Understanding auditory verbal hallucinations

Upthegrove, R; Broome, MR; Caldwell, K; Ives, J; Oyeboode, F; Wood, SJ

DOI:

[10.1111/acps.12531](https://doi.org/10.1111/acps.12531)

License:

None: All rights reserved

Document Version

Peer reviewed version

Citation for published version (Harvard):

Upthegrove, R, Broome, MR, Caldwell, K, Ives, J, Oyeboode, F & Wood, SJ 2016, 'Understanding auditory verbal hallucinations: a systematic review of current evidence', *Acta Psychiatrica Scandinavica*, vol. 133, pp. 352-367.
<https://doi.org/10.1111/acps.12531>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Upthegrove R, Broome MR, Caldwell K, Ives J, Oyeboode F, Wood SJ. Understanding auditory verbal hallucinations: a systematic review of current evidence. First published: 12 December 2015. DOI: 10.1111/acps.12531

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Understanding Auditory Verbal Hallucinations: a systematic review of current evidence.

Rachel Upthegrove^{*1,2}, Matthew R. Broome^{3,7}, Kimberly Caldwell^{1,2}, Jonathan Ives⁴,
Femi Oyebode^{1,2}, Stephen J Wood^{5,6}

1. Department of Psychiatry, School of Clinical & Experimental Medicine, University of Birmingham, UK
2. Birmingham and Solihull Mental Health Foundation Trust, UK
3. Department of Psychiatry, University of Oxford, UK
4. Medicine, Ethics, Society and History, The University of Birmingham, UK
5. School of Psychology, University of Birmingham, UK
6. Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne & Melbourne Health, Victoria, Australia
7. Warneford Hospital, Oxford Health NHS Foundation Trust, UK.

* corresponding author:

Dr Rachel Upthegrove MBBS MRCPsych PhD, Clinical Senior Lecturer, School of Clinical and Experimental Medicine, University of Birmingham, 25 Vincent Drive, Birmingham, B15 2F, UK, telephone + 0044121 301 2350, r.upthegrove@bham.ac.uk

Abstract

Objective: Auditory Verbal Hallucinations (AVHs) are core features of psychotic illness, and remain significant in predicting poor outcome and risk. There has been a wide range of approaches to understanding these experiences.

Method: A systematic literature review summarising different methods of investigation and their results; phenomenology, descriptive psychopathology, psychological, cognitive neurobiology and neuroimaging.

Results: 764 papers and texts were screened and 113 reviewed. Phenomenological studies are comparably few in number and psychopathology remains based on concepts defined in the early 20th century. Psychological models focus on voice content and emotional reaction, and suggest a continuum of AVHs from normal experience. Neuropsychological models include AVHs as misattribution of inner speech, whilst functional neuroimaging studies focus on the spontaneous activity and connectivity of auditory networks.

Conclusions: There has been a large growth in research on AVHs in recent decades dominated by neurobiological and neuroimaging studies. Future research should include focus on phenomenological aspects and AVHs change over the course of developing illness. Integration between branches of enquiry is needed and the risk is that without this, models are proposed and investigated that bear scant relevance to the symptom itself.

Key words: schizophrenia, psychosis, auditory verbal hallucination, psychopathology, neuroimaging, neurobiology.

Summations:

- Psychological models stress the importance of content and emotion
- Dimensional models propose AVHs as a continuum of normal experience
- Cognitive neurobiological models of AVHs include misattribution of inner speech, adherent memory, semantic processing errors, and abnormal connectivity

Considerations:

- Modern investigations of what constitutes the core features of AVHs are under-represented.
- Many models do not account for the rich complexity of AVH experience or how these may change over the development of a psychotic illness.
- Studies examining voice hearing in non-clinical samples have not been widely replicated and it remains unclear as to how relevant neurobiological models are in non-clinical and non-psychotic populations.

Introduction

Auditory verbal hallucinations (AVHs) occur frequently in schizophrenia and other psychotic illnesses, and are associated with significant amounts of distress, functional disability and risk (1). Although AVHs are believed to be one of the core symptoms of psychoses, AVHs can also be experienced in the context of many other disorders and syndromes, as well as in normal populations (2). AVH occur in 70% of patients with schizophrenia(3), 23% with bipolar disorder(4), 46% with borderline personality disorder (5)and have been reported in 10-20% of the general population(3). The lack of a physical test for AVHs results in a reliance on self-report of experiences, subjective presentation, clinical history and corroboration to determine when certain symptom clusters mean that a diagnosis can be made and warrant treatment. In investigating the causes of AVHs, what is and is not considered a core feature of the experience is determined by researchers with a-priori hypotheses. How we understand, conceptualise and define AVH is hence of great importance both for clinical practice, including diagnosis and the boundaries of mental illness, and for research into better treatments.

Models of AVH arise from different perspectives including descriptive psychopathology, psychology, cognitive neurobiology and neuroimaging (6-9). Each in turn examines and explains aspects of voice hearing with an evidence base and tradition of research. The conceptual framework of psychotic illness has changed in recent decades. Diagnostic categories in psychosis such as schizophrenia, schizoaffective disorder, and bipolar disorder are criticised for their lack of a point of rarity or distinction (10). There are clear moves to abandon this categorical approach in favour of a dimensional view of psychosis as a continuum from normal to abnormal experience (11, 12). However, models of AVHs are not conceived with the newer dimensional or syndrome framework of psychosis in mind (13). Historically, emphasis on psychopathology centred around the form of hallucination. AVH phenomenology was richly explored by Jaspers, Bleuler, and Kraepelin in the early twentieth century, with emphasis on form of symptoms as key defining features of categorical diagnoses (3). Within a dimensional view of psychosis, the range of diverse, subjective experiences of AVHs may indeed represent symptoms of brain dysfunction without specificity for a single disorder, or simply the extreme of normal experience. It is equally possible that the differences and complexity of AVHs in psychotic disorders represent different underlying disturbances, directly related to the pathophysiology of the disorder itself. The National Institute of Mental Health initiative to implement the Research Domain Criteria (RDoC) could serve as a stepping stone for the move away from categorical diagnoses and brings these challenges and questions increasingly into focus (14).

Aims

This review sets out to summarise current models of auditory verbal hallucinations in the context of how they have developed; descriptive psychopathology, cognitive neurobiological, psychological, dimensional and high risk models, together with their individual and collective strengths and weaknesses, as a starting point to the further integration of branches of enquiry.

Method

A Systematic review of the literature of AVHs was conducted in January 2015. Following PRISMA guidelines, a search in Medline, PubMed, EMBase and PsychInfo was conducted for neurobiological, psychological and phenomenological studies of AVH using MESH headings: auditory verbal hallucinat* OR auditory hallucinat* OR verbal hallucinat* OR (hear* voice*) OR (hallucinat* AND voice*) AND “neurobiolog* OR neuroimag* OR neurotrans* OR neurochem* OR “phenomen* OR “psychopath* OR psychol* OR cognit*. Inclusion criteria were primary studies written in English with the main focus on the definition, description or cause of auditory hallucinations. Exclusion criteria were case reports, conference abstracts, studies where AVH were assessed only as an outcome measure, papers concerning AVHs in epilepsy or other neurological disorder and intervention studies. Review papers and core textbooks were also read to ensure all relevant papers and summations of expertise were included. Given the development of methodology and growth of literature, neuroimaging research was limited to 2004-2014. See Figure 1 for study selection process.

*****Figure 1 about here*****

Results

888 papers were identified and 764 retrieved following inclusion criteria and removal of duplications. 764 articles were screened for inclusion (title and abstract) with 554 excluded. See figure 1 for details. 221 full text articles were assessed and the final review included 113 original articles. Table 1 (supplementary material) details each original paper included in the review. We give below a summation of the main findings grouped into descriptive psychopathology, psychological and phenomenological enquiry, cognitive neurobiological models and neuroimaging data. These categories demonstrate the challenge to integration of evidence and the remaining gaps in our evidence base.

Descriptive Psychopathology and historical background:

AVHs are classically differentiated into ‘true hallucinations’ or ‘pseudohallucinations’. By definition, true hallucinations are conceived of as indistinguishable from real perceptions except that there is no stimulus (6). For these purposes, a real

perception occurs in external objective space, has a character of objectivity, is received by the person experiencing it with an attitude of passivity, and the sensory elements which are full, fresh, and constant are unalterable by individual will. The AVHs seen in schizophrenia are conceptualised as a subset of true hallucinations and are complex in the sense they are not elementary sensations like rudimentary noises or single words. As expected they are experienced as coming from external space, the sensory qualities are clear and have all the character of objectivity. These 'voices' may be single or multiple, male or female or both and may be those of people known or recognised (9). The syntactical quality, of the 'third person' structure of AVHs in schizophrenia has diagnostic valence, but the reason this particular structure has carried such weight is less than clear. Whilst there is some change within DSM 5, these remain core features in descriptive psychopathology. In contrast, the concept of "pseudohallucinations" is derived from a formal characterization of images (6). Pseudohallucination has more recently been seen by some as a pejorative term, linked with a failure to believe experience rather than as originally intended as a capturing of other erroneous perceptions (2). Images are thought of as being figurative in nature, are subjective and occur within inner subjective space. The sensory quality of images is construed as incomplete, poorly delineated, relatively insufficient and dependent upon the will of the person experiencing the image. An understanding of this characterization of an image is helpful to underpin the formal definition of pseudohallucinations. In Kandinsky's formula pseudohallucinations (imaged type) are identical to real perceptions except for the fact that they occur in inner subjective space(9). Kräupl Taylor's formulation on the other hand defines pseudohallucinations (perceived type) as indistinguishable from true hallucinations except that insight into the abnormality of the experience is present (6, 9, 15). At the heart of the distinction is the notion that 'true' hallucinations, irrespective of any other feature, signal serious mental illness. Alongside this is the idea that 'true' hallucinations have a veridical quality to them, that is, these experiences are indistinguishable from real perceptions (16).

True hallucinations would thus, by definition have an external location and be heard in a manner indistinguishable from real sounds. External location has been used to define "true" hallucinations, and thus indicate the presence of severe mental illness. In classically defined AVHs heard in schizophrenia, Copolov showed that patients hearing more than one voice were more likely to experience these as external phenomena (17); but, in contrast, Daalman showed that internal and external AVHs were evenly distributed in psychotic and healthy voice hearers (18). Research has shown that a location of internal or external voices is not specific to certain diagnoses, and the majority of patients with schizophrenia can hear both internal and external voices. Location is also not necessarily related to distress, impairment or other clinical characteristics (19, 20). Thus whilst clinically there remains much emphasis on the form AVHs take the literature is not extensive and dates back to influences from the early 20th century.

Phenomenological enquiry:

The term “phenomenology” can refer to the detailed description of clinical features, signs and symptoms observed in pathological conditions, or alternatively to a method of analysing subjective experience that is rooted in a particular philosophical tradition. A phenomenological approach begins with the premise that the analysis of direct description can provide significant understanding into the nature of the experience itself. Todres states that in the context of a research methodology, phenomenology is characterized by a systematic investigation of subjectivity and a consideration of experience from the first-person perspective (21). The aim is to lay bare the essence of an experience and make it intelligible to others. In light of this first-person orientation, phenomenology can be viewed as the foundational science for psychopathology (3, 22), yet relatively few papers publish primary evidence on the phenomenology of AVH experience (16, 23-27). (See Table 1).

In one influential study, Nayani and David conducted a systematic study of the phenomenology of AVHs in participants with schizophrenia-spectrum diagnoses (26). They showed a pattern of increasing complexity of AVHs over time, with the addition of more voices and extended dialogues, and increased intimacy between subject and voice. Relatively few other recent studies have looked in detail at the subjective patient experience or attempted replication. Research has instead focused on specific questions, such as comparing the AVHs to thoughts, or the internal and external location, with the presumption that this specific feature was “core” or helped delineate what was AVH from other experience (17). Spatial location has been the focus of enquiry with links to underlying brain activation in one study, that shows that external location and subjective reality of AVHs is related to motor mechanisms of speech comprehension(28). Subjective vividness of AVH has been shown to be associated with sensory cortex recruitment (29).

One recent phenomenological investigation of AVH proposes four subtypes, termed ‘Constant Commanding and Commenting’, ‘Own Thought’, ‘Replay AVH’, and ‘Non-verbal AH’. McCarthy-Jones et al argue for increased emphasis on the phenomenology of experience to further understand and enrich models of voice hearing(30). There is still a need for improved empirical research on key AVH properties, in addition to that have which may be of value in explaining the relation between memory or inner speech and AVH (22). Garcia-Montes et al suggest that having an increased direct access to the experience of AVHs will assist in fine-tuning more detailed models, which are usually taken from research in basic psychology and extrapolated without further ado to the field of schizophrenia (31). The present approach could lead to a tendency to reduce symptoms or clinical phenomena to pre-made concepts which may or may not be relevant. Investigating the actual, lived experience and deriving new theories that fit the complexity of this experience is one way forward (8, 32, 33).

Psychological Models:

Voice content and emotional reaction:

In terms of content of AVHs, command hallucinations have received most attention. They do not have diagnostic power but are clinically important because of concern that the patient may act on them and hence harm may come to themselves or others. Fernyhough, building on Vygotsky's idea about the development of inner speech in children proposes inner speech begins with private speech as a form of overt, spoken speech that is not aimed at communication but rather has the format of commands, hence the ubiquity of command hallucinations in schizophrenia and other psychiatric disorders (34, 35). Inner speech models are further discussed below in cognitive neurobiological models.

The emotional reaction to, and content of, AVHs are important particularly in terms of subjective experience and risk (22). Research shows that the emotional reaction to hallucinations may trigger and contribute to the development and maintenance of AVHs (36, 37). Some report that it is not the location, frequency or complexity of AVHs that predicts "caseness", but rather the distress and anxiety caused by the subjective experience (38). In addition, hearing a dominant voice is clinically very relevant and directly linked to psychotic depression, suicide and violence (36, 39). A voice-hearer's experience with their dominant voice is proposed as a mirror of their social relationships in general, with experiences of feeling low in rank to both voices and others being associated with depression (40, 41). Cognitive behavioural therapy for AVH, and in particular for commanding voices, focuses on this power and control (42, 43).

Three studies have investigated the emotional response to voices using neuroimaging paradigms. Escarti found patients with AVHs showed increased activity in the parahippocampal gyrus and the amygdala during an auditory paradigm (44), and Sanjuan that patients with AVHs had a greater activation in the amygdala and the hippocampal gyrus than patients without hallucinations during processing of emotional words (45). This suggests that emotional control brain areas and networks are involved in voice production and that the processing of emotions may be significantly different in patient with AVHs. In the third study, Kang et al added further evidence that AVHs in schizophrenia may be related to functional disturbances of the brains emotion networks with a reduced responsiveness in the amygdala and hippocampus to negative stimuli (46).

In terms of the malevolent or benevolence of voices, few studies have looked at differences on neuroimaging paradigms, however two studies have found functional disturbances of the emotion-related networks, including reduced responsiveness in the amygdala and hippocampus associated with negative content AVHs (46, 47).

Within a dimensional understanding of psychosis, detailed below, the process by which AVH are generated would be similar along this dimension, regardless of other

symptoms or diagnostic category. The subsequent emotional reaction to anomalous auditory experience (distress, depression, anxiety) would determine illness or illness severity(48). This emotional response may in turn be explained by abnormalities in neural networks controlling emotion and emotional regulation, thus emotional regulation and affect would be the primary pathology (49). There is considerable reporting of post traumatic symptoms in psychosis, with some suggesting emotional trauma as causal pathway to psychosis, mediated by emotional instability or stress reactivity (50). However an affective response may not explain the differences between AVHs in the context of a psychotic illness as opposed to personality disorder, PTSD etc., if indeed there are differences. This is an area open for research.

AVHs as continuum of experience:

AVHs as a Dimension: Auditory verbal hallucinations can occur in otherwise healthy individuals with rates of up to 20% of the population (51). AVHs also occur in a range of non-psychotic illnesses, including in post-traumatic stress (PTSD) and borderline personality disorder (BPD) (3). To what extent the occurrence of AVH in non-clinical populations is related to our current understanding of AVH as a core symptom of psychosis is yet to be established. If AVHs are experienced by up to 20% of the normal population, it is important to ascertain whether this the same experience as AVH occurring in people with psychotic or non-psychotic illness. A recent qualitative study of AVHs in BPD showed these experiences can be longstanding and interfere with physical and emotional functioning. They also found no clear distinctions from psychotic symptoms described by patients suffering from schizophrenia (52).

One functional, magnetic resonance imaging (fMRI) study that examined voice hearers in a small non-clinical sample (n=7) showed that similar cortical areas were activated during voices as seen in schizophrenia samples, including the superior temporal sulcus, fronto-temporal language areas and the supplementary motor area (53). Another study in schizotypal personality disorder showed similar areas of activation in both psychotic and non-psychotic participants (54). Looijestijn et al investigated sound localization and demonstrated that in psychosis external AVHs were related to increased activity in the left planum temporale and right middle frontal gyrus cluster (55). The suggestion is that within a dimensional approach to AVHs, similar processes are involved in the production of AVH across diagnostic boundaries. However, Howes et al, in positron emission tomography (PET) studies showed that neurobiological distinction between clinical and non-clinical voices is possible: altered dopamine synthesis capacity does not underlie hallucinations occurring in non-clinical otherwise health groups, but is the case with patients with psychosis (56). In addition hemispheric dominance appears to be particular to AVHs in schizophrenia, and may reflect wider alterations in the schizophrenia itself(57, 58). Dierkeren have also shown that reduced functional lateralisation was specific to AVHs in schizophrenia compared to healthy voice hearers (58). How closely the

experience of these voices mirrors those in psychotic disorders, and which are the differentiating features, is not well understood, and it is not clear how, if at all, they are related.

AVH in prodromal and “at high risk” groups: Whilst it is now recognised that AVHs can occur in otherwise healthy individuals, the occurrence of attenuated or infrequent AVHs have also been used to define the possible development of a psychotic illness. Recognition, enhanced treatment, and study of first episode psychosis have been the major foci in psychosis research in recent years. This task is challenging as the boundaries between what is and is not “psychosis” extends to include the earliest phase of illness, including a prodromal ultra-high risk (UHR) phase. “Transition” to psychosis is made at a point along a proposed continuum, predefined by standard criteria, yet both prediction of transition from a pre-psychotic state to psychosis, and the clinical accuracy of such a transition point is not certain (59). Lower level and infrequent AVHs are core features of UHR criteria, yet we do not really know if they are caused by the same pathology as AVHs in schizophrenia (60, 61). Structured interviews, such as the Comprehensive Assessment of At Risk Mental States (CAARMS) and Structured Interview for Psychosis Symptoms (SIPS) consider hallucinations to be defining features of the at-risk mental state (62-65). In DSM-5 the proposed attenuated psychosis syndrome, presently in the Research Domains, includes attenuated hallucinations defined as “unusual or seldom worrisome experiences, with scepticism about their reality maintained” (66). Thus the clinical significance is loosely defined along insight, vividness, frequency and distress. Yet fluctuations along these features may also be seen within chronic AVHs, and so it is important to ask; what are the features of psychotic AVHs that distinguish them from those found in healthy individuals or that define a risk state for psychosis? (67). Positive psychotic symptoms, so generically defined, may be a poor way to distinguish between normal variants in the population, prodrome of a psychotic disorder, and those who have already “made transition” to a frank psychotic disorder (68).

AVHs were not viewed as a core feature of psychosis until DSMIII and influence from Schneiderian psychopathology (19). Whilst Schneider’s influence has waned in recent times, diagnostic criteria or definitions of clinical significance have yet to be redefined. Within UHR studies the presence of AVHs has mixed evidence for predicting future psychosis. Within the Dunedin longitudinal studies early presence of AVHs like experiences predicted both later psychosis and PTSD (69, 70). In the absence of the strict Schneiderian criteria, it is possible that AVHs may merely be an “epiphenomenon” within which the major difficulties in cognition, affect or other domains are more predictive of the developing illness. As neuroimaging and biological studies of AVHs have not often explored their specific presence in developing psychosis, normal or non-psychotic populations, one cannot assume that the evidence to date results from the experience of voices rather than the underlying condition (e.g. schizophrenia). It is possible that too much diagnostic and predictive

weight is placed on the presence of AVH, alternatively that the core features of AVHs that does herald clinical relevance has not been captured to date.

Cognitive Neurobiological Models

Studies retrieved and reviewed showed that four main theoretical models have arisen in recent years:

Misattribution of Inner Speech.

The theory of impaired self-monitoring in AVHs was put forward by Frith in the 1980s (71) and proposes that patients are not aware of self-generated thoughts due to impaired inner monitoring of cognitive processes. Patients thus conclude that somebody else, external to them, is the author of those thoughts. It is argued that self-monitoring deficits can explain a core group of schizophrenia symptoms characterized by a confusion of self from non-self, including AVHs, delusions of control and passivity phenomena(72). Feinberg, Allen and others further suggested AVHs could be related to an error in “corollary discharge”. This is the process by which the initiation of a thought or act, such as speech, is accompanied by an alteration in neuronal discharges that alert the individual to the fact that such a thought or act is self-generated (73, 74). With a self-generated thought or movement, accompanying signals to the sensory and motor cortex inform parts of the brain about an intended action, allowing the sensory areas to predict this possibility and code the sensory consequences as the expected consequence of this action. Allen et al. (8) showed that patients with AVHs were more likely to attribute their own speech externally than patients without AVHs. It is suggested that in schizophrenia there is a predictive coding error that accounts for the perceived externality or misattribution of internally generated speech to an external source (75, 76). There is, however, some criticism of this theory. The complexity and severity of AVHs (for example many voices speaking in the third person, making running commentary etc.) cannot be explained entirely by prediction error or inner speech model (77, 78).

Language Production

Studies have also looked at language production, speech production and perception, rather than specifically at inner speech itself in patients who experience AVHs. The left superior temporal cortex, which supports linguistic functions, has consistently been reported to activate during auditory-verbal hallucinations in schizophrenia patients (79-83). AVHs have been shown to be related to defined cortical areas linked to specific language functions. Homan et al investigated the metabolic changes in auditory hallucinations requiring a functional rather than an anatomical definition of speech production and found significant differences in Broca’s and Wernicke’s areas associated with voice hearing in patients with schizophrenia (84).

Aberrant Memory.

This model proposes that AVHs arise from aberrant memory activation and internal monitoring, and particularly fits the “voices as traumatic experiences” phenomenon. A failure of inhibition of recall and unintended memory activation results in intrusive memories arising “out of context” and with a perception of “otherness” (72, 85, 86). The model has attracted much interest, and generated speculation about the causal role of trauma in psychotic experience. Read et al suggest that the equivocation between inner memory and outer experience may be a defensive manoeuvre to avoid reliving the traumatic experience or acknowledging it as having happened. A mis-attribution of the internal memory to an external source would lead to a reduction in distress and to delusional explanations of the experience, whilst protecting against the true traumatic memory (32, 86, 87). Hippocampal hyperactivation is apparent during hallucinations, supporting this model of AVHs as traumatic intrusions (88). However the ownership, differing phenomenological experiences, complexity, location etc. are not explained by intrusive memories alone. Whilst there is evidence to suggest a higher incidence of traumatic childhood events in patients with psychosis, and in particular those with hallucinations (85), intrusive memories do not account for the more severe and complex auditory experiences; for example neutral voices commenting on actions, or benevolent voices seen as a comfort etc. that occur frequently in psychotic illnesses (36, 89).

Early Automatic Sensory Processing Errors

Patients with schizophrenia have a variety of clear cognitive deficits, centred on working memory, executive function and sensory processing. AVH may occur as the result of altered auditory processing and pre-attentive functioning, leading to a misinterpretation of auditory stimuli as voices (90, 91). When investigating schizophrenia with electroencephalogram (EEG) recordings, differences have been found in event-related potentials (ERP) when compared to normal controls (92). ERPs are the wave recording of the brain’s response to a specific sensory, cognitive, or motor event. Event-related mismatch negativity (MMN) is an ERP that is elicited by any discriminable change in stimulation irrespective of whether or not one is consciously aware of such a change (93). With the investigation of auditory differences in schizophrenia, MMN is elicited by auditory stimuli that may deviate in any number of ways from a standard, with deviations in frequency, duration, intensity and location clearly shown to elicit a different (delayed) response in subjects with AVH compared to controls (94, 95). It is proposed that the MMN is an indication of pre-attentive cognition. In schizophrenia numerous studies have shown a deficit in MMN in both the timing and amplitude (63, 92, 94). However, yet again the complexity, ownership, and rich phenomenological experience of AVHs are not readily explained by this model alone, and studies in clinical populations outside schizophrenia are largely absent(96).

Neuroimaging Studies

Cognitive neurobiological models have in part been informed by the growth of neuroimaging studies investigating AVHs, which also report primary evidence outside the four main theories detailed above. These can be grouped in to structural and functional studies:

Structural:

Evidence suggests a correlation between AVHs presence and severity of AVHs in schizophrenia and structural brain changes in grey matter volume (GMV).

Decrements are found in the insula, right superior temporal and fusiform gyri, and left inferior and superior temporal gyri (including Heschl's gyrus), thalamus, left and right cerebellum, and posterior cingulate cortex (75, 97-104). Cortical thickness reduction is widespread, in frontal, parietal, occipital, and temporal lobes (105, 106). One study found associations between GMV loss and specific features of hallucination severity: symptom duration, location, frequency and intensity (107). In terms of white matter (WM), studies have found WM deficits in the frontal and temporal areas associated with AVHs, suggesting that disconnectivity in the left fronto-temporal area may contribute to the pathophysiology of AVH in schizophrenia (108, 109) with some evidence of specific focus on the arcuate fasciculus (110).

Functional and Connectivity studies

Structural studies of WM suggest deficiencies in integrity in the brain's connectivity associated with AVHs (108). Functional MRI (fMRI) studies of patients with schizophrenia and AVHs have informed models such as that of the misattribution or misidentification of inner speech (111-113). fMRI also been done when the brain is "at rest", i.e. not engaged in directed activity, and these studies demonstrate a reduced connectivity in the primary and secondary auditory cortex, and language processing areas, in patients with schizophrenia with AVHs when compared to patients without AVHs or healthy controls (53, 114-124). fMRI and PET studies have demonstrated differences in connectivity from areas known for processing and decoding speech (125-129). Spontaneous activity in auditory networks during voice hearing itself has also been shown in symptom capture studies (53, 55, 130-133). It is also suggested that patients are sensitive to hear words and may misperceive background or aberrant noise. The secondary auditory cortex is involved in object perception, i.e. deciding where a sound comes from, and thus increases in resting activity here may also result in an over-perception, attributing significance to background noise that the patient is overly disposed to hear (134-136). In addition, a reduction in "top down" modulation from higher order areas involved in speech and language processing during AVHs has been shown (137).

The difficulty in auditory and speech processing is thought to be a frontal, executive function deficit, the result of elementary neuronal dysfunction seen as a core feature of schizophrenia (138). This dysfunction may underlie not just the mechanisms of

AVHs, but cognitive distortions, thinking errors and disordered speech seen in psychosis (137, 139). Allen et al propose a combined alteration in the balance between top down modulation and bottom up processing to be key in AVHs in schizophrenia. The top down modulation is where higher brain functioning enables focus and attention on important objects and cues, and this is disordered in AVHs. This results in aberrant or spurious noise being given significance. Bottom up difficulties, result from increased resting state or spontaneous activity in the auditory cortex and lead to more “noise” for the higher brain areas to process, with subsequently more errors (8, 140).

How this “bottom up” spontaneous activity occurs is still unclear, however there is increasing studies of the brain’s resting state, and how this may be disordered in schizophrenia and AVHs. Dierks showed an increase in resting state activity in the superior and middle temporal gyrus, in a symptom capture method, which including both the secondary and primary auditory cortex during AVHs (80, 114). Other symptoms capture studies also highlight temporal to frontal language areas(54) Thus it is suggested that the auditory cortex was both “turned on”; showing increased activity in the endogenous state and “tuned in”; to orientate the perception towards an internally driven activity rather than external stimulus (134, 141, 142). Linking back to abnormalities in inner speech, some authors have investigated language networks with significant results suggesting a supra-regional network model of AVHs in schizophrenia with a selective vulnerability to AVHs the result of specific anatomical connections to posterior temporal regions (143).

Criticisms of a “top down bottom-up” include that this still does not explain the personal significance of voice content, the perception of voices as being the voice of others, or how auditory networks become activated. Building on resting state evidence, several fMRI studies in schizophrenia recently point to an elevated activity in the default mode network (DMN) (144). The DMN is a network of brain regions that are active when the individual is not focused on the outside world and the brain is at wakeful rest. It consists of the medial temporal lobe, medial prefrontal cortex and posterior cingulate cortex along with areas of the parietal cortex(145). There is a decrease in task induced deactivation (i.e. reducing activity in areas of the brain not in use during goal orientated tasks) in psychosis (146). There may be a correlation between increased connectivity within the DMN and positive symptom severity in psychosis (8). Northoff et al propose an abnormal interaction between the auditory cortex and DMN may be responsible for AVHs. A high resting state DMN induces a high resting state in the auditory cortex (134), and the subsequent abnormal interaction is experienced as an external event which is perceived as a voice(8) .

Integrating functional brain imaging findings to structural evidence, functional cerebral asymmetry has also been found. Compared to a non-hallucination schizophrenia group, the left Wernicke’s area was significantly activated by both left and right-sided voices in an auditory task (147, 148). In teasing out state vs trait aspects, Kuhn found the state of experiencing AVHs related to brain regions that

have been implicated in speech production i.e., Broca's area, whereas trait proneness to AVHs seems to be related to areas involved in auditory stimuli processing and speech perception, ie, auditory cortex (149). In terms of brain metabolism, magnetic resonance spectroscopy studies have shown some evidence of association between severity of AVHs and left temporal/Heschl gyrus metabolism (84, 150, 151).

Despite the focus clinically on external versus internal AVHs, only two brain imaging studies explored internal versus external location. Results suggested that internal location may be linked to developmental vulnerability whereas external location is specific to brain activity in the planum temporale and prefrontal regions (55), and that there may be opposite deviations in white matter volume and sulcus displacement at the temporo-parietal junction(152).

Discussion

This systematic review of studies investigating AVHs identified 113 primary papers, with approaches reflecting descriptive psychopathology, phenomenology, psychological, neurobiological and neuroimaging models. Neurobiological and neuroimaging studies have grown the most in recent years and may prove key to advancing our understanding of AVHs. However, descriptive psychopathology remains heavily influenced by the historical perspective and modern phenomenological studies are relatively few. Thus the question of whether the core features of AVHs, as elucidated by phenomenological enquiry and descriptive psychopathology, are consistent with the areas of neurobiological investigation remains open. Although AVHs are experienced by many as having a distinct 'auditory' quality (i.e. they are experienced as being heard), cognitive neurobiological models have yet to account for this phenomena, and also fail to explain the complexity of whole experience. Other models, such as Inner Speech, also struggle to account for patients' own experience of inner speech, which may be no different to healthy individuals. There also remains the question of why some patients report hearing the voice of another or multiple different voices rather than their own inner speech. Why do some patients engage in conversation or hear their own thoughts spoken aloud? Internalising parental dialogue to inner speech as development from childhood occurs, with abnormality here changing this inner speech to a voice perception, is an attractive model, explaining the command nature of some voices and linked to developing neurobiological pathways. However, whilst all the models mentioned above have some explanatory power, they are unable to explain many details and may not be able to explain all paths to AVH experience. Indeed, the current focus of investigation may be too reductionist. The attempt to define the experience using one or two pathognomonic features risks missing other perhaps more important aspects. Rather, a full and detailed understanding of the phenomenological range (experience and symptom profile) of AVHs is necessary to ensure that any model it underpins accommodates the true nature of experience.

AVHs as currently understood are not necessarily disease-related and are certainly not disease-specific. Our clinical distinctions between internal vs. external experience and hallucinations vs. pseudohallucinations may not be robust or valid (153, 154). Widely used assessment tools, such as the Psychotic Rating Scales PSYRATS (155) have defined which aspects of AVHs are to be investigated without clear evidence that these are either the aspects research should be focusing on, or those which define clinically significant experiences from “normal” voice-hearing. McCarthy-Jones et al call for AVHs subtypes to be developed to improve our understanding of the biological mechanisms; including categories of hypervigilance, inner-speech, memory and epileptic AVHs (30). This is a start to a more sophisticated understanding of experience.

Phenomenological enquiry, without presupposition, begins with taking a blank sheet approach to the exploration of symptoms and experiences without assumption. It is possible that AVHs are anchored in a very different experience to that currently rated or tested for. This is important for the development of biological models of AVH, linking into better treatments for patients. All current models fail individually to explain the full experience of AVHs; be this location, complexity, distress, loudness or other features we are not currently measuring. We are also not certain which features are the defining aspects of AVHs in psychosis, the core part of their experience that signals pathology. Detailed phenomenological enquiry, somewhat neglected since the mid-20th century in psychosis research, may be key. Within this context, given the difficulties highlighted within the UHR work, a revisiting of the phenomenology of AVHs is needed, resulting in the accurate understanding of the symptoms and experience of hearing voices in and of itself (14). In clinical practice the lack of a diagnostic test for AVH results in clinicians and researchers relying heavily on the description and history of symptoms (14, 33, 156). Thus how we define the AVHs symptom is of utmost importance, including whether sub categories and differentiation between psychotic and non-psychotic AVHs exist. It is only relatively recently, with DSMIII using Schneider’s criteria, that hallucinations became almost definitional of psychosis (19). Further exploration of AVHs in psychotic and other populations has key relevance to improving the theoretical framework within which this debate and decisions around illness and disease boundaries are made.

A dimensional continuum approach to psychosis assumes that the aetiological process underpinning the experience is the same for AVHs in normal populations, emerging mental disorder and schizophrenia with severity increasing along a continuum. Yet presently there is not sufficient evidence that this is valid. It is unclear whether the experience of AVHs differs by categorical diagnosis or stage of illness, for example first versus multiple episodes. Whether we take a categorical symptom based or dimensional approach, a thorough understanding of the experience of symptoms (that is, a true reflection of individuals’ experiences) should be the starting point of investigative models. Otherwise we run the risk of continuing to investigate

an experience whose real nature is very different to that framed by what we expect using pre-defined, possibly outdated, imported constructs.

There are limitations to this review which need to be considered. Areas of exclusion of our search included AVHs experienced in epilepsy and studies on interventions, both of which will provide further evidence and scope of understanding. Other areas of omission include a rehearsal of the more historical psychodynamic approach. However the inclusion of all aspects of AVH investigation would be beyond the scope of one review, and our aim was to highlight areas of potential further integration. In addition papers not written in English will result in differing cultural experience and explanations for voice hearing also to be excluded. Further review is needed here. However we have presented a large amount of research in summary form, and bring forward suggestion as to how these might further be investigated with a symptom specific rather than categorical diagnostic approach, in keeping with NIMH RDoC criteria (157).

We propose that future research needs to initiate with detailed understanding of the subjective experience, enabling a modern psychopathological basis to neurobiological understanding. See figure 2 for illustration. We identified a small number of researchers are beginning to look at AVHs with a truly integrated approach (33). However further studies with replication and inclusion of models reflecting the actual experience of AVHs are needed. From this increased knowledge we can then address the evidence gaps with clear implications for improved clinical interventions. In addressing key questions researchers should focus on:

1. Using a blank sheet phenomenological approach, what is the actual experience of AVHs?
2. How do AVHs change over the development of a psychotic illness? For example is complexity a measure of severity?
3. How relevant are neurobiological models of AVHs to non-clinical and non-psychotic AVHs?
4. Does a more accurately defined phenomenological experience enable newer neuroimaging and biological models to be proposed?

Studies are needed to explore the “unique” aspects, if they exist, of AVHs in schizophrenia and through the full spectrum of voice hearing populations. Information gained has the potential to inform more accurately identifiable diagnostic phenotypes, clearly observable characteristics, and further promote translational accuracy into clinical relevance.

Acknowledgements: Part funded by Caring Minds Charitable Trust

Declaration of Interest: None

Figure 1: Study Selection Process

Figure 2 Current relationship between AVH models of enquiry: red arrows signal directions for increased integration

References

1. BRAHAM LG, TROWER P, BIRCHWOOD M. Acting on command hallucinations and dangerous behavior: A critique of the major findings in the last decade. *Clinical Psychology Review*. 2004;**24**:513-28.
2. PIERRE JM. Hallucinations in Nonpsychotic Disorders: Toward a Differential Diagnosis of “Hearing Voices”. *Harvard Review of Psychiatry*. 2010;**18**:22-35.
3. LARØI F, SOMMER IE, BLOM JD, et al. The Characteristic Features of Auditory Verbal Hallucinations in Clinical and Nonclinical Groups: State-of-the-Art Overview and Future Directions. *Schizophrenia Bulletin*. 2012 July 1, 2012;**38**:724-33.
4. UPTHEGROVE R, CHARD C, JONES L, et al. Adverse childhood events and psychosis in bipolar affective disorder. *The British Journal of Psychiatry*. 2015;**206**:191-7.
5. KINGDON DG, ASHCROFT K, BHANDARI B, et al. Schizophrenia and borderline personality disorder: similarities and differences in the experience of auditory hallucinations, paranoia, and childhood trauma. *The Journal of nervous and mental disease*. 2010;**198**:399-403.
6. BERRIOS G, DENING T. Pseudohallucinations: A conceptual history. *Psychological Medicine*. 1996;**26**:753-64.
7. CHADWICK P, BIRCHWOOD M. The omnipotence of voices A cognitive approach to auditory hallucinations. *The British journal of psychiatry : the journal of mental science*. 1994;**164**:190-201.
8. ALLEN P, MODINOS G, HUBL D, et al. Neuroimaging auditory hallucinations in schizophrenia: from neuroanatomy to neurochemistry and beyond. *Schizophrenia Bulletin*. 2012;**38**:695-703.
9. OYEBODE F. *Sims' symptoms in the mind: an introduction to descriptive psychopathology*. Elsevier Health Sciences; 2008.
10. CRADDOCK N, OWEN MJ. The Kraepelinian dichotomy – going, going... but still not gone. *The British Journal of Psychiatry*. 2010 February 1, 2010;**196**:92-5.
11. FUSAR-POLI P, CARPENTER WT, WOODS S, MCGLASHAN T. Attenuated Psychosis Syndrome: Ready for DSM-5.1? *Annual review of clinical psychology*. 2014.
12. VAN OS J. ‘Salience syndrome’ replaces ‘schizophrenia’ in DSM-V and ICD-11: psychiatry’s evidence-based entry into the 21st century? *Acta Psychiatrica Scandinavica*. 2009;**120**:363-72.

13. JOHNS LC, VAN OS J. THE CONTINUITY OF PSYCHOTIC EXPERIENCES IN THE GENERAL POPULATION. *Clinical Psychology Review*. 2001;**21**:1125-41.
14. FORD JM, MORRIS SE, HOFFMAN RE, et al. Studying Hallucinations Within the NIMH RDoC Framework. *Schizophrenia Bulletin*. 2014 July 1, 2014;**40**:S295-S304.
15. TAYLOR FK. On pseudo-hallucinations. *Psychol Med*. 1981;**11**:265-71.
16. JUNGINGER J, FRAME CL. Self-report of the frequency and phenomenology of verbal hallucinations. *The Journal of nervous and mental disease*. 1985;**173**:149-55.
17. COPOLOV D, TRAUER T, MACKINNON A. On the non-significance of internal versus external auditory hallucinations. *Schizophrenia Research*. 2004;**69**:1-6.
18. DAALMAN K, BOKS M, DIEDEREN K, et al. The same or different? A phenomenological comparison of auditory verbal hallucinations in healthy and psychotic individuals. *J Clin Psychiatry*. 2011;**72**:320-5.
19. BERRIOS GE. The history of mental symptoms: descriptive psychopathology since the nineteenth century. Cambridge University Press; 1996.
20. NEMEROFF CB, WEINBERGER D, RUTTER M, et al. DSM-5: a collection of psychiatrist views on the changes, controversies, and future directions. *BMC medicine*. 2013;**11**:202.
21. TODRES L. Embodied enquiry: Phenomenological touchstones for research, psychotherapy, and spirituality. 2007.
22. MCCARTHY-JONES S, KRUEGER J, LARØI F, BROOME M, FERNYHOUGH C. Stop, look, listen: the need for philosophical phenomenological perspectives on auditory verbal hallucinations. *Frontiers in human neuroscience*. 2013;**7**.
23. KALHOVDE AM, ELSTAD I, TALSETH A-G. Understanding the Experiences of hearing Voices and Sounds Others do not Hear. *Qualitative health research*. 2013:1049732313507502.
24. GARWOOD L, DODGSON G, BRUCE V, MCCARTHY-JONES S. A preliminary investigation into the existence of a hypervigilance subtype of auditory hallucination in people with psychosis. *Behavioural and cognitive psychotherapy*. 2015;**43**:52-62.
25. GARRETT M, SILVA R. Auditory hallucinations, source monitoring, and the belief that “voices” are real. *Schizophrenia Bulletin*. 2003;**29**:445-57.
26. NAYANI TH, DAVID AS. The auditory hallucination: a phenomenological survey. *Psychological Medicine*. 1996;**26**:177-90.
27. ESCHER S, ROMME M, BUIKS A, DELESPAUL P, VAN OS J. Independent course of childhood auditory hallucinations: a sequential 3-year follow-up study. *The British journal of psychiatry Supplement*. 2002;**43**:s10-8.
28. RAIJ TT, VALKONEN-KORHONEN M, HOLI M, THERMAN S, LEHTONEN J, HARI R. Reality of auditory verbal hallucinations. *Brain*. 2009;**132**:2994-3001.
29. JARDRI R, THOMAS P, DELMAIRE C, DELION P, PINS D. The neurodynamic organization of modality-dependent hallucinations. *Cerebral Cortex*. 2013;**23**:1108-17.
30. MCCARTHY-JONES S, THOMAS N, STRAUSS C, et al. Better Than Mermaids and Stray Dogs? Subtyping Auditory Verbal Hallucinations and Its Implications for Research and Practice. *Schizophrenia Bulletin*. 2014 July 1, 2014;**40**:S275-S84.
31. GARCÍA-MONTES JM, CANGAS A, PÉREZ-ÁLVAREZ M, FIDALGO AM, GUTIÉRREZ O. The role of meta-cognitions and thought control techniques in predisposition to auditory and visual hallucinations. *British Journal of Clinical Psychology*. 2006;**45**:309-17.
32. LONGDEN E, MADILL A, WATERMAN MG. Dissociation, trauma, and the role of lived experience: Toward a new conceptualization of voice hearing. *Psychological bulletin*. 2012;**138**:28-76.
33. MCCARTHY-JONES S, TRAUER T, MACKINNON A, SIMS E, THOMAS N, COPOLOV DL. A new phenomenological survey of auditory hallucinations: evidence for subtypes and implications for theory and practice. *Schizophrenia bulletin*. 2014;**40**:231-5.
34. FERNYHOUGH C. Alien voices and inner dialogue: towards a developmental account of auditory verbal hallucinations. *New Ideas in Psychology*. 2004;**22**:49-68.

35. VYGOTSKY LS. Mind in society: The development of higher psychological processes. Harvard university press; 1980.
36. BIRCHWOOD M, IQBAL Z, UPTHEGROVE R. Psychological pathways to depression in schizophrenia: studies in acute psychosis, post psychotic depression and auditory hallucinations. *European archives of psychiatry and clinical neuroscience*. 2005;**255**:202-12.
37. WATSON PWB, GARETY PA, WEINMAN J, et al. Emotional dysfunction in schizophrenia spectrum psychosis: the role of illness perceptions. *Psychological medicine*. 2006;**36**:761-70.
38. HILL K, VARESE F, JACKSON M, LINDEN DEJ. The relationship between metacognitive beliefs, auditory hallucinations, and hallucination-related distress in clinical and non-clinical voice-hearers. *British Journal of Clinical Psychology*. 2012;**51**,434-447
39. UPTHEGROVE R, BIRCHWOOD M, ROSS K, BRUNETT K, MCCOLLUM R, JONES L. The evolution of depression and suicidality in first episode psychosis. *Acta Psychiatrica Scandinavica*. 2010;**122**:211-8.
40. BIRCHWOOD M, GILBERT P, GILBERT J, et al. Interpersonal and role-related schema influence the relationship with the dominant 'voice' in schizophrenia: a comparison of three models. *Psychological medicine*. 2004;**34**:1571-80.
41. UPTHEGROVE R, ROSS K, BRUNET K, MCCOLLUM R, JONES L. Depression in first episode psychosis: The role of subordination and shame. *Psychiatry research*. 2014;**217**:177-84.
42. TROWER P, BIRCHWOOD M, MEADEN A, BYRNE S, NELSON A, ROSS K. Cognitive therapy for command hallucinations: randomised controlled trial. *The British Journal of Psychiatry*. 2004;**184**:312-20.
43. BIRCHWOOD M, CHADWICK P. The omnipotence of voices: testing the validity of a cognitive model. *Psychological medicine*. 1997;**27**:1345-53.
44. ESCARTÍ MJ, DE LA IGLESIA-VAYÁ M, MARTÍ-BONMATÍ L, et al. Increased amygdala and parahippocampal gyrus activation in schizophrenic patients with auditory hallucinations: An fMRI study using independent component analysis. *Schizophrenia Research*. 2010;**117**:31-41.
45. SANJUAN J, LULL JJ, AGUILAR EJ, et al. Emotional words induce enhanced brain activity in schizophrenic patients with auditory hallucinations. *Psychiatry Research: Neuroimaging*. 2007;**154**:21-9.
46. KANG JI, KIM J-J, SEOK J-H, CHUN JW, LEE S-K, PARK H-J. Abnormal brain response during the auditory emotional processing in schizophrenic patients with chronic auditory hallucinations. *Schizophrenia Research*. 2009;**107**:83-91.
47. HORGÁ G, FERNÁNDEZ-EGEA E, MANÉ A, et al. Brain metabolism during hallucination-like auditory stimulation in schizophrenia. *PloS one*. 2014;**9**:e84987.
48. BADCOCK JC, PAULIK G, MAYBERY MT. The role of emotion regulation in auditory hallucinations. *Psychiatry research*. 2011;**185**:303-8.
49. FREEMAN D, GARETY PA. Connecting neurosis and psychosis: the direct influence of emotion on delusions and hallucinations. *Behaviour research and therapy*. 2003;**41**:923-47.
50. KRABBENDAM L, MYIN G, INEZ, HANSEN M, et al. Development of depressed mood predicts onset of psychotic disorder in individuals who report hallucinatory experiences. *The British journal of clinical psychology / the British Psychological Society*. 2005;**44**:113-25.
51. BAK M, MYIN-GERMEYS I, HANSEN M, et al. When Does Experience of Psychosis Result in a Need for Care? A Prospective General Population Study. *Schizophr Bull*. 2003 January 1, 2003;**29**:349-58.
52. SLOTEMA C, DAALMAN K, BLOM J, DIEDEREN K, HOEK H, SOMMER I. Auditory verbal hallucinations in patients with borderline personality disorder are similar to those in schizophrenia. *Psychological medicine*. 2012;**42**:1873-8.
53. LINDEN DE, THORNTON K, KUSWANTO CN, JOHNSTON SJ, VAN DE VEN V, JACKSON MC. The brain's voices: comparing nonclinical auditory hallucinations and imagery. *Cerebral Cortex*. 2011;**21**:330-7.

54. DIEDEREN KM, DAALMAN K, DE WEIJER AD, et al. Auditory hallucinations elicit similar brain activation in psychotic and nonpsychotic individuals. *Schizophrenia Bulletin*. 2012;**38**:1074-82.
55. LOOIJESTIJN J, DIEDEREN KM, GOEKOOP R, et al. The auditory dorsal stream plays a crucial role in projecting hallucinated voices into external space. *Schizophrenia Research*. 2013.
56. HOWES OD, SHOTBOLT P, BLOOMFIELD M, et al. Dopaminergic Function in the Psychosis Spectrum: An [18F]-DOPA Imaging Study in Healthy Individuals With Auditory Hallucinations. *Schizophrenia Bulletin*. 2013;**39**:807-14.
57. CROW T. Schizophrenia as failure of hemispheric dominance for language. *Trends in neurosciences*. 1997;**20**:339-43.
58. DIEDEREN KM, DE WEIJER AD, DAALMAN K, et al. Decreased language lateralization is characteristic of psychosis, not auditory hallucinations. *Brain*. 2010;**133**:3734-44.
59. YUNG A, R., YUEN H, PAN, BERGER G, et al. Declining Transition Rate in Ultra High Risk Prodromal Services: Dilution or Reduction of Risk? *Schizophrenia Bulletin*. 2007;**33**:673-681
60. RUHRMANN S, SCHULTZE-LUTTER F, SALOKANGAS RK, et al. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Archives of general psychiatry*. 2010;**67**:241-51.
61. NELSON B, YUEN HP, WOOD SJ, et al. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. *JAMA psychiatry*. 2013;**70**:793-802.
62. LARSEN TK, MELLE I, AUESTAD B, et al. Early detection of psychosis: positive effects on 5-year outcome. *Psychological Medicine*. 2011; **41**,1461-1469
63. YOUN T, PARK H-J, KIM J-J, KIM MS, KWON JS. Altered hemispheric asymmetry and positive symptoms in schizophrenia: equivalent current dipole of auditory mismatch negativity. *Schizophrenia research*. 2003;**59**:253-60.
64. MILLER T, J., MCGLASHAN T, H., ROSEN J, LIFSHEY, et al. Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *The American journal of psychiatry*. 2002;**159**:863-5.
65. CANNON TD, CADENHEAD K, CORNBLATT B, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of General Psychiatry*. 2008;**65**:28.
66. ASSOCIATION AP. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington DC; 2013.
67. YUNG AR, NELSON B, THOMPSON A, WOOD SJ. The psychosis threshold in Ultra High Risk (prodromal) research: Is it valid? *Schizophrenia Research*. 2010;**120**:1-6.
68. OS JV, MURRAY RM. Can we identify and treat "schizophrenia light" to prevent true psychotic illness? *BMJ*. 2013; 346
69. FISHER HL, CASPI A, POULTON R, et al. Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. *Psychological medicine*. 2013;**43**:2077-86.
70. JOHNSTONE EC, EBMEIER KP, MILLER P, OWENS DG, LAWRIE SM. Predicting schizophrenia: findings from the Edinburgh high-risk study. *The British Journal of Psychiatry*. 2005;**186**:18-25.
71. FRITH CD, DONE DJ. Towards a neuropsychology of schizophrenia. *The British Journal of Psychiatry*. 1988;**153**:437-43.
72. MCGUIRE P, DAVID A, MURRAY R, et al. Abnormal monitoring of inner speech: a physiological basis for auditory hallucinations. *The Lancet*. 1995;**346**:596-600.
73. FEINBERG I. efference copy and corollary discharge. *Schizophrenia bulletin*. 1978;**4**:636-40.
74. DE WEIJER AD, NEGGERS SF, DIEDEREN K, et al. Aberrations in the arcuate fasciculus are associated with auditory verbal hallucinations in psychotic and in non-psychotic individuals. *Human brain mapping*. 2013;**34**:626-34.
75. FORD JM, MATHALON DH. Corollary discharge dysfunction in schizophrenia: can it explain auditory hallucinations? *International Journal of Psychophysiology*. 2005;**58**:179-89.

76. ALLEN P, FREEMAN D, JOHNS L, MCGUIRE P. Misattribution of self-generated speech in relation to hallucinatory proneness and delusional ideation in healthy volunteers. *Schizophr Res.* 2006;**84**:281-8.
77. VERCAMMEN A, KNEGTERING H, BRUGGEMAN R, ALEMAN A. Subjective loudness and reality of auditory verbal hallucinations and activation of the inner speech processing network. *Schizophrenia bulletin.* 2011;**37**:1009-16.
78. FISHER DJ, LABELLE A, KNOTT VJ. Auditory hallucinations and the mismatch negativity: processing speech and non-speech sounds in schizophrenia. *International Journal of Psychophysiology.* 2008;**70**:3-15.
79. LEE SH, CHUNG YC, YANG JC, KIM YK, SUH KY. Abnormal speech perception in schizophrenia with auditory hallucinations. *Acta Neuropsychiatrica.* 2004;**16**:154-9.
80. HOMAN P, KINDLER J, HUBL D, DIERKS T. Auditory verbal hallucinations: imaging, analysis, and intervention. *European archives of psychiatry and clinical neuroscience.* 2012;**262**:91-5.
81. PLAZE M, BARTRÉS-FAZ D, MARTINOT J-L, et al. Left superior temporal gyrus activation during sentence perception negatively correlates with auditory hallucination severity in schizophrenia patients. *Schizophrenia research.* 2006;**87**:109-15.
82. SMITH DM, GRANT B, FISHER DJ, BORRACCI G, LABELLE A, KNOTT VJ. Auditory verbal hallucinations in schizophrenia correlate with P50 gating. *Clinical Neurophysiology.* 2013;**124**:1329-35.
83. FISHER DJ, LABELLE A, KNOTT VJ. Auditory hallucinations and the P3a: attention-switching to speech in schizophrenia. *Biological psychology.* 2010;**85**:417-23.
84. HOMAN P, VERMATHEN P, VAN SWAM C, et al. Magnetic resonance spectroscopy investigations of functionally defined language areas in schizophrenia patients with and without auditory hallucinations. *NeuroImage.* 2014;**94**:23-32.
85. VARESE F, SMEETS F, DRUKKER M, et al. Childhood Adversities Increase the Risk of Psychosis: A Meta-analysis of Patient-Control, Prospective- and Cross-sectional Cohort Studies. *Schizophrenia Bulletin.* 2012;**38**:661-71.
86. WATERS F, BADCOCK J, MICHIE P, MAYBERY M. Auditory hallucinations in schizophrenia: intrusive thoughts and forgotten memories. *Cognitive neuropsychiatry.* 2006;**11**:65-83.
87. READ J, OS JV, MORRISON A, ROSS CA. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica.* 2005;**112**:330-50.
88. JARDRI R, POUCHET A, PINS D, THOMAS P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *American Journal of Psychiatry.* 2011;**168**:73-81.
89. BIRCHWOOD M, MICHAIL M, MEADEN A, et al. Cognitive behaviour therapy to prevent harmful compliance with command hallucinations (COMMAND): a randomised controlled trial. *The Lancet Psychiatry.* 2014;**1**:23-33.
90. O'DONNELL BF, MACKIE K. The Mismatch Negativity: A Translational Probe of Auditory Processing in Cannabis Users. *Biological psychiatry.* 2014;**75**:428-9.
91. ROSENFELD AJ, LIEBERMAN JA, JARSKOG LF. Oxytocin, dopamine, and the amygdala: a neurofunctional model of social cognitive deficits in schizophrenia. *Schizophrenia bulletin.* 2011;**37**:1077-87.
92. FISHER DJ, LABELLE A, KNOTT VJ. The right profile: mismatch negativity in schizophrenia with and without auditory hallucinations as measured by a multi-feature paradigm. *Clinical Neurophysiology.* 2008;**119**:909-21.
93. DUNCAN CC, BARRY RJ, CONNOLLY JF, et al. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology.* 2009;**120**:1883-908.

94. SHELLEY AM, WARD P, CATTS S, MICHIE PT, ANDREWS S, MCCONAGHY N. Mismatch negativity: an index of a preattentive processing deficit in schizophrenia. *Biological psychiatry*. 1991;**30**:1059-62.
95. KNOTT V, SHAH D, MILLAR A, et al. Nicotine, auditory sensory memory, and sustained attention in a human ketamine model of schizophrenia: moderating influence of a hallucinatory trait. *Frontiers in pharmacology*. 2012;**3**:172.
96. VAN LUTTERVELD R, ORANJE B, KEMNER C, et al. Increased psychophysiological parameters of attention in non-psychotic individuals with auditory verbal hallucinations. *Schizophrenia Research*. 2010;**121**:153-9.
97. O'DALY OG, FRANGOU S, CHITNIS X, SHERGILL SS. Brain structural changes in schizophrenia patients with persistent hallucinations. *Psychiatry Research: Neuroimaging*. 2007;**156**:15-21.
98. PALANIYAPPAN L, BALAIN V, RADUA J, LIDDLE PF. Structural correlates of auditory hallucinations in schizophrenia: a meta-analysis. *Schizophrenia research*. 2012;**137**:169-73.
99. NECKELMANN G, SPECHT K, LUND A, et al. MR morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. *International Journal of Neuroscience*. 2006;**116**:9-23.
100. NENADIC I, SMESNY S, SCHLÖSSER RG, SAUER H, GASER C. Auditory hallucinations and brain structure in schizophrenia: voxel-based morphometric study. *The British Journal of Psychiatry*. 2010;**196**:412-3.
101. GASER C, NENADIC I, VOLZ H-P, BÜCHEL C, SAUER H. Neuroanatomy of 'hearing voices': a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. *Cerebral Cortex*. 2004;**14**:91-6.
102. MODINOS G, COSTAFREDA SG, VAN TOL M-J, MCGUIRE PK, ALEMAN A, ALLEN P. Neuroanatomy of auditory verbal hallucinations in schizophrenia: a quantitative meta-analysis of voxel-based morphometry studies. *Cortex*. 2013;**49**:1046-55.
103. SIMONS CJ, TRACY DK, SANGHERA KK, et al. Functional magnetic resonance imaging of inner speech in schizophrenia. *Biological psychiatry*. 2010;**67**:232-7.
104. MODINOS G, VERCAMMEN A, MECHELLI A, KNEGTERING H, MCGUIRE PK, ALEMAN A. Structural covariance in the hallucinating brain: a voxel-based morphometry study. *Journal of psychiatry & neuroscience: JPN*. 2009;**34**:465.
105. VAN SWAM C, FEDERSPIEL A, HUBL D, et al. Possible dysregulation of cortical plasticity in auditory verbal hallucinations—a cortical thickness study in schizophrenia. *Journal of psychiatric research*. 2012;**46**:1015-23.
106. MARTÍ-BONMATÍ L, LULL JJ, GARCÍA-MARTÍ G, et al. Chronic Auditory Hallucinations in Schizophrenic Patients: MR Analysis of the Coincidence between Functional and Morphologic Abnormalities 1. *Radiology*. 2007;**244**:549-56.
107. KUBERA KM, SAMBATARO F, VASIC N, et al. Source-based morphometry of gray matter volume in patients with schizophrenia who have persistent auditory verbal hallucinations. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2014;**50**:102-9.
108. SEOK J-H, PARK H-J, CHUN J-W, et al. White matter abnormalities associated with auditory hallucinations in schizophrenia: a combined study of voxel-based analyses of diffusion tensor imaging and structural magnetic resonance imaging. *Psychiatry Research: Neuroimaging*. 2007;**156**:93-104.
109. HUBL D, DOUGOUD-CHAUVIN V, ZELLER M, et al. Structural analysis of Heschl's gyrus in schizophrenia patients with auditory hallucinations. *Neuropsychobiology*. 2010;**61**:1.
110. ROTARSKA-JAGIELA A, OERTEL-KNOECHEL V, DEMARTINO F, et al. Anatomical brain connectivity and positive symptoms of schizophrenia: a diffusion tensor imaging study. *Psychiatry Research: Neuroimaging*. 2009;**174**:9-16.
111. MECHELLI A, ALLEN P, AMARO E, et al. Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. *Human brain mapping*. 2007;**28**:1213-22.

112. WOLF ND, SAMBATARO F, VASIC N, et al. Dysconnectivity of multiple resting-state networks in patients with schizophrenia who have persistent auditory verbal hallucinations. *Journal of psychiatry & neuroscience: JPN*. 2011;**36**:366.
113. MOU X, BAI F, XIE C, et al. Voice recognition and altered connectivity in schizophrenic patients with auditory hallucinations. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2013;**44**:265-70.
114. DIERKS T, LINDEN DE, JANDL M, et al. Activation of Heschl's gyrus during auditory hallucinations. *Neuron*. 1999;**22**:615-21.
115. ALLEN P, LARØI F, MCGUIRE PK, ALEMAN A. The hallucinating brain: A review of structural and functional neuroimaging studies of hallucinations. *Neuroscience and Biobehavioral Reviews*. 2008;**32**:175-91.
116. AMAD A, CACHIA A, GORWOOD P, et al. The multimodal connectivity of the hippocampal complex in auditory and visual hallucinations. *Molecular psychiatry*. 2014;**19**:184-91.
117. KOEDA M, TAKAHASHI H, MATSUURA M, ASAI K, OKUBO Y. Cerebral responses to vocal attractiveness and auditory hallucinations in schizophrenia: a functional MRI study. *Frontiers in human neuroscience*. 2013;**7**:221
118. SHINN AK, BAKER JT, COHEN BM, ÖNGÜR D. Functional connectivity of left Heschl's gyrus in vulnerability to auditory hallucinations in schizophrenia. *Schizophrenia research*. 2013;**143**:260-8.
119. GAVRILESCU M, ROSSELL S, STUART GW, et al. Reduced connectivity of the auditory cortex in patients with auditory hallucinations: a resting state functional magnetic resonance imaging study. *Psychological Medicine*. 2010;**40**:1149-58.
120. HOFFMAN RE, FERNANDEZ T, PITTMAN B, HAMPSON M. Elevated functional connectivity along a corticostriatal loop and the mechanism of auditory/verbal hallucinations in patients with schizophrenia. *Biological psychiatry*. 2011;**69**:407-14.
121. HOFFMAN RE, PITTMAN B, CONSTABLE RT, BHAGWAGAR Z, HAMPSON M. Time course of regional brain activity accompanying auditory verbal hallucinations in schizophrenia. *The British Journal of Psychiatry*. 2011;**198**:277-83.
122. SOMMER IE, CLOS M, MEIJERING AL, DIEDEREN KM, EICKHOFF SB. Resting state functional connectivity in patients with chronic hallucinations. *PloS one*. 2012;**7**:43516.
123. DIEDEREN K, NEGGERS S, DE WEIJER A, et al. Aberrant resting-state connectivity in non-psychotic individuals with auditory hallucinations. *Psychological medicine*. 2013;**43**:1685-96.
124. DIEDEREN K, CHARBONNIER L, NEGGERS S, et al. Reproducibility of brain activation during auditory verbal hallucinations. *Schizophrenia research*. 2013;**146**:320-5.
125. CLOS M, DIEDEREN KM, MEIJERING AL, SOMMER IE, EICKHOFF SB. Aberrant connectivity of areas for decoding degraded speech in patients with auditory verbal hallucinations. *Brain Structure and Function*. 2014;**219**:581-94.
126. ĆURČIĆ-BLAKE B, LIEMBURG E, VERCAMMEN A, et al. When Broca goes uninformed: reduced information flow to Broca's area in schizophrenia patients with auditory hallucinations. *Schizophrenia bulletin*. 2013;**39**:1087-95.
127. LIEMBURG EJ, VERCAMMEN A, TER HORST GJ, CURCIC-BLAKE B, KNEGTERING H, ALEMAN A. Abnormal connectivity between attentional, language and auditory networks in schizophrenia. *Schizophrenia research*. 2012;**135**:15-22.
128. HORGÁ G, PARELLADA E, LOMÉÑA F, et al. Differential brain glucose metabolic patterns in antipsychotic-naïve first-episode schizophrenia with and without auditory verbal hallucinations. *Journal of psychiatry & neuroscience*:2011;**36**:312.
129. RISH I, CECCHI G, THYREAU B, et al. Schizophrenia as a network disease: disruption of emergent brain function in patients with auditory hallucinations. *PloS one*. 2013;**8**:e50625.
130. VAN DE VEN VG, FORMISANO E, RÖDER CH, et al. The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage*. 2005;**27**:644-55.
131. LENNOX BR, PARK SGB, MEDLEY I, MORRIS PG, JONES PB. The functional anatomy of auditory hallucinations in schizophrenia. *Psychiatry Research: Neuroimaging*. 2000;**100**:13-20.

132. SHERGILL SS, BRAMMER MJ, AMARO E, WILLIAMS SC, MURRAY RM, MCGUIRE PK. Temporal course of auditory hallucinations. *BR J PSYCHIATRY*. 2004;**185**:516-7.
133. SOMMER IE, DIEDEREN KM, BLOM J-D, et al. Auditory verbal hallucinations predominantly activate the right inferior frontal area. *Brain*. 2008;**131**:3169-77.
134. NORTHOFF G, QIN P. How can the brain's resting state activity generate hallucinations? A 'resting state hypothesis' of auditory verbal hallucinations. *Schizophrenia Research*. 2011;**127**:202-14.
135. HORGÁ G, SCHATZ KC, ABI-DARGHAM A, PETERSON BS. Deficits in predictive coding underlie hallucinations in schizophrenia. *The Journal of Neuroscience*. 2014;**34**:8072-82.
136. SUGIMORI E, MITCHELL KJ, RAYE CL, GREENE EJ, JOHNSON MK. Brain mechanisms underlying reality monitoring for heard and imagined words. *Psychological science*. 2014;**25**:403-13.
137. ALEMAN A, BÖCKER KB, HIJMAN R, DE HAAN EH, KAHN RS. Cognitive basis of hallucinations in schizophrenia: role of top-down information processing. *Schizophrenia research*. 2003;**64**:175-85.
138. FREEDMAN D, BROWN AS. The developmental course of executive functioning in schizophrenia. *International Journal of Developmental Neuroscience*. 2011;**29**:237-43.
139. HOFFMAN RE, RAPAPORT J, MAZURE CM, QUINLAN DM. Selective Speech Perception Alterations in Schizophrenic Patients Reporting Hallucinated. 1999;**156**:393-399
140. AMAD A, CACHIA A, GORWOOD P, et al. The multimodal connectivity of the hippocampal complex in auditory and visual hallucinations. *Molecular psychiatry*. 2013;**19**:184-91.
141. HUGDAHL K. "Hearing voices": Auditory hallucinations as failure of top-down control of bottom-up perceptual processes. *Scandinavian journal of psychology*. 2009;**50**:553-60.
142. FORD JM, ROACH BJ, JORGENSEN KW, et al. Tuning in to the voices: a multisite fMRI study of auditory hallucinations. *Schizophrenia bulletin*. 2009;**35**:58-66.
143. CATANI M, CRAIG MC, FORKEL SJ, et al. Altered integrity of perisylvian language pathways in schizophrenia: relationship to auditory hallucinations. *Biological psychiatry*. 2011;**70**:1143-50.
144. VERCAMMEN A, KNEGTIERING H, DEN BOER JA, LIEMBURG EJ, ALEMAN A. Auditory hallucinations in schizophrenia are associated with reduced functional connectivity of the temporo-parietal area. *Biological psychiatry*. 2010;**67**:912-8.
145. WHITFIELD-GABRIELI S, FORD JM. Default mode network activity and connectivity in psychopathology. *Annual review of clinical psychology*. 2012;**8**:49-76.
146. PALANIYAPPAN L, MALLIKARJUN P, JOSEPH V, WHITE TP, LIDDLE PF. Regional contraction of brain surface area involves three large-scale networks in schizophrenia. *Schizophrenia research*. 2011;**129**:163-8.
147. ZHANG Z, SHI J, YUAN Y, HAO G, YAO Z, CHEN N. Relationship of auditory verbal hallucinations with cerebral asymmetry in patients with schizophrenia: an event-related fMRI study. *Journal of psychiatric research*. 2008;**42**:477-86.
148. KIM J-J, KU J, LEE H, CHOI SH, KIM IY. Distinct neural responses used to gain insight into hallucinatory perception in patients with schizophrenia. *Journal of psychiatric research*. 2012;**46**:1318-25.
149. KÜHN S, GALLINAT J. Quantitative meta-analysis on state and trait aspects of auditory verbal hallucinations in schizophrenia. *Schizophrenia bulletin*. 2010:sbq152.
150. NENADIC I, DIETZEK M, LANGBEIN K, et al. Superior temporal metabolic changes related to auditory hallucinations: a 31P-MR spectroscopy study in antipsychotic-free schizophrenia patients. *Brain Structure and Function*. 2014;**219**:1869-72.
151. REULBACH U, BLEICH S, MAIHÖFNER C, KORNHUBER J, SPERLING W. Specific and unspecific auditory hallucinations in patients with schizophrenia. *Neuropsychobiology*. 2007;**55**:89-95.
152. PLAZE M, PAILLIERE-MARTINOT ML, PENTTILA J, et al. "Where do auditory hallucinations come from?"--a brain morphometry study of schizophrenia patients with inner or outer space hallucinations. *Schizophr Bull*. 2011 Jan;**37**:212-21.

153. WATERS F, WOODWARD T, ALLEN P, ALEMAN A, SOMMER I. Self-recognition deficits in schizophrenia patients with auditory hallucinations: a meta-analysis of the literature. *Schizophrenia bulletin*. 2012;**38**:741-50.
154. LAWRIE SM, HALL J, MCINTOSH AM, OWENS DGC, JOHNSTONE EC. The 'continuum of psychosis': scientifically unproven and clinically impractical. *The British Journal of Psychiatry*. 2010 December 1, 2010;**197**:423-5.
155. HADDOCK G, MCCARRON J, TARRIER N, FARAGHER E. Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychological Medicine*. 1999;**29**:879-89.
156. MCGORRY PD, NELSON B, AMMINGER GP, et al. Intervention in individuals at ultra-high risk for psychosis: a review and future directions. *Journal of Clinical Psychiatry*. 2009;**70**:1206.
157. INSEL T, CUTHBERT B, GARVEY M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*. 2010;**167**:748-51.