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The influence of stimulus detection on activation patterns during auditory hallucinations

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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.

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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.

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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

Mricron software (http://www.sph.sc.edu/comd/rorden/mricron/) and overlaid on an anatomical template for visualization purposes.

3. Results

3.1. Auditory verbal hallucinations

Significant convergence across AVH-studies was found in several brain regions. The largest clusters of activation were found in the left putamen, the right insula and the left postcentral gyrus. Furthermore, activation was observed in the right medial frontal gyrus, the right inferior frontal gyrus and the left insula. Other significantly activated brain regions across studies included the right postcentral gyrus, the bilateral claustrum, the left superior temporal gyrus, the left precentral gyrus and the left parahippocampal gyrus. Cerebellar and thalamic regions were also activated. Detailed information about the coordinates of local maxima is shown in Table 3 and a visual representation of the results is provided in Fig. 1.

3.2. Auditory target detection

Significant convergence across auditory target detection studies was found in the bilateral superior temporal gyrus, the anterior cingulate gyrus, the bilateral insula, the right claustrum, the left postcentral gyrus, the left posterior cingulate gyrus and the left precentral gyrus. Furthermore, activation was observed in the bilateral inferior parietal lobule, left amygdala, bilateral putamen, bilateral culmen, inferior occipital gyrus, bilateral middle frontal gyrus, right inferior frontal gyrus and left superior frontal gyrus. Cerebellar and thalamic regions were also activated. Detailed information about the coordinates of local maxima is shown in Table 4 and a visual representation of the results is provided in Fig. 1.

Table 3
Results of the AVH meta-analysis.

Cluster	Brain region	Laterality	MNI coordinates[a]			Cluster size (mm^3)
			x	y	z	
1	Putamen extending into the insula and precentral gyrus	Left	−44	0	6	1640
2	Insula	Right	53	11	−4	1304
3	Postcentral gyrus	Left	−47	−17	46	928
4	Pulvinar (thalamus) extending into the claustrum	Left	−30	−29	6	568
5	Medial frontal gyrus	Right	6	6	61	504
6	Culmen	Right	20	−54	−21	440
7	Inferior frontal gyrus (pars opercularis)	Right	60	8	12	224
8	Inferior frontal gyrus (pars orbitalis)	Right	48	24	0	208
9	Medial geniculum body	Left	−16	−24	−4	192
10	Insula	Left	−55	−19	16	176
11	Postcentral gyrus	Right	56	−16	20	168
12	Insula	Left	−48	−40	24	168
13	Postcentral gyrus	Right	64	−16	36	160
14	Postcentral gyrus	Right	60	−24	44	160
15	Claustrum	Right	40	−4	4	152
16	Insula	Right	44	16	10	152
17	Superior temporal gyrus	Left	−60	−56	20	152
18	Postcentral gyrus	Left	−60	−20	40	152
19	Precentral gyrus	Left	−50	6	33	136
20	Parahippocampal gyrus	Left	−24	−33	−6	128
21	Claustrum	Right	28	27	−5	128
22	Pyramis	Right	20	−64	−30	112

[a] Coordinates are in the stereotaxic space of the weighted center for each cluster showing converging activation across AVH-studies.

3.3. Areas solely activated during AVH

The left thalamic pulvinar area, left claustrum, right medial frontal gyrus, left medial geniculum body, right postcentral gyrus, left parahippocampal gyrus and right pyramis of the cerebellum were found to be activated during AVH and not during auditory stimulus detection.

3.4. Areas activated during AVH and auditory stimulus detection at spatially distinct regions

The left putamen, bilateral insula, left precentral and postcentral gyrus, right culmen, right inferior frontal gyrus, right claustrum and left superior temporal gyrus were activated in both meta-analyses, but at spatially distinct regions.

3.5. Conjunction analysis

A conjunction analysis on AVH and auditory target detection showed overlap between activated brain regions in the pars opercularis of the left inferior frontal gyrus and the left transverse temporal gyrus (Fig. 1). Detailed information about the coordinates of local maxima is shown in Table 5 and a visual representation of the results is provided in Fig. 1.

4. Discussion

We compared brain activity during auditory stimulus detection to activity during auditory verbal hallucinations (AVH) using two meta-analyses. The aim of this comparison was to disentangle brain activity specifically related to AVH from potentially non-specific aspects related to the detection and signaling of AVH. We found that the left thalamic pulvinar area, left claustrum, right medial frontal gyrus, left medial geniculum body, right postcentral gyrus, left parahippocampal gyrus and right pyramis of the cerebellum were uniquely activated during AVH. The left putamen, bilateral insula, left precentral and postcentral gyrus, right culmen, right inferior frontal gyrus, right claustrum and left superior temporal gyrus were activated in both meta-analyses, but at spatially distinct regions, suggesting different involvement in AVH compared to stimulus detection. Convergent activity at the same locations during AVH and stimulus detection was observed in the pars opercularis of the left inferior frontal gyrus (IFG) and the left transverse temporal gyrus (Heschl's gyrus). This implies that the activity observed in these areas during AVH symptom capture studies may not be specific for AVH, but could be related to the signaling of AVH.

Among the areas that uniquely activated during AVH were three peaks located in the right postcentral gyrus. Activity in this area may be related to the generation of inner speech (Shergill et al., 2002) and incorrect interpretation of inner speech has been hypothesized to underlie the genesis of AVH (Feinberg, 1978). Furthermore, activation of the left parahippocampal gyrus was found in the AVH meta-analysis only, suggesting that this region is specifically associated with AVH. Activity in this area during the experience of AVH has previously been linked to memory processes involved in the genesis of AVH (Jardri et al., 2010). Both meta-analyses showed activation in similar brain areas at spatially distinct regions, including the right IFG. AVH were related to activity in the pars opercularis and the pars orbitalis, while stimulus detection was related to activity in the pars triangularis and a distinct part of the pars opercularis. This implies that the activation of right IFG regions during the experience of AVH is not related to stimulus detection or manual signaling. Perhaps activation of the right IFG in AVH reflects language production as has been suggested in previous studies (Sommer et al., 2008; Sommer and Diederen, 2009). The results of our two meta-analyses suggest that the areas in the AVH analysis having spatially distinct

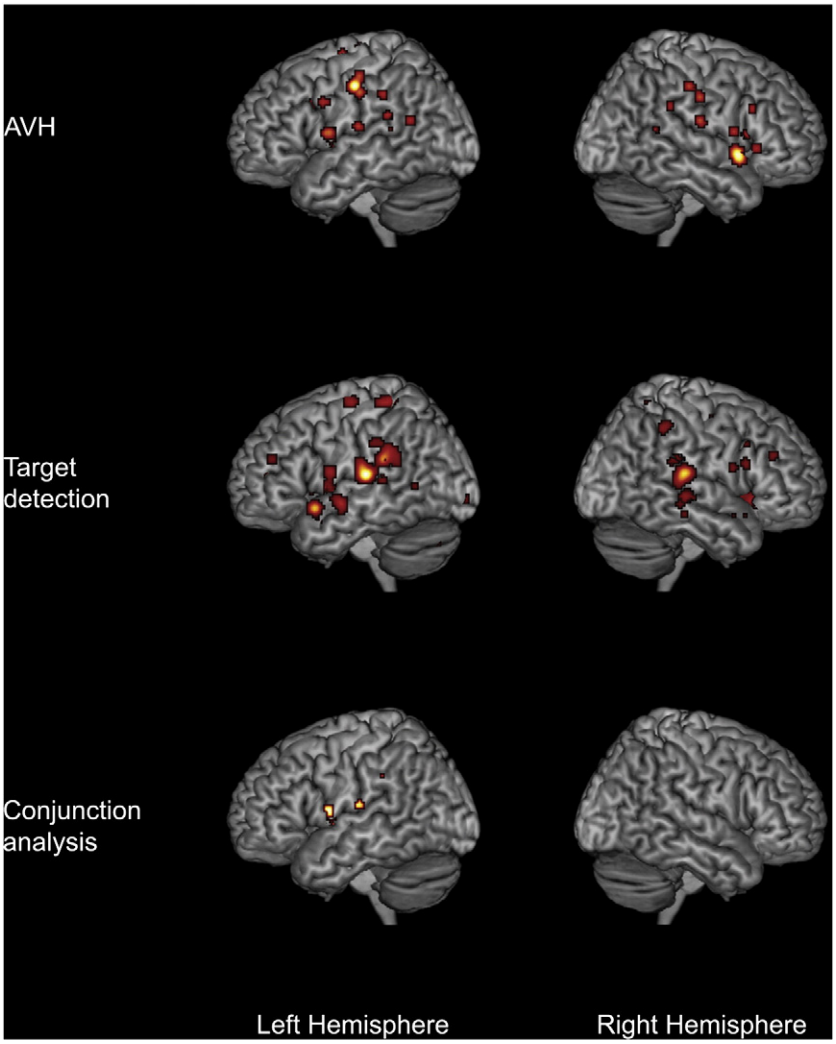

Fig. 1. ALE-maps of converging activation across AVH-studies (first row), auditory target detection studies (second row) and an AVH target detection conjunction (third row). Abbreviations: L = left, R = right. All clusters were > 100 mm^3 corrected with false discovery rate (FDR), $P<0.05$.

locations compared to the stimulus detection analysis may provide targets for neuromodulation to alter AVH proneness. An example of such a focal treatment is repetitive transcranial magnetic stimulation (rTMS), which has been used to target the area of maximal hallucinatory activation calculated from individual functional magnetic resonance imaging (fMRI) scans (Hoffman et al., 2007; Sommer et al., 2007, 2010). While the claustrum, thalamic pulvinar area, medial geniculum body, parahippocampal gyrus, pyramis, culmen, putamen and insula may be located too deeply to influence their activity with regular rTMS, stimulation at the inferior frontal, precentral, postcentral, superior temporal and medial frontal gyri is feasible with standard TMS coils. Alternatively, individuals may be trained to decrease activity of these regions with a neurofeedback paradigm (McCarthy-Jones, 2012).

Findings from the conjunction analysis suggest that the activation of the left transverse temporal gyrus and the pars opercularis of the left inferior frontal gyrus may not be specific for AVH but could also be related to the process of auditory target detection and the manual response to signal the hallucinatory episode. This suggestion contrasts with the widely accepted view that the activity of the left inferior frontal area during AVH is related to speech generation as it includes Broca's area (Jardri et al., 2010). However, it may be hard to distinguish between specific and non-specific activities in these areas in studies that apply button-press paradigms to signal AVH. These findings show that button-press designs for symptom capture studies are problematic as they introduce additional neurocognitive processes related to stimulus detection, motor preparation and execution. A number of studies have already attempted to circumvent the button-press paradigm. Shergill et al. (2000) proposed an alternative design, the random-sampling paradigm, in which no manual response is required. This sparse imaging design capitalizes on the lag of several seconds between neuronal activity and the maximum blood-oxygen-level dependent (BOLD) signal. The patient verbally indicates when the random scan starts whether he or she hallucinated in the few seconds preceding the scan. In this way, the acquired scans can contain AVH episodes that are not contaminated with motor-related activity. While this design elegantly circumvents several problems of the button-press design, many hallucinatory episodes will be missed by means of random sampling, which severely decreases power. Moreover, similar to the button-press paradigm, attention effects are likely to be induced by this design, as patients are required to continuously monitor whether they experienced hallucinations in the preceding seconds. A second approach was recently employed by Jardri et al. (in press). They acquired a resting state scan in which patients did not receive any instructions. After completion of the fMRI scan, patients were questioned about the duration and timing of their AVH during the scan. By the use of independent component analysis (ICA), these characteristics were compared to

Table 4
Results of the auditory stimulus detection meta-analysis.

Cluster	Brain region	Laterality	MNI coordinates[a]			Cluster size (mm^3)
			x	y	z	
1	Superior temporal gyrus extending into the insula	Left	−60	−29	19	4232
2	Anterior cingulate gyrus	Right	0	12	42	3232
3	Superior temporal gyrus	Right	60	−27	13	1952
4	Insula extending into the precentral gyrus	Left	−47	1	8	1512
5	Claustrum extending into the putamen	Right	35	19	−4	1424
6	Lateral posterior nucleus (thalamus) extending into the mammillary body	Left	−14	−18	6	1096
7	Medial dorsal nucleus (thalamus)	Right	10	−15	4	1008
8	Superior temporal gyrus	Left	−49	12	−11	888
9	Postcentral gyrus	Left	−36	−38	65	736
10	Superior temporal gyrus	Left	−56	−6	−7	696
11	Anterior lobe extending into the culmen	Right	18	−56	−28	688
12	Superior temporal gyrus extending into the insula	Right	53	−24	−3	536
13	Posterior cingulate gyrus	Left	2	−30	26	496
14	Precentral gyrus	Left	−36	−14	65	376
15	Inferior parietal lobule	Right	54	−41	46	304
16	Amygdala extending into the putamen	Left	−30	−3	−13	296
17	Putamen	Right	24	3	−12	248
18	Inferior parietal lobule	Left	−51	−32	36	240
19	Inferior occipital gyrus	Left	−17	−94	−3	224
20	Culmen	Left	−6	−69	−3	176
21	Middle frontal gyrus	Left	−28	44	12	168
22	Inferior parietal lobule	Right	69	−33	24	168
23	Inferior frontal gyrus (pars triangularis)	Right	62	16	21	160
24	Superior frontal gyrus	Left	−38	42	24	144
25	Middle frontal gyrus	Right	39	36	26	136
26	Superior temporal gyrus	Left	−68	−36	9	128
27	Superior temporal gyrus	Right	45	−28	16	128
28	Inferior frontal gyrus (pars opercularis)	Right	52	7	18	120

[a] Coordinates are in the stereotaxic space of the weighted center for each cluster showing converging activation across target detection studies.

the independent component (IC) time courses, to help select the ICs that captured hallucinations. This design effectively prevents the problems that are related to a button-press paradigm. This method relies heavily on insight of the patient when hallucinations took place while they were not instructed to pay attention to the phenomenon.

Designs as described above should be further explored to successfully circumvent the button-press paradigm. Another recommendation for future research is to combine an AVH button-press task and an auditory target detection task in an fMRI experiment. Such an approach allows for a cross-over comparison of activated brain regions for AVH and auditory target detection. Moreover, it avoids the problem of comparison across dissimilar groups.

Table 5
Results of the conjunction analysis.

Cluster	Brain region	Laterality	MNI coordinates			Cluster size (mm^3)
			x	y	z	
1	Pars opercularis of the inferior frontal gyrus/precentral gyrus/insula	Left	−48	2	8	872
2	Transverse temporal gyrus	Left	−56	−20	15	160

4.1. Limitations

The results of the present study should be interpreted with some caution. A difference in power may exist between the two meta-analyses. First, meta-analysis of neuroimaging AVH studies is limited by the small sample sizes of most studies (Kompus et al., 2011). Although both meta-analyses included a similar number of studies, the meta-analysis concerning auditory stimulus detection consisted of a significantly greater overall sample, leading to greater power in the stimulus detection meta-analysis than the AVH meta-analysis. Increasing power in the AVH analysis may lead to an increased number of uniquely activated areas in the AVH analysis, and subsequently to additional conjoint activity with the stimulus detection analysis. Second, AVH are heterogeneous across subjects, while the tones presented in the auditory detection tasks are kept constant within a study. This may also have affected power in the AVH studies compared to the auditory detection studies. Third, the tones that were presented in the auditory target detection studies were presented for a short time (typically shorter than 1 s), while hallucinations are often longer in duration (Daalman et al., 2011; van Lutterveld et al., 2012). A further limitation is that the preponderance of AVH studies included in the present meta-analysis was conducted in patients with a psychotic disorder whereas the auditory detection studies were performed in healthy control subjects. It may be possible that brain activity related to target detection is not completely similar in healthy subjects and schizophrenia patients. However, previous work indicated that schizophrenia patients show a similar pattern of brain activity as healthy controls during auditory stimulus detection, although this activity was lower compared to the control subjects in several regions (Kiehl et al., 2005a). Furthermore, a study by Ngan et al. (2003) showed largely similar brain activation in both populations doing a target detection task. However, differences were found in the left middle temporal gyrus and the right cuneus. As these areas were not implicated in the AVH meta-analysis, they are not likely to influence the conjunction analysis in the current study. A final limitation is the dissimilar number of foci across conditions.

In sum, we assessed commonalities in brain activation during AVH and auditory stimulus detection. Overlap in activation was found in the left inferior frontal gyrus and left transverse temporal gyrus, which indicates that the activation in these areas might not be specifically related to AVH. Other areas, including the right postcentral gyrus and the left parahippocampal gyrus, were uniquely activated in the AVH paradigm and are areas on which future focal treatment strategies could focus.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.01.004.

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Contributors

Remko van Lutterveld and Kelly Diederen designed the study, analyzed the data, and wrote the manuscript. Sanne Koops collected the data, analyzed the data, and wrote the first draft of the paper. Marieke Begemann was involved in data analysis. Iris Sommer supervised the study and edited the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest statement

The authors have no conflicts of interest to report.

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