Schizophrenia Research 146 (2013) 314–319

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

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

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

Jasper Looijestijn [a,b,*], Kelly M.J. Diederen [c], Rutger Goekoop [a], Iris E.C. Sommer [c], Kirstin Daalman [c], René S. Kahn [c], Hans W. Hoek [a,b,d], Jan Dirk Blom [a,b]

[a] Parnassia Psychiatric Institute, Kiwistraat 43, 2552 DH, The Hague, the Netherlands
[b] University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB, Groningen, the Netherlands
[c] Rudolf Magnus Institute for Neuroscience, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands
[d] Department of Epidemiology, Columbia University, 168th St No. 236, New York, NY, USA

ARTICLE INFO

Article history:
Received 14 February 2012
Received in revised form 20 January 2013
Accepted 6 February 2013
Available online 1 March 2013

Keywords:
Verbal auditory hallucination
Functional magnetic resonance imaging
Sound localization

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, the 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 neurofunctional 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.

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 (Bleuler, 1950; Nayani and David, 1996). 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 (Hunter et al., 2003; Copolov et al., 2004; Plaze et al., 2011). 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 (Hagen, 1868; Kandinsky, 1885). As a corollary, IVAHs have been associated primarily with personality disorders and non-psychotic experiences, whereas EVAHs are traditionally regarded as 'hard symptom' characteristic of schizophrenia and other psychotic disorders (Sedman, 1966). However, other sources have argued that IVAHs are true hallucinations which simply lack an additional characteristic present in EVAHs (Parish, 1897), and which tend to be experienced as equally 'real' (Copolov et al., 2004). 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 (Daalman et al., 2011).

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.

Abbreviations: IVAH, internal verbal auditory hallucination; EVAH, external verbal auditory hallucination.

* Corresponding author at: Parnassia Psychiatric Institute, Kiwistraat 43, 2552 DH, The Hague, the Netherlands. Tel.: +31 6 42522516.
E-mail address: j.looijestijn@parnassia.nl (J. Looijestijn).

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.02.004

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 (Schnupp and Carr, 2009). The auditory signal then passes on to the auditory cortices, where additional networks facilitate the localization of sounds, and ultimately to the conscious experience of sound location. The experience of internal or external sounds is furthermore dependent on the head-related transfer function (HRTF) (Boyd et al., 2012). 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 (Mishkin et al., 1983). The existence of comparable 'what' and 'where' pathways has been hypothesized for auditory processing (Rauschecker and Scott, 2009), 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 (Romanski et al., 1999). Research in humans implicated similar brain regions to play a role in auditory localization in humans (Bushara et al., 1999; Maeder et al., 2001; Arnott et al., 2005; Altmann et al., 2007; Deouell et al., 2007). 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 (Arnott et al., 2004).

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 (Tian et al., 2001). Hunter et al. (2003) used headphone stereotactic stimulation in healthy subjects with incorporation of the HRTF. Normal appliance of sounds through headphones creates an internal experience of sounds, while 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 (Plaze et al., 2011).

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 min) 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 (Diederen et al., 2010). The 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 and data acquisition). 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 the 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) (Andreasen et al., 1992). The mean duration of VAHs was 136 s 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 (Haddock et al., 1999). 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 (Kay et al., 1987).

2.3. Scanning paradigm and data acquisition

Functional neuroimaging maps were obtained with the aid of a Philips Achieva 3 T 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) (Neggers et al., 2008). 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 224×256×160, matrix 64×64×40, and 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 min, 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

Table 1
PSYRATS auditory hallucinations location item.

Location score	Description
0	No voices present
1	Voices are perceived inside the head only
2	Voices are perceived outside the head, but close to the ears or head. Voices inside the head may also be present.
3	Voices are perceived within or close to the ears, and outside of the head, away from the ears
4	Voices are perceived outside the head only