



Review article

The neural mechanisms of hallucinations: A quantitative meta-analysis of neuroimaging studies



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ABSTRACT

Activation likelihood estimation meta-analysis of functional neuroimaging data was used to investigate the neural mechanisms underlying auditory-verbal and visual hallucinations (AVHs and VHs). Consistent activation across studies during AVHs, but not VHs, in Wernicke's and Broca's areas is consistent with involvement of speech and language processes in the experience of hearing voices when none are present. Similarly, greater activity in auditory cortex during AVHs and in visual cortex during VHs supports models proposing over-stimulation of sensory cortices in the generation of these perceptual anomalies. Activation across studies in the medial temporal lobe highlights a role for memory intrusions in the provision of content for AVHs, whereas insula activation may relate to the involvement of awareness and self-representation. Finally, activation in the paracingulate region of medial prefrontal cortex during AVHs is consistent with models implicating reality monitoring impairment in the misattribution of self-generated information as externally perceived. In the light of the results, the need for unified theoretical frameworks that account for the full range of hallucinatory experiences is discussed.

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1. Introduction

The phenomenon of hallucinations, whereby perceptions with no basis in the external world are endogenously generated by the mind, may be one of the best reflections of the notion that reality is inherently subjective. Indeed, [Dennett \(1991\)](#) noted the tight relationship between questions regarding the nature of hallucinations and those that explore the nature of consciousness. A hallucination has been formally defined as a “sensory experience which occurs in the absence of corresponding external stimulation of the relevant sensory organ, has a sufficient sense of reality to resemble a veridical perception, over which the subject does not feel they have direct and voluntary control, and which occurs in the awake state” ([David, 2004](#)). Hallucinations are a core symptom of schizophrenia, and are also manifest in a range of other clinical and nonclinical populations, including bipolar disorder ([Baethge et al., 2005](#)) and Parkinson's disease ([Fénelon et al., 2000](#)), as well as in many individuals who are not mentally ill ([Tien, 1991](#)). These erroneous perceptions can span a multitude of sensory modalities: in schizophrenia, visual and auditory hallucinations have a prevalence of approximately 27% and 59% respectively, and for nonclinical individuals these rates are around 6% ([Waters et al., 2014](#)) and 10–15% ([Sommer et al., 2010](#)) respectively. Olfactory, somatic, and gustatory hallucinations have also been recorded ([Tousi and Frankel, 2004](#); [Takaya et al., 2005](#); [Ohayon, 2000](#)). Due to the intrusive and uncontrollable nature of these internally generated perceptions, they can be distressing and disabling. Understanding the cognitive and neural mechanisms underlying the experience of hallucinations in these populations therefore has considerable scientific and clinical significance.

There are two main types of functional neuroimaging studies of hallucinations: state and trait studies. In state studies, participants are scanned while experiencing a hallucination and indicate its onset and offset with a button press or a balloon squeeze. State studies typically have within-subject designs, involving a contrast of brain activity in the resting versus hallucinatory state. In trait studies, the comparison is usually between hallucinators and non-hallucinators with regards to their brain activity during the resting state or an experimental task. Such studies can also utilize hallucination severity scores as regressors when analysing neural activity ([Ford et al., 2015](#)).

Although several research groups have explored the neural underpinnings of the hallucination experience, there has been limited theoretical overlap or established consensus. This is in part due to the challenge of capturing spontaneous hallucinations in the neuroimaging scanner, and consequently the small sample sizes of many studies, which makes generalization difficult. The subjective nature of hallucinations may also mean individual differences in the underlying neural substrates, which could confound conclusions based on case studies. Thus, as noted by [Jardri et al. \(2011\)](#) regarding auditory hallucinations, the findings of state studies are inconsistent. On the one hand, some have reported activations in sensorimotor areas, such as the primary auditory cortex ([Dierks et al., 1999](#); [van de Ven et al., 2005](#)) or Broca's area ([McGuire et al., 1993](#)) during auditory verbal hallucinations (AVHs), and occipital and temporal cortices during visual hallucinations (VHs; [Ffytche et al., 1998](#)). Such findings support the view that hallucinations originate from dysfunctions in modality-specific sensory processing regions. On the other hand, the hippocampus and parahippocampal gyrus have been identified as exhibiting brain activity during AVHs ([Copolov et al., 2003](#)) and VHs ([Oertel et al., 2007](#)), suggesting the additional involvement of memory processes in the hallucinatory experience. Other experiments have revealed more distributed networks of cortical and subcortical activity (e.g. [Shergill et al., 2000](#)). Hence, there is still significant ambiguity about the neural mechanisms that underlie hallucinations, an uncertainty

that is amplified by the lack of unified theories that account for hallucinations in multiple modalities.

Qualitative literature reviews are critical for informing cognitive theories of hallucinations (e.g., [Allen et al., 2008](#); [de Leede-Smith and Barkus, 2013](#)), but there is a danger of overestimating the evidence in favour of dominant theories and neglecting valuable data. Coordinate-based meta-analyses (CBMA) offer a more objective quantification of the existing evidence independently of past interpretations of the data. As outlined by [Fox et al. \(1998\)](#), meta-analyses of neuroimaging findings differ from traditional meta-analysis techniques in that they are “effect-location” rather than “effect-size” analyses. Instead of estimating the cross-study effect magnitude, CBMAs seek to identify brain regions exhibiting a consistent effect ([Bartra et al., 2013](#)). This meta-analytic technique avoids a number of weaknesses of effect-size meta-analyses; for instance, whereas publication bias can lead to exaggerations of effect sizes, this inflation is not as probable for estimations of effect locations ([Fox et al., 1998](#)). Hence, using CBMA to assess all suitable state studies of hallucinations is a useful technique for exploring the functional nature of the hallucinating brain.

We are aware of four meta-analyses published to date that have assessed brain activity across state studies of hallucinations. [Jardri et al. \(2011\)](#) examined cortical activations during AVHs in schizophrenia, analysing ten studies involving 68 patients and reporting significant activation across studies in a bilateral network including Broca's area, primary auditory cortex, bilateral insula, and left hippocampus and parahippocampal gyrus. In a similar meta-analysis conducted by [Kompus et al. \(2011\)](#), 12 studies were analysed which included individuals with mixed diagnoses (predominantly schizophrenia) who experienced AVHs. Kompus et al. observed AVH-related activity in the left insula, left hippocampus, left primary auditory cortex, and right inferior frontal gyrus (the right homologue of Broca's area). They also compared these results with a meta-analysis of brain activations associated with exogenous processing of external auditory stimuli, demonstrating that an overlapping area in the left primary auditory cortex was activated during endogenously (i.e. AVHs) and exogenously evoked processing. Interestingly, this region was more active during AVHs than during external auditory processing. Further meta-analyses were conducted by [Kühn and Gallinat \(2012\)](#) and [van Lutterveld et al. \(2013\)](#) of AVHs in 10 studies of individuals with schizophrenia and 10 studies of individuals with mixed diagnoses, respectively. Overall, whereas these four meta-analyses reported similar cross-study activations of the auditory cortex and Broca's area, there were notable differences between the findings, such as in the involvement of Wernicke's area and the right homologue of Broca's area as well as in more disparate cortical and subcortical regions. These inconsistencies might perhaps be explained by the small number of studies analysed by each meta-analysis, and the use of different statistical thresholds among other methodological variations.

The present meta-analysis has three aims that go beyond what has been previously undertaken in the field. Firstly, it will include hallucinations of different modalities; although there have been quantitative meta-analyses of AVHs in schizophrenia, this is the first to analyse the state of the evidence for VHs, and to compare the results of auditory and visual hallucinations. Secondly, the study is not confined to hallucinations in schizophrenia, and will include appropriate studies from a number of clinical and nonclinical populations. Thirdly, the present study is the most comprehensive meta-analysis conducted on the topic of hallucinations thus far, combining findings from 23 independent datasets and incorporating studies spanning the last 20 years (1995–2015).

The quantitative meta-analytic procedure employed here is the activation likelihood estimation (ALE; [Eickhoff et al., 2012](#)) method, which models the convergence of activation coordinates across studies and generates statistical maps of consistent brain activity. A

major advantage of the ALE meta-analysis technique is that it relies on the precise coordinates of reported activity rather than broad author-assigned anatomical labels; this ensures fewer errors and higher spatial resolution (Turkeltaub et al., 2002; Di Martino et al., 2009; Laird et al., 2005b). An alternative approach is multilevel kernel density analysis (MKDA), which measures the proportion of foci exhibiting activity within a specified radius of each voxel (Wager et al., 2009). Salimi-Khorshidi et al. (2009) have demonstrated that ALE is the preferable CBMA method in that it generates results that are most comparable to the “gold standard” provided by image-based meta-analyses (IBMA). Without access to the full imaging data for each study required for IBMA, ALE is a preferred method for meta-analytical comparison of neuroimaging findings. Recently, ALE meta-analyses have been used to study the neural networks underlying prospective memory (Cona et al., 2015), emotion regulation (Kohn et al., 2014), and language comprehension (Rodd et al., 2015), among other topics in the psychological and behavioural sciences, demonstrating its strength and versatility.

2. Methods

2.1. Systematic literature search

A systematic selection of appropriate peer-reviewed functional neuroimaging studies was undertaken by searching the databases of PubMed (<http://www.pubmed.org/>), SciVerse Scopus (<http://www.scopus.com/>), and Google Scholar (<http://www.scholar.google.com/>). The keyword combination “hallucination AND (fmri OR ‘functional magnetic resonance’ OR neuroimaging OR pet OR “positron emission tomography”)”, yielded 354 articles in total when the search results were merged and duplicates were eliminated (February 2015). This number includes references cited in previous meta-analyses and review papers examining hallucinations.

Articles were evaluated according to the following inclusion and exclusion criteria. Inclusion criteria: (1) A state rather than trait

study of AVHs or VHs, such that neuroimaging data were acquired while the individual was experiencing hallucinations; (2) Primary research study using human participants; (3) Participants clearly indicated the presence and duration of a hallucination by button press or squeezing a ball, or verbally after the event; (4) Study used a functional neuroimaging technique (fMRI or PET); (5) Coordinates of whole-brain activations during hallucinations were provided in Montreal Neurological Institute (MNI) or Talairach standard stereotactic space. Exclusion criteria: (1) The study measured brain activation prior to or after hallucination onset, instead of during the hallucination experience; (2) The study used an experimental technique to induce hallucinations, rather than measuring spontaneous, endogenously evoked hallucinations; (3) The subject had experienced significant brain damage; (4) Analysis was based solely on one or more regions of interest (ROIs), for instance it used anatomical masks or coordinates from other studies – this is important as including ROI analyses might lead to a bias towards predefined regions in the meta-analysis.

The titles and abstracts of the 354 papers generated by the literature search were reviewed, and a large number were rejected as they conspicuously did not meet the inclusion criteria. This led to a shortlist of 38 articles for full-text review, which were carefully screened and analysed by at least two of the present authors. Papers which elicited uncertainty regarding selection were discussed in detail until a consensus was reached.

Email contact was made with the authors of eight papers where the study met the inclusion criteria but where whole-brain coordinates had not been included in the original articles. Three replies with the inclusion of data provided further datasets for the analysis. Three studies that were included in Kompus et al.’s (2011) meta-analysis were excluded from the current analysis. In one case this was to avoid duplicating data from the same subjects who had been involved in another study included in the analysis (Diederer et al., 2010), whereas the other two studies failed to meet the present inclusion criteria: Shergill et al.’ (2001) study included somatic hallucinations, and in Barkus et al.’ (2007) study, the hallucinations were not freely initiated.

Table 1
Studies included in the ALE meta-analysis.

Study	Population	SubjectsN	FociN	Stereotaxic Space
Auditory Verbal Hallucinations				
Blom et al. (2011)	Alice in Wonderland syndrome	1	31	Talairach
Copolov et al. (2003) ¹	Schizophrenia	8	6	Talairach
Diederer et al. (2012) ²	Healthy subjects	21	19	MNI
Diederer et al. (2013)	Psychotic disorders	33	34	MNI
Dierks et al. (1999)	Schizophrenia	3	27	Talairach
Jardri et al. (2013)	Psychotic disorders	14	11	Talairach
Lennox et al. (2000)	Schizophrenia	4 × 1	19	Talairach
Linden et al. (2010)	Healthy subjects	7	21	Talairach
Raij et al. (2009)	Psychotic disorders	11	6	Talairach
Shergill et al. (2000)	Schizophrenia	6	20	Talairach
Shergill et al. (2004)	Schizophrenia	2	5	Talairach
Silbersweig et al. (1995) ¹	Schizophrenia	5	9	Talairach
Sommer et al. (2008)	Schizophrenia	24	21	MNI
	Total AVHs	190	229	
	13 studies, 16 datasets			
Visual hallucinations				
Ffytche et al. (1998)	Charles Bonnet syndrome	4 × 1	16	Talairach
Goetz et al. (2014)	Parkinson’s disease	1	36	MNI
Jardri et al. (2013)	Schizophrenia	15	8	Talairach
Oertel et al. (2007)	Schizophrenia	1	17	Talairach
	Total visual hallucinations	21	77	
	4 studies, 7 datasets			

Note: 1 = PET study, all other studies used fMRI; 2 = Only data from healthy subjects was used to avoid duplication with results from Diederer et al. (2013).

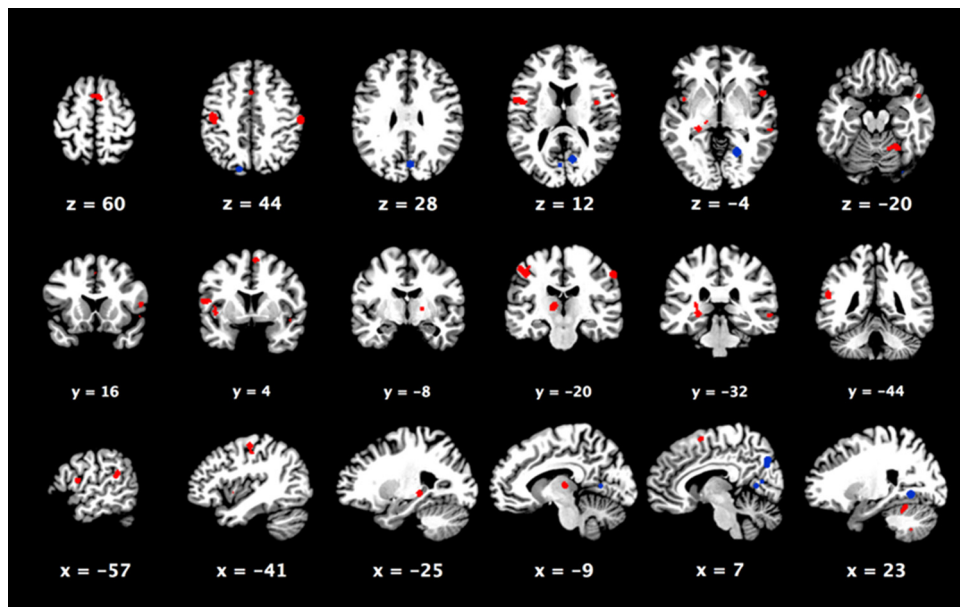


Fig. 1. Results of the ALE meta-analyses for auditory-verbal and visual hallucinations. Red = AVH; Blue = VH. Representative slices are shown in axial (top), coronal (middle) and sagittal (bottom) views with MNI planar coordinates given below each image. AVHs were associated with significant activity in regions that included Broca's and Wernicke's areas, insula, medial temporal lobe, and paracingulate region of medial prefrontal cortex. VHs were associated with significant activity in lingual and fusiform cortices, and dorsal cuneus and precuneus. See text for further details. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2. Study categorisation and extraction of coordinate data

Studies were categorised according to the type of hallucination (auditory or visual) and subject population (schizophrenia, Parkinson's disease, etc., Table 1). Significant peak activity coordinates were extracted from each study (the majority of studies used a statistical threshold of $p < 0.05$ with whole-brain multiple comparisons correction, and some used $p < 0.001$ uncorrected). Coordinates provided in Talairach space were converted to MNI format using the Lancaster transform tal2icbm provided by BrainMap's GingerALE 2.3.2 software (Lancaster et al., 2007).

In papers that included separate data for each scanned patient (Lennox et al., 2000 and Ffytche et al., 1998), these data were included separately in the GingerALE meta-analysis, resulting in 23 datasets from 17 studies in total (Table 1). Note that although a smaller number of neuroimaging datasets were included for VHs than AVHs, the number of foci obtained from these exceeded the minimum considered necessary for ALE analysis (Jardri et al., 2011).

2.3. Activation likelihood estimation (ALE) meta-analysis

Activity foci reported in each study were modelled by creating 3D Gaussian probability distributions centred at each reported x, y, z coordinate. In BrainMap's GingerALE 2.3.2, the width of the distribution, reflecting spatial uncertainty, was adjusted to accommodate between-subject variance. The modelled probability distributions for all reported foci were then combined to form a modelled activation (MA) map for that condition (VH or AVH) for each study. Given the adjustment for sample size, studies with larger numbers of subjects had tighter Gaussian distributions for all foci within an MA and hence provided greater weight to those foci when combined in the meta-analysis. Following the union of MAs across studies, activation probabilities, or ALE scores, were determined for each voxel. To enable statistical inference about spatial patterns of activation, the null hypothesis assumes that spatial patterns of activation are associated randomly across studies. A null

distribution was achieved by randomly sampling a voxel from one MA map and then doing the same for every other MA map and obtaining the union of activation probabilities in exactly the same way as for the real MAs. This process was repeated 10^{11} times to allow an ALE null distribution to be estimated, against which the derived data could be assessed (Eickhoff et al., 2009). The nonparametric p values for the ALE maps for each condition were then thresholded using the false discovery rate (FDR) whole-brain multiple comparisons correction method. For this study the FDR was set at $p < 0.05$ FDR using the more conservative p_N threshold within the GingerALE software, which makes no assumptions about the correlation of data, with a minimum cluster volume of 200 mm^3 using 'all extrema' peak cluster analysis to aid identification of individual areas of activation within large single clusters.

For the contrast analyses between AVH and VH conditions, the differences between ALE scores were calculated (Eickhoff et al., 2011). Two ALE contrast images were created by directly subtracting one input image from the other on a voxel by voxel basis (AVH – VH and VH – AVH). As this process does not take into account the differences in the sample sizes in the two analyses, GingerALE created simulated data by pooling the foci from both meta-analyses (AVH + VH) and then randomly dividing them into two new groupings of the same size as the original datasets. An ALE image was created for each new dataset and then subtracted from the other and compared to the observed data. After many permutations this process resulted in a voxel-wise p value image showing where the observed data values were located on the distribution of possible values in that voxel, based on a null distribution that took into account the difference in the sample sizes. To simplify interpretation, the values were then converted to Z scores. An uncorrected threshold of $p < 0.05$ and a minimum cluster volume of 200 mm^3 was used for the subtraction analysis to avoid Type II errors given that the individual ALE results had already been thresholded using whole-brain FDR correction (Eickhoff et al., 2012; Laird et al., 2005a). Final ALE cluster maps were exported as NIfTI files into Mango brain visualisation software (<http://ric>.

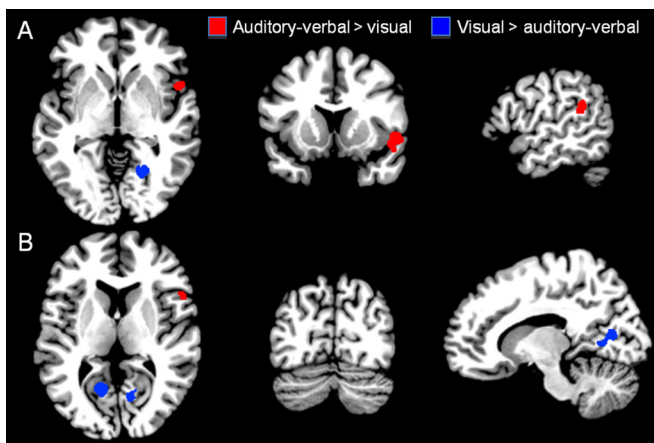


Fig. 2. Results of the ALE meta-analysis subtraction contrasts between auditory-verbal and visual hallucinations. (A) The subtraction contrast of AVHs > VHs elicited significant activity in speech and language processing areas such as superior temporal gyrus, Wernicke's area and the right homologue of Broca's area; (B) for VHs > AVHs, significant activity was observed in visual processing regions including lingual gyrus, occipital cortex, and cuneus.

uthscsa.edu/mango/), and were overlain onto a canonical anatomical T1 brain template (Colin27.T1_seg.MNI.nii).

3. Results

The results of the ALE meta-analyses for AVHs and VHs are presented in Table 2 and displayed visually in Fig. 1. Significant cross-study brain activity during AVHs was observed in a number of large clusters centred in bilateral somatosensory cortex (BA 2/3), bilateral insula (BA 13) and superior temporal gyrus (BA 22/13).

AVH-related activity was also observed in Broca's area and its right hemisphere homologue (BA 44/45), and in Wernicke's area/secondary auditory cortex (BA 22) (but not in the right hemisphere homologue of Wernicke's area). Further significant activity was observed in the left hippocampus/parahippocampal gyrus, the right motor cortex (BA 6), in bilateral thalamus and cerebellum, and in the right anterior cingulate including in the vicinity of the paracingulate sulcus. In contrast, visual hallucinations were associated with significant activity in extrastriate visual areas around the ventral lingual and fusiform gyri (BA 19), and in the more dorsal cuneus and precuneus regions (BA 18). VH-related activity was also observed in the cerebellum, on the posterior declive surface adjacent to the occipital lobe.

Thus, distinct activation patterns were observed for AVHs and VHs, with few apparent areas of overlap, suggesting little commonality in brain activity for hallucinations across the different sensory modalities. This observation was confirmed by the results of a conjunction analysis that found no significant areas of common activation across the auditory and visual modalities. Significant differences in activity associated with the two kinds of hallucinations were assessed with the use of subtraction contrasts, the results of which are presented in Table 3 and displayed visually in Fig. 2. The subtraction analysis of AVHs > VHs revealed significant clusters in the right homologue of Broca's area, in Wernicke's area, and a region of anterior BA 22 in the superior temporal gyrus. In contrast, areas of secondary and association visual cortex exhibited significantly greater activity for VHs than AVHs.

4. Discussion

The present meta-analysis investigated the neural activity that characterizes the hallucinating brain by combining and statistically

analysing functional neuroimaging studies that captured hallucinations in the brain scanner. Experiments were divided according to the sensory modality in which hallucinations were experienced to reveal similarities and differences in brain activation patterns. Replicating Jardri et al.'s (2011) meta-analytic findings, significant cross-study activation was observed in Broca's area during AVHs, a region classically associated with speech production. Significant activity in this region was not observed during VHs, a distinction that emphasizes the role of modality-specific regions in the emergence of hallucinations and supports models of AVHs as arising from a disorder in inner speech (Jones and Fernyhough, 2007), since such inner speech similarly activates Broca's area (Huang et al., 2002; McGuire et al., 1996). Interestingly, significant convergence was also found in the right homologue of Broca's area, which is implicated in response inhibition (Aron et al., 2004). This finding is consistent with theories stressing the role of top-down impairments in the evocation of hallucinations, especially given that activity in this area (inferior frontal gyrus) has previously been found to be specific to auditory hallucinations in comparison to auditory target detection (van Lutterveld et al., 2013).

Another of the clearest findings from the present meta-analysis was the involvement of the bilateral insula when examining AVHs alone, and in the subtraction analysis that contrasted AVHs with VHs. The insula has not been the focus of previous imaging studies of hallucinations, but its involvement is in line with proposals that insula dysfunction may play a role in schizophrenia (Wylie and Tregellas, 2010) and in hallucinations associated with neurodegenerative diseases (Blanc et al., 2014). Additionally, large activation clusters in the postcentral gyri were identified for AVHs, replicating the findings of some (Kompus et al., 2011; Kühn and Gallinat, 2012; van Lutterveld et al., 2013), but not all (Jardri et al., 2011), previous meta-analyses of hallucinations. Given that these clusters overlap with several areas including somatosensory and motor cortices, these activations could signify sensory-motor feedback associated with speech muscle activity that is sometimes detectable during hallucinations and subvocalizations of inner speech (Inouye and Shimizu, 1970; Stephane et al., 2001). Alternatively, it may be that the postcentral gyri activation is an artefact of the button-press or balloon-squeeze movement that participants make when indicating hallucination onset and offset (Kühn and Gallinat, 2012). As seen in Table 2, other prominent areas of activation identified for AVHs included hippocampal, thalamic, and cerebellar structures, and the paracingulate region of medial prefrontal cortex. In contrast, VHs were primarily associated with significant activation in the bilateral secondary and associate visual cortices.

The implications of the present findings may be considered in light of three common themes that have been identified among existing theories relating to the mechanisms of hallucination generation: hallucinations as being due to (i) impairments in bottom-up or top-down processing, (ii) deficits in memory recollection processes, and (iii) failures in source attribution.

4.1. Bottom-up and top-down processing impairments

Perception is generally considered to be a constructive process that requires both external sensory inputs ('bottom-up' information) and modulation from 'top-down' conceptual influences arising from task goals and prior experience (Biederman, 1972; Massaro and Simpson, 1987), such that failure in either top-down or bottom-up processing might result in a false perceptual experience. The evidence indicates that both types of processes are implicated in the generation of hallucinations, where the illusion of perceptual content can arise from deficits in top-down attentional modulation, disinhibition, and perceptual expectations, in addition to impaired bottom-up processing of external sensory information

Table 2
Significant ALE results for auditory-verbal and visual hallucinations.

Brain region	L/R	BA	x	y	z	Extrema value	Vol. (mm ³)	Notes: Cluster includes/overlaps
Auditory Verbal Hallucinations								
Postcentral Gyrus	L	3	−46	−18	44	17	2104	
Postcentral Gyrus	L	2	−52	−22	50	15		
Postcentral Gyrus	L	3	−40	−16	54	14		
Superior Temporal Gyrus	R	22	54	12	−6	14	1608	
Insula	R	13	48	8	−12	13		
Precentral gyrus	L	6	−56	4	12	15	1392	Broca's area
Insula	L	13	−44	0	4	11		
Insula	L	13	−42	4	−2	10		
Postcentral Gyrus	R	2	60	−22	44	17	1048	
Postcentral Gyrus	R	3	64	−16	36	11		
Cerebellum	R		26	−54	−20	14	1024	
Cerebellum	R		16	−56	−20	11		
Thalamus	L		−12	−20	4	16	888	
Midbrain	L		−16	−24	−4	10		
Parahippocampal Gyrus	L	27	−26	−32	−4	12	792	Hippocampus
Thalamus	L		−28	−32	8	11		
Superior Temporal Gyrus	L	13	−58	−46	20	12	792	Wernicke's area
Insula	L	13	−48	−40	24	10		
Superior Temporal Gyrus	L	22	−60	−56	20	9		
Inferior frontal gyrus	R	44	56	16	8	12	752	Homologue of Broca's area
Inferior frontal gyrus	R	45	50	24	0	11		
Inferior frontal gyrus	R	44	60	8	12	10		
Medial frontal gyrus	R	6	6	6	60	12	664	Motor cortex
Medial frontal gyrus	L	6	−2	8	60	11		
Cerebellum	R		26	−62	−46	12	560	
Cerebellum	R		16	−58	−52	10		
Insula	R	13	40	0	12	11	352	
Clastrum	R		40	−4	4	10		
Medial frontal gyrus	L	32	0	12	46	12	344	Paracingulate sulcus
Middle Temporal Gyrus	R	21	60	−32	−6	10	224	
Thalamus	R		18	−10	2	10	216	
Visual Hallucinations								
Lingual gyrus	R	19	12	−62	4	8	1672	Associate visual cortex
Cuneus	R	30	12	−68	10	8		
Cuneus	R	18	4	−76	30	8	1360	Secondary visual cortex
Cuneus	R	18	6	−76	36	8		
Lingual gyrus	R	19	20	−60	−4	8	1056	Associate visual cortex
Lingual gyrus	L	19	−14	−62	4	8	904	Associate visual cortex
Cuneus	L	19	−14	−80	40	7	760	Associate visual cortex
Cerebellum	R		32	−84	−16	4	736	Associate visual cortex
Fusiform gyrus	R	19	32	−86	−10	4		
Cuneus	L	23	−4	−76	16	8	648	Secondary visual cortex

Note: The size of each cluster is given in mm³ together with the coordinates of peak activation (in MNI atlas space) and the extrema value (ALE value, or Z-score for the contrast analysis) that indicates the relative effect size for each peak. In large clusters providing more than one peak, the foci of peak activations are listed separately and the cluster volume is left as blank. L = left hemisphere; R = right hemisphere; BA = Brodmann area; Vol = cluster volume.

or the aberrant activation of sensory cortices (Aleman and Larøi, 2008).

In accordance with bottom-up models, the present ALE meta-analysis observed activity in secondary auditory cortex during AVHs, and in secondary and association visual cortex during VHs. The regions that were found to be active during AVHs, including the middle and superior temporal gyri, have been consistently linked to externally-evoked sound processing (Rauschecker and Tian, 2000; Binder, 1997). Inferior frontal regions around Broca's area also displayed heightened activity during AVHs, which hints at an interaction between speech generation and speech perception processes that give rise to the phenomenological experience of sound in the absence of external stimuli. Moreover, VHs were associated with occipital lobe activity, consistent with findings of lingual gyrus activation during VHs following visual deprivation (Sireteanu et al., 2008), and Taylor et al. (2011) observation that VHs could be initiated by applying TMS over the occipital lobe. Similarly, VHs can occur following injury to visual processing areas in the parietal and occipital lobes (Kölmel, 1985; Wunderlich et al., 2000). Allen et al. (2008) have proposed that bottom-up impairment can lead to hal-

lucinations via the hyperactivation of secondary sensory cortices, which provides the perceptual content for the experience. This over-perceptualisation may act to modulate associated top-down processes in anterior cingulate, prefrontal, premotor and cerebellar cortices, resulting in poor self-monitoring and a false sense of agency. This in turn would lead individuals to experience their own internal auditory or visual activity as vivid external percepts.

The insula activation observed during AVHs is also consistent with models of bottom-up and top-down disruption. This region has been implicated in auditory processing (Bamiou et al., 2003), consistent with the present finding of enhanced activity during auditory but not visual hallucinations. Palaniyappan and Liddle (2012) have proposed that insula dysfunction may be important in psychosis more generally – a disorder more commonly characterized by auditory than visual hallucinations. It is notable that significant insula activation was not associated with VHs in the present analysis, which may be due to inherent differences in hallucinations in these sensory modalities or to methodological issues such as the smaller number of published neuroimaging studies for VHs (although the number exceeded the minimum considered nec-

Table 3

Significant ALE results for subtraction contrasts between auditory-verbal and visual hallucinations.

Brain region	L/R	BA	x	y	z	Extrema value	Vol. (mm ³)	Notes: Cluster includes/overlaps
Auditory Verbal Hallucinations > Visual Hallucinations								
Superior Temporal Gyrus	R	22	55	13	−4	2.2	1496	
Superior Temporal Gyrus	R	22	55	13	−8	2.2		
Superior Temporal Gyrus	R	38	54	10	−20	2.1		
Superior Temporal Gyrus	R	38	52	12	−16	2.0		
Insula	R	13	50	14	−4	2.0		
Insula	R	13	46	12	−11	1.9	736	Wernicke's area
Insula	R	13	48	4	−13	1.8		
Superior Temporal Gyrus	L	13	−56	−44	23	2.1		
Superior Temporal Gyrus	L	13	−57	−46	18	2.0		
Superior Temporal Gyrus	L	22	−60	−54	22	1.9		
Insula	L	13	−50	−40	26	1.9	512	Homologue of Broca's area
Inferior frontal gyrus	R	45	52	25	2	2.2		
Precentral gyrus	R	44	54	19	4	2.0		
Visual Hallucinations > Auditory Verbal Hallucinations								
Lingual gyrus	R	18	12	−72	6	2.6	1128	Secondary visual cortex
Cerebellum	R		14	−65	1	2.0		
Cuneus	R	23	12	−74	12	1.9	1008	Associate visual cortex
Lingual gyrus	R	19	22	−66	−4	3.5		
Culmen	R		21	−63	−7	2.7		
Lingual gyrus	L	19	−18	−63	4	3.1	904	Associate visual cortex
Lingual gyrus	L	18	−12	−68	6	2.6		
Middle occipital gyrus	R	18	36	−86	−8	3.7	624	Secondary visual cortex
Fusiform gyrus	R	19	33	−86	−9	3.4		
Cerebellum	R		36	−84	−18	3.0		

Note: The size of each cluster is given in mm³ together with the coordinates of peak activation (in MNI atlas space) and the extrema value (ALE value, or Z-score for the contrast analysis) that indicates the relative effect size for each peak. In large clusters providing more than one peak, the foci of peak activations are listed separately and the cluster volume is left as blank. L = left hemisphere; R = right hemisphere; BA = Brodmann area; Vol = cluster volume.

essay for ALE analysis; [Jardri et al., 2011](#)). Future studies examining VHs may reveal greater overlap between the neural underpinnings of AVHs and VHs, particularly in regions such as the insula, paracingulate sulcus, and insula, which are not directly implicated in bottom-up perceptual processing.

4.2. Memory and thought intrusion

A second line of theories emphasizes failure to suppress irrelevant thoughts or memories as underlying the experience of hallucinations ([West, 1962](#); [Badcock et al., 2005](#)), such that unintentional memory retrieval may occur during AVHs ([Waters et al., 2006](#)) or VHs ([Oertel et al., 2007](#)). Support for this perspective comes from findings of enhanced intrusion errors and false recognition in memory tests in both healthy individuals with a proneness to hallucinations and in patients with schizophrenia ([Brébion et al., 2007, 2010](#)) as well as a link between ruminations and hallucinations mediated by intrusive thoughts (as in [Jones and Fernyhough's \(2009\)](#) Inner Speech model of AVHs). Correspondingly, significant cross-study activation was observed in the present data in the left hippocampus and parahippocampal gyrus for AVHs, regions which are implicated in memory encoding and retrieval, and, in particular, in conscious recollection of the context in which previous events were experienced ([Squire and Schacter, 2002](#)). Consistent with this idea, structural and functional impairments and asymmetries in medial temporal regions have been observed in schizophrenia ([McDonald et al., 2000](#); [Harrison, 2004](#)).

[Waters et al. \(2006\)](#) have suggested that a combination of deficits in intentional inhibition and in contextual memory is critical to the generation of AVHs. A failure in recollection of context might indicate difficulties in recognising the source of an activated memory intrusion as mnemonic, while a further impairment in intentional inhibition may result in memory representations that intrude into consciousness in a manner beyond the control of the individual ([Aleman and Larøi, 2008](#)). In support of their theory,

[Waters et al. \(2006\)](#) indicated that ninety percent of patients with schizophrenia in their sample who experienced AVHs had deficits in both of these abilities, compared with only a third of patients with schizophrenia who did not experience hallucinations.

An alternative explanation of the AVH-related hippocampal activity found in the current meta-analysis is that the hippocampus might be involved in sensory gating that helps regulate the brain's attentional response to repeated sensory stimuli ([Grunwald et al., 2003](#)). Sensory gating acts to facilitate perceptual processing to concentrate on relevant stimuli while decreasing the processing of repeated stimuli, and so reducing noise in the environment ([Hirano et al., 2010](#)). Patients with schizophrenia may show aberrant gating responses, with increased responses in the left hippocampus during sensory gating conditions ([Tregellas et al., 2007, 2009](#)).

4.3. Misattribution deficits

The third prominent hypothesis has proposed that hallucinations originate from a failure in discriminating between internally and externally generated information. This internally derived information may be inner images or speech, voices, memories, vivid daydreams or bodily sensations ([Aleman and Larøi, 2008](#)), and different mechanisms have been suggested to explain how hallucinations might arise from the misattribution of such information ([Frith and Done, 1988](#); [Seal et al., 2004](#); [Ditman and Kuperberg, 2005](#); [Nieznanski, 2005](#); [Larøi and Woodward, 2007](#)). According to this perspective, deficits in reality monitoring or in the self-monitoring of internal thought may lead self-generated inner speech to be interpreted as intrusive external voices during AVHs ([Mechelli et al., 2007](#); [Kumari et al., 2010](#)). Hence, misattribution theories would hypothesize the involvement of brain areas associated with self-monitoring and self-perception during such hallucinatory experiences. This prediction is supported by findings of impairments in self-recognition and reality monitoring among hallucinating schizophrenic patients ([Waters et al., 2012b](#);

Vinogradov et al., 1997). Given that a hallucination can be thought of as inability to distinguish between an endogenously and exogenously generated sensory experience (Frith and Done, 1988), and the proposed role of the insula in self-representation (Kircher et al., 2001) and perception of other “selves” (Ochsner et al., 2008), it may be that “a breakdown of these functions of the insula could lead to the perception of an alien non-self attached to the internally-created sensory experience” (Wylie and Tregellas, 2010). Thus, the insula activity observed in the present AVH meta-analysis may reflect dysfunctional or insufficient activation for recognizing that the sensory experience has an internal rather than external source. It may be that failure of the meta-analysis to observe significant insula activity associated with VHs can be explained by the comparatively lower number of VH studies that could be included (although see above). Furthermore, functional impairments associated with poor reality monitoring in patients with schizophrenia have been found in the pulvinar thalamus and superior-middle temporal and inferior frontal gyri (Kumari et al., 2010) – regions exhibiting significant activity during AVHs in the present meta-analysis.

Another possibility is that abnormal activation during hallucinations might be expected in the medial prefrontal cortex, which has been linked to reality monitoring ability (Simons et al., 2008; Vinogradov et al., 2008; Brandt et al., 2014). Reduced medial prefrontal activity during reality monitoring has been observed in healthy individuals who are prone to psychosis (Simons et al., 2008), and in patients with schizophrenia (Vinogradov et al., 2008). However, if medial prefrontal regions support monitoring functions that tend to be consistently engaged across both hallucinatory and non-hallucinatory states, then activity in this area may often be subtracted out by analyses that directly contrast the two states. It is noteworthy that default mode network abnormalities with respect to the medial prefrontal cortex have been demonstrated in individuals with schizophrenia (Kühn and Gallinat, 2013) and their first-degree relatives (Whitfield-Gabrieli et al., 2009). Furthermore, a study in healthy volunteers has linked reality monitoring ability to structural variability within the nearby medial prefrontal region of the paracingulate sulcus (Buda et al., 2011), a specific morphological variation that recent data in schizophrenia suggest can differentiate patients who hallucinate from those who do not (Garrison et al., 2015). Significant activity in the area of the right paracingulate sulcus during AVHs was detected in the present ALE meta-analysis, consistent with the involvement of this region of prefrontal cortex, and with an impairment in reality monitoring, in the generation of hallucinations.

4.4. Integrated models of hallucinations

While the discussion of bottom-up and top-down processes, memory intrusion impairments, and misattributions provides structure to the evaluation of theories of hallucination generation, it is not meant to be all-encompassing. These factors are not mutually exclusive, and a variable combination of factors is likely to be involved in generating the features and phenomenological content of hallucinations in different clinical and non-clinical conditions. Evidence for the combined involvement of several factors comes from observed structural and functional dysconnectivity particularly related to speech and auditory processing regions for AVHs and visual processing regions for VHs (Vercammen et al., 2010; Geoffroy et al., 2014; Rotarska-Jagiela et al., 2009; Ford et al., 2015). These findings are consistent with dysfunctional monitoring and modulation of one brain region over another, as is suggested for example in models of memory intrusion with intentional disinhibition outlined above.

It is clear that integrated models of hallucination generation are needed which address the wide phenomenology and variability in

these experiences. One approach taken by Allen et al. (2008) is to focus on a neuroanatomical model of AVHs which includes both the brain regions involved and the proposed connections between them. This model highlights the role of monitoring and volition processes together with emotional regulation and attention in modulating the output from sensory processing areas. Other integrated models have been proposed (e.g. Aleman and Larøi, 2008; Beck and Rector, 2003; Waters et al., 2012a), including Jones and Fernyhough's (2009) Inner Speech model, which synthesizes several factors to suggest how a hallucination might be generated, including the overstimulation of brain areas involved in perception and in speech and language production, together with deficits in monitoring processes combined with factors relating to emotional regulation and attention. Encouraging greater comparison between the neural and cognitive processes of auditory and visual hallucinations could drive theories to become more integrated across modalities and functions, and thereby more comprehensive.

4.5. Limitations

A strength of the meta-analytic procedure implemented here was that in comparison to previous quantitative meta-analyses of AVHs (none have examined VHs), which used at most 158 foci (van Lutterveld et al., 2013), the ALE analysis here included 229 foci for auditory hallucination studies alone. This is due to the data collection procedure employed, such that authors of papers which did not report the original coordinates were personally contacted to increase the precision and comprehensiveness of the analysis. A coherent coordinate-based ALE map requires at least 20 foci (Jardri et al., 2011), and the number of coordinates used here far exceeded this, for both AVHs and VHs. Additionally, in the present analysis, the minimum size for activation clusters was defined as 200 mm³, which is at least as conservative (Kompus et al., 2011; Jardri et al., 2011) or more conservative (van Lutterveld et al., 2013) than past meta-analyses in the field. Nevertheless, this conservative cluster size means that smaller activation clusters may have been undetected. An additional caveat is that a number of neuroimaging studies with interesting results were excluded from the meta-analysis due to their reliance on region of interest (ROI) analysis or lack of responsiveness to email inquiry for the original coordinates. Furthermore, although rarely acknowledged in publications, the majority of studies do not distinguish between functional activations versus deactivations. It is generally considered that positive BOLD responses from fMRI likely reflect neuronal excitation whereas negative BOLD signals indicate inhibition (Logothetis, 2008; Haller and Bartsch, 2009), but these were rarely differentiated in studies of hallucinations. fMRI and PET data may also be specifically problematic for the study of hallucinations, as it may be that the causal neural mechanisms are present as part of hallucinators' intrinsic, default network activity and not merely as outcomes of hallucinatory perceptions. This potential issue is also a challenge for other time-dependent neuroimaging activation effects (Kalus et al., 2015).

4.6. Conclusion and future directions

The present meta-analysis highlights a number of implications for future directions in the field of hallucination research. Firstly, neuroimaging studies should focus on clinical and nonclinical groups beyond schizophrenia, such as bipolar disorder and borderline personality disorder, which are associated with hallucinations yet are poorly represented in the neuroimaging literature. Broadening the scope in this way would shed light on the commonalities and differences in the nature of hallucinations between these groups, and may help resolve the ongoing debate in the literature regarding whether a single model underpins both clinical and nonclinical

hallucinations (Waters et al., 2012a). Secondly, further investigations of hallucinations spanning different modalities would be fruitful and informative. As evident by the interesting contrasts and conjunctions revealed here, the science of hallucinations would benefit greatly from neuroimaging of audiovisual, olfactory, and tactile hallucinations. Such studies would aid in developing more robust theories for conceptualizing the modality-dependent and modality-independent cognitive processes underlying hallucinations.

Evaluating the present findings in relation to the available theoretical frameworks for hallucinations, it can be hypothesized with some certainty that multiple cognitive processes are at play during hallucinations across different populations and sensory modalities. The results support the conjecture that dysfunctional activation in regions typically associated with episodic memory retrieval and with reality- and self-monitoring may facilitate the generation of erroneous percepts evoked via interactions between past memories and abnormal activity in sensory brain areas. Future research should pursue a greater understanding of whether and how these mechanisms interrelate. ALE analysis offers an important quantitative lens into the hallucinating brain and the neural landscape of these internally generated perceptions, allowing us a glimpse into their origin and nature.

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