Chapter 3

The auditory dorsal stream plays a crucial role in projecting hallucinated voices into external space

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ABSTRACT

Introduction Verbal auditory hallucinations (VAHs) are experienced as spoken voices which seem to originate in the extracorporeal environment or inside the head. Animal and human research has identified a ‘where’ pathway for sound processing comprising the planum temporale, middle frontal gyrus and the inferior parietal lobule. We hypothesize that increased activity of that ‘where’ pathway mediates the exteriorization of VAHs. Methods The fMRI scans of 52 right-handed psychotic patients experiencing frequent VAHs were compared with the reported location of hallucinations, as rated with the aid of the PSYRATS-AHRS. For each subject, a unique VAH activation model was created based on the VAH timings, and subsequently convolved with a gamma function to model the hemodynamic response. In order to examine the neuro-functional equivalents of perceived VAH location, second-level group effects of subjects experiencing either internal (n = 24) or external (n = 28) VAHs were contrasted within planum temporale, middle frontal gyrus, and inferior parietal lobule regions of interest (ROIs). Results Three ROIs were tested for increased activity in relation with the exteriorization of VAHs. The analysis revealed a left-sided medial planum temporale and a right-sided middle frontal gyrus cluster of increased activity. No significant activity was found in the inferior parietal lobule. Conclusions Our study indicates that internal and external VAHs are mediated by a fronto-temporal pattern of neuronal activity while the exteriorization of VAHs stems from additional brain activity in the auditory ‘where’ pathway, comprising the planum temporale and prefrontal regions.

Non-standard abbreviations: IVAH - Internal Verbal Auditory Hallucination EVAH - External Verbal Auditory Hallucination
1. INTRODUCTION

Internal verbal auditory hallucinations (IVAHs) are voices experienced inside the head. They are traditionally distinguished from external verbal auditory hallucinations (EVAHs), which have an apparent source in extracorporeal space.\(^1,2\) There is a long-standing debate on whether the phenomenological difference between these two types of hallucination is relevant from a clinical and a neurophysiological point of view.\(^3,5\) In conformity with the 19th-century tradition of designating IVAHs as ‘pseudohallucinations’, it has been argued that these are not actual hallucinations, but rather forms of imagery, or phenomena lying on a continuum between imagery and true hallucinations.\(^6,7\) As a corollary, IVAHs have been associated primarily with personality disorders and non-psychotic experiences, whereas EVAHs are traditionally regarded as ‘hard symptoms’ characteristic of schizophrenia and other psychotic disorders.\(^8\) However, other sources have argued that IVAHs are true hallucinations which simply lack an additional characteristic present in EVAHs, and which tend to be experienced as equally ‘real’.\(^9\) A recent comparison of 111 healthy voice hearers and 118 voice hearers with a psychotic disorder revealed that IVAHs and EVAHs are distributed evenly among both groups.\(^10\)

The debate on the clinical significance of the IVAH/EVAH distinction might be pushed forward by increased insight into the neurophysiological correlates of these phenomena. The spatial localization of sounds has been studied quite extensively, but those studies provide only indirect evidence of the mechanisms underlying the exteriorization of endogenously mediated sounds.

The localization of sounds from our environment depends on the interaural time difference (ITD) and the interaural intensity difference (IID). Synaptic input from both cochleas connects to the ipsilateral and contralateral superior olives in the midbrain, where the signal goes through encoding algorithms capable of registering very fine temporal differences.\(^11\) The auditory signal then passes on to the auditory cortices, where additional networks facilitate the localization of sounds, and ultimately the conscious experience of sound location. The experience of internal or external sounds is furthermore dependent on the head-related transfer function (HRTF).\(^12\) The HRTF describes how bodily characteristics such as ears, head and torso have source-location-specific signal altering effects used for further neural determination in frontal and transversal plane. Within the visual system, optical stimuli are topographically projected onto the primary visual cortex, from where they reach more specific ‘what’ and ‘where’ pathways.\(^13\) The existence of comparable ‘what’ and ‘where’ pathways has been hypothesized for auditory processing, hinting at a sound localization network extending beyond the primary and secondary auditory cortices. Experimental studies in monkeys combining anatomical and functional research have indeed shown that the
localization of sounds takes place in posterior temporal regions and the dorsolateral prefrontal cortex \(^{15}\). Research in humans implicated similar brain regions to play a role in auditory localization in humans \(^{16-20}\). A meta-analysis of functional imaging studies in healthy humans, designed to identify the ‘where’ pathway, indicates that the posterior temporal lobe, middle frontal gyrus (MFG) areas along the superior frontal sulcus, and the inferior parietal lobule (IPL) function within this stream \(^{21}\).

Other studies focused on the role of the planum temporale (PT), part of the posterior temporal lobe, in sound localization, designating it as the probable junction of the ‘what’ and ‘where’ pathways \(^{22}\). Hunter et al. \(^4\) used headphone stereotactic stimulation in healthy subjects with incorporation of the HRTF. Normal appliance of sounds through headphones creates an internal experience of sounds, whilst modification of the spectrotemporal patterns simulating the HRTF successfully externalizes sounds. They showed that the localization of exogenous sounds (as opposed to auditory imagery) is associated with increased left PT activity. A study that focused on the anatomical differences underlying EVAHs and IVAHs found opposed white-matter and sulcus displacements in the right temporoparietal junction, with intermediary scores for a control group \(^5\).

The aim of this paper is to investigate whether the phenomenological differences between EVAHs and IVAHs can be substantiated neurophysiologically by differential activation within the acoustic ‘where pathway’. We used blood-oxygenation-level-dependent (BOLD) functional MRI in 52 hallucinating subjects to test the hypothesis that within our regions of interest the planum temporale, the middle frontal gyrus, and the inferior parietal lobule, externally experienced voices are characterized by significantly more activity than internally experienced voices.

2. METHODS

2.1 Subjects

Fifty-two right-handed psychotic patients experiencing frequent VAHs (at least three episodes per 15 minutes) were recruited from the Parnassia Group, The Hague, and the University Medical Center, Utrecht, the Netherlands. A minor portion of these patients (33\%) has been described in a prior publication \(^{23}\). Exclusion criteria were the presence of neurological disorders, structural brain deficits, a frequency of less than three hallucinations per scanning session, and having more >25\% ambiguous VAH-responses (see Scanning Paradigm). We chose not to include healthy controls in our study design, as this could not be expected to provide any additional information in relation to our research question. Patients had a mean age of 38.2 years, with thirty-two patients (62\%) being male. All patients were diagnosed in accordance with
Internal vs. external voices

DSM-IV criteria as suffering from schizophrenia (77%), schizoaffective disorder (4%), psychosis not otherwise specified (13%), or personality disorder (6%). Interviews were carried out by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH)\(^\text{24}\). The mean duration of VAHs was 136 seconds during scanning sessions (i.e., 28% of total fMRI acquisition time). All patients were on stable dosages of antipsychotics. After the subjects were provided with a complete description of the study, written informed consent was obtained in accordance with the Declaration of Helsinki. The study was approved by the Human Ethics Committee of the University Medical Center Utrecht.

2.2 Phenomenological data

The localization of VAHs was determined using the Dutch version of the Psychotic Symptom Rating Scales-Auditory Hallucinations Rating Scale (PSYRATS-AHRS), an eleven-item structured interview assessing the phenomenological characteristics of auditory hallucinations\(^\text{25}\). On the day of scanning, complete interviews pertaining to the experience of VAHs during the past three months were carried out by trained interviewers. Subsequently, cases were divided into two subject groups, depending on the perceived location of VAHs (see table 1). The first group consisted of subjects experiencing internal VAHs, equaling a PSYRATS-AHRS location item score of 1. The second group consisted of subjects experiencing external VAHs, as well as subjects experiencing predominantly external VAHs and possibly some internal VAHs (see table 1, location item score 2), equaling a PSYRATS-AHRS location item score of 2, 3 or 4. In addition, the PANSS was used to compare the patients’ clinical characteristics.

<table>
<thead>
<tr>
<th>Location score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No voices present</td>
</tr>
<tr>
<td>1</td>
<td>Voices are perceived inside the head only</td>
</tr>
<tr>
<td>2</td>
<td>Voices are perceived outside the head, but close to the ears or head. Voices inside the head may also be present.</td>
</tr>
<tr>
<td>3</td>
<td>Voices are perceived within or close to the ears, and outside of the head, away from the ears</td>
</tr>
<tr>
<td>4</td>
<td>Voices are perceived outside the head only</td>
</tr>
</tbody>
</table>

2.3 Scanning paradigm and data acquisition

Functional neuroimaging maps were obtained with the aid of a Philips Achieva 3 Tesla Clinical MRI scanner using a fast 3D PRESTO SENSE sequence, achieving full brain coverage within 0.608 s (to detect brain activity in relation to hallucinations with a relatively brief duration)\(^\text{26}\). Scanning resulted in eight hundred 3D images, depicting
BOLD contrast acquired at the following parameter settings: 40 coronal slices, TR/TE 21.75/32.4 ms, flip angle 10°, FOV 224 x 256 x 160, matrix 64 x 64 x 40, voxel size 4 mm isotropic. After completion of the functional scan, a high-resolution anatomical scan was carried out for co-registration. Activity during hallucinations was measured for a duration of 8 minutes, during which fMRI scans were continuously made. Subjects were instructed to squeeze a balloon when they experienced VAHs, and to release it when the hallucinations subsided. The digital output of the balloon squeezes was vulnerable to inconsistent balloon presses, and sometimes required interpretation. Subjects with over 25% of ambiguous VAH-responses were excluded. This criterion led to the exclusion of nine subjects in the IVAH-group and five subjects in the EVAH-group, resulting in the 52 subjects currently studied.

2.4 fMRI data analysis
The FMRIB software library (FSL, Oxford, http://www.fmrib.ox.ac.uk/fsl) was used for data analyses. Pre-statistical processing consisted of motion correction; non-brain removal; spatial normalization to a standard Montreal Neurological Institute template based on the T1-weighted scans with high anatomical contrast; spatial smoothing using a Gaussian kernel of FWHM 8 mm; and high-pass temporal filtering (sigma = 100s). Time-series statistical analysis was carried out with local autocorrelation correction. For each subject, a unique VAH activation model was created based on the VAH timings, and subsequently convolved with a gamma function to model the hemodynamic response. Registered within-scanner hallucination epochs were contrasted with non-hallucinatory epochs to obtain hallucinatory activity per subject. In order to examine the neurofunctional equivalents of the perceived VAH location, second-level effects of IVAHs (i.e., location item score 1) and EVAHs (i.e. location item score 2, 3 and 4) were subsequently contrasted. Planum temporale, middle frontal gyrus, and inferior parietal lobule regions of interest (ROIs) were used to test our hypothesis, as well as to reduce multiple comparisons. The ROIs were extracted from the Harvard-Oxford probabilistic atlas (distributed within FSL). Significance of statistical images was determined using $Z > 2.3$ to define contiguous clusters. Then a corrected cluster significance threshold of $p < 0.05$ was used for each cluster its Gaussian random field derived significance level. When significant activity clusters were found using this contrast, the mean percentage signal change with regard to the baseline condition (no hallucination) were extracted from these region-of-interest (ROI) locations for all location subgroups (i.e., 1, 2, 3, and 4). The results were plotted to display the actual signal change related to the perceived location in these regions.
3. **RESULTS**

3.1 **Subjects**

Our 52 subjects were mainly medication-resistant schizophrenia patients (77%). Table 2 shows the group clinical characteristics per subject group (IVAHs or EVAHs). Statistical testing revealed a significant difference for the beliefs on the origin of the voices, indicating that voices experienced in extracorporeal space are associated with an external origin of the voices. A trend was seen for the VAH timings derived from the balloon presses, suggesting that the EVAH group had a longer total duration of the VAHs during the acquisition of scans.

| Table 2 – Summary of clinical data per subject group |
|------------------------------------------|------------------|------------------|------------------|
|                                | Internal VAH     | External VAH     | Group comparison p |
| N                              | 24               | 28               |                  |
| Age (years)                   | 36.9 (10.7)      | 39.2 (10.0)      | 0.335            |
| Sex                           | Male 71%         | 54%              | 0.258            |
| DSM-IV diagnosis              | schizophrenia    | 17               | 23               |
| Schizoaffective disorder      | 1                | 1                |
| Psychosis not otherwise specified | 4              | 3                |
| Personality disorder          | 2                | 1                |
| Chlorpromazine equivalents    | 321.2 (284.6)    | 228.0 (158.8)    | 0.333            |
| VAH timings (per 480 s scan)  |                  |                  |                  |
| Average duration              | 7.6 (6.3)        | 11.6 (13.4)      | 0.48             |
| Total duration                | 162.6 (107.4)    | 113.8 (96.9)     | 0.071            |
| PANSS                         |                  |                  |                  |
| Total positive score          | 16.2 (3.6)       | 18.5 (4.6)       | 0.081            |
| Total negative score          | 17 (5.6)         | 18.4 (5.6)       | 0.359            |
| Total general psychopathology | 31.8 (8.0)       | 35.3 (8.6)       | 0.133            |
| Total score                   | 65.3 (14.4)      | 72.1 (15.5)      | 0.119            |
| PSYRATS auditory hallucinations |                |                  |                  |
| Loudness                      | 1.6 (0.7)        | 1.9 (1.0)        | 0.531            |
| Beliefs on Origin             | 2.3 (1.2)        | 2.9 (1.0)        | 0.035*           |
| Amount of negative content    | 2.5 (1.3)        | 3.1 (0.9)        | 0.198            |
| Degree of negative content    | 2.4 (0.9)        | 2.8 (0.8)        | 0.387            |
| Amount of distress            | 3.0 (1.2)        | 3.0 (1.2)        | 0.641            |
| Intensity of distress         | 2.7 (1.1)        | 2.8 (0.8)        | 0.092            |
| Disruption to life            | 2.5 (1.3)        | 2.6 (0.9)        | 0.164            |
| Controllability               | 3.0 (1.2)        | 3.3 (1.0)        | 0.296            |

Mean (SD). All per location group characteristics were tested using an independent samples Mann-Whitney U test (scaled variables), or a Chi-square test (nominal variables).
3.2 Verbal auditory hallucination network

Figure 1 shows a whole-group analysis of brain activity during the conscious experience of VAHs using cluster correction at Z-score ≥ 2.3 (cluster threshold) and a p < 0.05 threshold for cluster size. Multiple brain regions were involved, including bilateral inferior and middle frontal areas, bilateral insula, the anterior cingulate gyrus, and predominantly left-sided superior temporal gyrus, as well as a motor network which included left motor cortex and the right cerebellum (most likely corresponding with the balloon presses, see Methods section). The established regions of activity were in conformity with prior fMRI studies on VAHs.29-31

![Figure 1 – Brain regions active during the conscious experience of VAHs](image)

Functional maps were created using cluster correction at Z-score ≥ 2.3 (cluster threshold) and p<0.05 (threshold for cluster size). Axial view of mean structural subject brain in standard space at MNI coordinates z = -25, -5, 15, 35, 55. Orange-yellow color coding for VAH activity with lighter color referring towards Zmax.

3.3 Contrast between internally and externally perceived VAH location

Three ROIs were tested for a significantly higher BOLD signal strength in EVAHs as opposed to that in IVAHs (EVAHs > IVAHs), and a reverse contrast (IVAHs > EVAHs) using cluster correction at Z-score ≥ 2.3, with P < 0.05 threshold for cluster size. The EVAH > IVAH contrast produced a cluster of 45 voxels located in the medial left-sided planum temporale, just posterior of Heschl’s gyrus, and a cluster of 660 voxels located in the right-sided dorsolateral prefrontal cortex and premotor cortex (see figure 2, table 3). No significant activity was observed in the inferior parietal lobule ROI for the EVAH > IVAH contrast. The three ROIs revealed no significant activity for the negative contrast (IVAH > EVAH). To further differentiate our findings, the VAH-related percentage signal change per cluster per location group was extracted for the observed clusters. Figure 3 demonstrates that the signal change is around zero percent for IVAHs, whereas EVAHs co-occur with signal increases in the listed brain regions. The brain areas not involved in the mediation of IVAHs are recruited during the exteriorization of VAHs. One subject was identified as an outlier in both the planum temporale ROI and the middle frontal gyrus ROI when applying the Chauvenet criteria on the percentual signal change of the EVAH > IVAH activation cluster (figure...
Figure 2 – Brain regions associated with the conscious experience of external VAHs
Functional maps were created at Z-score ≥ 2.3 (cluster threshold) and P<0.05 (threshold for cluster size). Green color coding for the planum temporale ROI, blue color coding for the middle frontal gyrus ROI. Axial view of mean subject structural brain at MNI coordinates z = 12, 20, 28, 36.

Table 3 – Brain regions EVAH > IVAH

<table>
<thead>
<tr>
<th>Brain region</th>
<th>x, y, z</th>
<th>Cluster size</th>
<th>Z-max</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Planum Temporale (BA 22)</td>
<td>-37, -34, 13</td>
<td>45</td>
<td>2.89</td>
</tr>
<tr>
<td>R Middle Frontal Gyrus (BA 9)</td>
<td>37, 19, 32</td>
<td>660</td>
<td>3.52</td>
</tr>
</tbody>
</table>

Z-scores correspond to cluster center of gravity, given at stereotactic MNI-coordinates with brain regions referring to the Harvard-Oxford probability map as distributed within FSL.

3). Additional analyses with exclusion of this subject did not alter the results in any significant manner. The PT activation cluster changed from 45 to 39 voxels, with Zmax from 2.89 to 2.87 and the MFG activation cluster changed from 660 to 653 voxels, with Zmax from 3.52 to 3.48.

Figure 3A+3B – Percentual signal change with exteriorization of VAH
The mean percentage signal change per location group per activation cluster displays an increase with more profound exteriorization of VAHs. Location groups refer to table 1. * outlier data point, see results.
Our results demonstrate that, on a group level, external verbal auditory hallucinations and internal verbal auditory hallucinations are mediated by a fronto-temporal brain network, while exteriorization is mediated by additional activity within the auditory system’s sound localization or ‘where’ pathway. This pathway comprises the planum temporale and dorsolateral prefrontal cortical areas. The clusters of activity that we found correspond with those reported in animal and human studies. No differences were found in the inferior parietal lobule. The increase in planum temporale activity concomitant with EVAHs occurred solely on the left side, which is in concordance with simulation studies of verbal auditory hallucinations in healthy human subjects by Hunter et al. This location is congruent with the results of fMRI studies on the localization of sounds. As posterior superior temporal regions are thought to constitute the junction of the ‘what’ and ‘where’ pathways of the auditory system, we propose that the planum temporale functions as the starting point of the auditory localization pathway. Prior studies report planum temporale activity during sound location changes not dependent on attentive listening or active localization, which supports the notion of a basic spatial encoding function for this structure. The only study on structural brain differences underlying EVAHs and IVAHs suggests an altered anatomy of the right temporo-parietal junction (TPJ). They used voxel-based-morphometry and found a gradient from decreased white matter volume in EVAH subjects, to intermediary values for healthy controls, and increased values for IVAH subjects. In a secondary analysis they also found gradient-wise superior temporal sulcus displacements nearby the TPJ. The TPJ is in close anatomical relation with the planum temporale. Loss of function might lead to a loss of white matter at the right TPJ, or vice versa. Either way, the diminished white matter at the right TPJ by Plaze et al. and the increased function of the left planum temporale found in our study might reflect the same process leading up to externalization of endogenous sounds. The study by Hunter et al. applied three sound lateralization conditions (left – balanced – right) and found left planum temporale activity in all three outside-head minus inside-head conditions, with the strongest contrast in the right lateralized condition supportive of dependency of left-lateralized activity of the PT in externalized sounds. Lastly, a recent meta-analysis of voxel-based morphometry studies examining VAHs reports left superior temporal gyrus abnormalities as most consistently associated with VAH severity, and altered hemispheric lateralization in those regions has been reported to be associated with schizophrenia. Our results suggest the involvement of the dorsolateral prefrontal cortex (DLPFC) and premotor cortex (PMC) in the mediation of EVAHs. The DLPFC has an essential function in visuospatial working memory in primates and humans, as well as in auditory localization processing.
ensuing DLPFC activity found in our study may be considered the output part of the ‘where’ pathway, where information from different ‘upstream’ modalities projects onto functionally specific prefrontal neuron populations \(^{38}\). The retrieved PMC activity can either be attributed to subsequent motor planning in reaction to the perceived EVAHs, or to the representation of the motor code for verbalization of the experienced EVAHs, in conformity with the motor theory of language \(^{36}\). Prior studies have indicated that the inferior parietal lobule (IPL) may also be part of the human sound localization network \(^{18,20,32,39}\), but we were unable to confirm this for VAH. Lowering of the statistical threshold to \(p < 0.005\) uncorrected, minimum cluster of 20 did not reveal any differences between EVAHs and IVAHs in the inferior parietal lobule ROI. An elaborated model of the auditory ‘where’ pathway by Rauschecker \(^{36}\) postulates the IPL to function in the evaluation of a DLPFC- and PMC-derived efference copy containing motor articulations, and a posterior superior-temporal-region-derived sensory afference copy, thus allowing for an ‘optimal state estimation’. In line with this model IPL activity has been found to further increase when localizing moving targets \(^{40}\). It might well be possible that prolonged episodes of uninterrupted EVAHs lead to habituation, and hence to a ceasing of optimal state estimations. It has also been argued that IPL activity may be quite specific for active sound localization tasks \(^{16,33}\). As our experiment involved unattended sound location processing, the IPL might not acquire enough contrast.

A comparison of the clinical data revealed a difference in the attributed origin of VAHs between the IVAH group and the EVAH group. Phenomenological surveys are ambiguous on whether the perceived location of VAHs is decisive in determining the attributed origin of the voices, and it has been suggested that the duration of the illness may act as a confounder \(^{2,3,41}\). In our study, however, the EVAH group had a stronger belief that their voices originated from an external person or entity. The EVAH group showed a trend towards a longer duration of VAHs during scanning (33.9% vs. 23.7% of fMRI acquisition time). As the established clusters of activity display around zero per cent increase during the occurrence of VAHs in the IVAH group, with increasing percentage signal changes for more externally perceived VAHs, it is unlikely for said effect to be derived from a diminished power of the rest-versus-hallucination condition on the subject level.

The present study is limited by the relative difficulty to obtain suitable scans, due to interindividual anatomical differences, high within-scanner anxiety levels, and relatively large variations in hallucination frequency, duration, and non-hallucinatory intervals. However, the established group-level VAH network was in concordance with earlier studies \(^{29,31}\). All patients were interviewed on the day of scanning, and requested to indicate the perceived location of VAHs as experienced during the three months preceding the scanning session. As a consequence, their reports may not fully
correspond with the location actually perceived within the scanner. Conversely, the reported location of VAH-related activity tends to be reliable over multiple inquiries\(^5,41\).

Our results support the thesis that VAHs are mediated by a fronto-temporal pattern of neuronal activity and that IVAHs are neurophysiologically distinguished from EVAHs by their lack of activity within the ‘where’ pathway. These results indicate that the ‘where’ pathway plays a crucial role in the projection of hallucinated voices into external auditory space. On the basis of those findings we advise to exert some caution in designating IVAHs as ‘pseudohallucinations’. To better understand the relationships and hierarchy within the networks involved in the mediation of EVAHs and IVAHs, a next step might be to establish the functional connectivity between the various brain regions of interest, and to study the timings of brain activity within those regions of interest\(^42\). The use of transient lesioning with transcranial magnetic stimulation might well be capable to aid in further differentiating the position of the where pathway in the chain of neural events. Finally, we believe that future studies may well benefit from a more sophisticated method of assessing the reported VAH location in individual patients.
5. REFERENCES


