly M.J. Diederen [a,b,1], Sanne Koops [a], Marieke J.H. Begemann [a], Iris E.C. Sommer [a,b]

[a] Department of Psychiatry, University Medical Center, Utrecht, The Netherlands
[b] Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 23 February 2012
Received in revised form 2 January 2013
Accepted 3 January 2013
Available online 1 February 2013

Keywords:
Auditory hallucination schizophrenia
Stimulus detection
Auditory target detection
Inferior frontal gyrus
Heschl's gyrus

ABSTRACT

Introduction: Neuroimaging studies investigating auditory verbal hallucinations (AVH) have revealed involvement of several cortical structures. These findings may however be biased by brain activity related to stimulus detection and motor processes associated with the task to indicate the presence of AVH. Disentangling brain activation specifically related to AVH and to additional cognitive processes may help focus on the true neuronal substrates of AVH and strengthen the development of new focal treatment strategies.

Methods: Brain activation during AVH as indicated by button press was compared to brain activation during auditory stimulus detection indicated by button press. We performed two neuroimaging meta-analyses, assessing 10 AVH and 11 auditory stimulus detection studies. A random-effects activation likelihood estimation was performed using GingerALE to assess commonalities and differences across AVH and stimulus detection studies.

Results: Activity in the claustrum, pulvinar area, medial geniculum body, pyramis, culmen, putamen, insula, and parahippocampal, medial frontal, precentral, postcentral, superior temporal and right inferior frontal gyri was found to be specifically related to AVH. The pars opercularis of the left inferior frontal gyrus and the left transverse temporal gyrus were activated to a similar extent during AVH and auditory stimulus detection.

Discussion: Development of new focal treatment strategies for AVH may focus on the areas uniquely activated in the AVH analysis. The pars opercularis and the transverse temporal gyrus may not be directly involved in the experience of AVH itself, but rather in auditory stimulus detection.

1. Introduction

Auditory verbal hallucinations (AVH) are one of the prominent symptoms of psychosis. Indeed, approximately 70% of schizophrenia patients present with this symptom (Nayani and David, 1996; Slade and Bentall, 2002). AVH can be highly distressing, often disrupt social functioning and increase the risk for suicide (Falloon and Talbot, 1981; Cheung et al., 1997). Although the precise pathophysiological mechanism of AVH remains unknown, previous studies put a step forward in elucidating the brain processes related to this symptom by assessing brain activation during the state of AVH. In these 'symptom-capture' studies, hallucination episodes were contrasted with hallucination-free episodes, and results revealed significant activation of the bilateral inferior frontal gyri, bilateral (parieto)temporal areas and medial temporal lobe structures during AVH (Diederen et al., 2010; Jardri et al., 2010). One problem with this approach is that the activation of some of the areas implicated in the experience of AVH may not be specific for the actual experience, but related to additional cognitive processes needed to indicate the presence of voices during the scans such as stimulus detection and motor activity. The non-specific parts of these paradigms resemble auditory target detection studies, in which a subject is typically asked to respond to a target sound that is contrasted to a baseline sound. Indeed, auditory target detection studies elicit activation patterns that resemble those observed during AVH, including activation in the inferior frontal and (parieto)temporal areas (Kiehl et al., 2001, 2005b; Arja et al., 2010). Elucidating the involvement of brain regions that are not specifically involved in AVH may help focus on the true neurobiological underpinnings of hallucinations. To this end, we conducted two meta-analyses, with one analysis assessing the AVH symptom-capture literature and the other one assessing auditory target detection studies.

* Corresponding author at: University Medical Center, Department of Psychiatry, B01.206, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. Tel.: +31 887550880; fax: +31 887555509.
E-mail address: R.vanlutterveld@umcutrecht.nl (R. van Lutterveld).

[1] Both authors contributed equally to this paper.

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.01.004

2. Methods

2.1. Selection of studies

A systematic search of peer-reviewed articles in the English language was conducted to identify studies on AVH and auditory target detection published between January 1990 and October 2011, using the databases Pubmed and Embase. The following keywords were used for studies on AVH: "Hallucinations" <AND> ("fMRI" <OR> "PET"). The following keywords were used for studies on target detection: "Target detection" <OR> "stimulus detection" <OR> "novel stimuli" <OR> "novelty" <OR> "search task" <OR> "oddball" <AND> ("fMRI" <OR> "PET"). Furthermore, reference lists of the included studies were used to identify additional studies. A total of 484 target detection studies and 302 AVH studies were retrieved. These articles were assessed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/statement.htm; Supplementary Data S1 and S2). Articles on AVH and stimulus detection were excluded if they did not meet the following criteria:

1) A whole-brain analysis was conducted. Region of interest (ROI) analyses were excluded as this might bias the results towards predefined regions.
2) Independent component analyses (ICA) were excluded since they are not easily comparable with other fMRI or PET analyses (Tie et al., 2008).
3) Studies investigating fMRI signals during event-related potentials (ERPs) were excluded as possible mismatches between electroencephalography (EEG) and fMRI may influence the comparability of these studies with fMRI/PET-only studies (Ritter and Villringer, 2006).
4) Participants indicated the presence of auditory target stimuli or AVH by button press.

An additional criterion for the AVH analysis was:

5) A within-subjects contrast of periods of hallucinations versus non-hallucinations was studied.

Additional criteria for the stimulus detection analysis included:

6) The paradigm is an *auditory* target detection task with non-speech sounds. Auditory target detection tasks with speech targets were excluded to prevent identifying brain regions associated with the perception of speech instead of with the detection of an auditory stimulus. Stimulus detection studies have been conducted in several sensory modalities, including tactile, visual and auditory. We focused our analysis on auditory studies as the experience of AVH is in this domain.
7) A within-subjects contrast of brain activity during target sounds with non-target sounds was studied.

For studies with missing or incomplete data, an attempt was made to complete the data by email contact with the corresponding author. This attempt was successful only for the non-psychotic individuals with AVH in Diederen et al. (2011). Additional details regarding inclusion and exclusion of specific studies are provided in Supplementary Data S3. In total, 10 whole-brain AVH imaging studies were included with a total of 80 participants and 158 foci. In addition, 11 whole-brain target detection imaging studies were included with a total of 284 participants and 334 foci. All of the included AVH studies are provided in Table 1 and the included stimulus detection studies are provided in Table 2. From each of these studies, the significant ($P<.05$) coordinates (x,y,z) that were observed were extracted. Coordinates that were reported in Talairach space were converted to MNI coordinates using the Lancaster transform tal2icbm (Lancaster et al., 2007).

Table 1
Included studies measuring brain activity associated with auditory verbal hallucinations.

Study	Imaging method	N	Population diagnosis	No. of foci	Coordinates
Blom et al. (2011)	fMRI	1	Psychotic disorder	31	Talairach
Diederen et al. (2011)	fMRI	21	Non-psychotic AVH	19	MNI
Sommer et al. (2008)	fMRI	24	Psychotic disorder	21	MNI
Hoffman et al. (2008)	fMRI	6	Psychotic disorder	6	Talairach
Shergill et al. (2004)	fMRI	2	Psychotic disorder	5	Talairach
Copolov et al. (2003)	PET	8	Psychotic disorder	6	Talairach
Shergill et al. (2000)	fMRI	6	Psychotic disorder	27	Talairach
Lennox et al. (2000)	fMRI	1 (×4)	Psychotic disorder	19	Talairach
Dierks et al. (1999)	fMRI	1 (×3)	Psychotic disorder	15	Talairach
Silbersweig et al. (1995)	PET	5	Psychotic disorder	9	Talairach

2.2. Meta-analysis procedure: activation likelihood estimation (ALE)

The two meta-analyses were performed using a widely used technique for coordinate-based meta-analysis of neuroimaging studies. Data were analyzed using the activation likelihood estimation (ALE) method implemented in the GingerALE 2.1 software (http://brainmap.org/ale; Eickhoff et al., 2009). This method treats reported foci as spatial probability distributions centered at the given coordinates. In this method, all the reported activation foci for each study are first modeled as three-dimensional Gaussian probability functions, which are summed across the experiments to generate a map of interstudy consistencies that estimate the likelihood of activation on a voxel-to-voxel basis. To find statistically significant areas of convergence between studies, a reference distribution was made to represent a random distribution between studies. The false discovery rate (FDR) method was used to correct for multiple comparisons at a significance threshold of $P<0.05$ and a cluster size threshold of $100\ mm^3$. The analysis was constrained to the gray matter mask implemented in GingerALE. To test for overlap between the convergence found in the AVH and the auditory target detection analysis we computed a conjunction analysis between the ALE maps of the two meta-analyses. ALE results were exported as NifTI files into the

Table 2
Included studies measuring brain activity associated with auditory target detection in healthy subjects.

Study	Imaging method	N	No. of foci	Coordinates	Contrast
Witt et al. (2010)	fMRI	33	28	MNI	Target tone vs baseline tone
Arja et al. (2010)	fMRI	34	40	MNI	Target tone vs baseline tone
Petit et al. (2007)	fMRI	8	24	MNI	Target tone vs baseline tone
Laurens et al. (2005)	fMRI	10	48	Talairach	Go vs NoGo tone
Kiehl et al. (2001)	fMRI	10	35	Talairach	Target tone vs baseline tone
Stevens et al. (2000)	fMRI	10	23	Talairach	Target tone vs baseline tone
Friedman et al. (2009)	fMRI	15	35	MNI	Target tone vs baseline tone
Vouloumanos et al. (2001)	fMRI	15	5	Talairach	Complex nonspeech vs simple tones
Kiehl et al. (2005b)	fMRI	100	38	MNI	Target tone vs baseline tone
Liddle et al. (2006)	fMRI	28	31	Talairach	Target tone vs baseline tone
Wolf et al. (2008)	fMRI	21	27	MNI	Target tone vs baseline tone