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Draining the pond and catching the fish: Uncovering the ecosystem of auditory verbal hallucinations

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ABSTRACT

The various models proposed for the mediation of auditory verbal hallucinations (AVH) implicate a considerable number of brain areas and mechanisms. To establish which of those mechanisms are actually involved in the mediation of AVH, we developed a novel method to analyze functional MRI data, which allows for the detection of the full network of mutually interacting brain states, and the identification of those states that are relevant to the mediation of AVH, while applying a minimum number of preconceived assumptions. This method is comparable to the draining of a pond to lay bare the full ecosystem that affects the presence of a particular fish species. We used this model to analyze the fMRI data of 85 psychotic patients experiencing AVH. The data were decomposed into 98 independent components (ICs) representing all major functions active in the brain during scanning. ICs involved in mediating AVH were identified by associating their time series with the hallucination time series as provided by subjects within the scanner. Using graph theory, a network of interacting ICs was created, which was clustered into IC modules. We used causal reasoning software to determine the direction of links in this network, and discover the chain of events that leads to the conscious experience of hallucinations. Hallucinatory activity was linked to three of the seven IC clusters and 11 of the 98 ICs. ICs with the most influential roles in producing AVH-related activity were those within the so-called salience network (comprising the anterior cingulate gyrus, right insula, Broca's homologue, premotor cortex, and supramarginal gyrus). Broca's area and the cerebellar regions were significantly, but more distantly involved in the mediation of AVH. These results support the notion that AVH are largely mediated by the salience network. We therefore propose that the mediation of AVH in the context of schizophrenia spectrum disorders involves the attribution of an excess of negative salience by anterior-cingulate areas to linguistic input from Broca's right homologue, followed by subsequent processing errors in areas further 'downstream' the causal chain of events. We provide a detailed account of the origin of AVH for this patient group, and make suggestions for selective interventions directed at the most relevant brain areas.

Non-standard abbreviations

SM module	sensorimotor module
C-E-R module	cognition evaluation response module
VI-EM module	visual imagery/episodic memory module

1. Introduction

Auditory verbal hallucinations (AVH) are the most prevalent types of hallucination in individuals diagnosed with a schizophrenia spectrum disorder, as well as in individuals without a diagnosis, psychiatric or otherwise (Ohayon, 2000). They have been the object of extensive neuroimaging research over the last 20 years and various hypotheses have been proposed concerning their mediation (Blom, 2015). As

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recently summarized by Curcic-Blake et al. (Curcic-Blake et al., 2017), the four major hypotheses involve: i) memory intrusion into language processing, ii) disrupted self-monitoring of inner speech, iii) aberrant cerebral lateralization, and iv) unbalanced top-down and bottom-up processing. As all four models overlap somewhat with respect to the brain regions involved, hybrid models for AVH postulate an overflow of default-mode-network-derived information into sensory association cortices or into central executive networks (CEN), with the ensuing intrusions of these networks being falsely attributed to an external source (Northoff & Qin, 2010; Jardri et al., 2013; Palaniyappan, 2012; Looijestijn et al., 2015). In the 'triple network model' it is hypothesized that such imbalances between the default-mode network (DMN) and CEN are mediated by a disrupted function of the salience network (SN) when the latter fails to attribute appropriate salience to input from resting-state and active-state (central executive) modi. The triple network model has been studied by Manoliu et al. (2013), where they find decreased activity of the right anterior insula to be associated with increased connectivity between the DMN and CEN, as well as hallucination severity. Alternatively, intrusions into CENs are thought to derive from unstable neural networks at a lower spatiotemporal level that erratically switch between their high-frequency active state and their low-frequency resting state (Looijestijn et al., 2015; Loh et al., 2007).

Functional MRI studies have reported that hallucination-related brain activity precedes the conscious experience of hallucinations by as much as nine seconds, which is way before subjects become conscious of the hallucination (Diederen et al., 2010; Hoffman et al., 2011; Shergill, 2004). The experience of hallucinations therefore is thought to depend on a chain of neural events that precedes it. In a recent study by Lefebvre et al. (2016), examination of the triple network model is elaborated by including the hippocampus in their hypothesis and they focus on transitions between different phases surrounding the hallucinatory state. Evidence was found that increased hippocampal input to the SN is involved in switching to a hallucinatory state. Notwithstanding, the nature of the causal chain of events has so far remained largely unclear, since current methods of functional imaging were limited in their ability to examine this chain of events. Most fMRI studies have used strongly model-based methods to identify brain activity, which involves searching the brain for specific patterns of interest. As the detection of hallucinations in fMRI studies is especially challenging due to their unprompted occurrence in subjects (Leroy et al., 2017), this often requires strongly specified models to obtain statistical power; or, in the case of data-driven studies, a selective use of data (components of interest) (Jardri et al., 2013; Manoliu et al., 2013; Lefebvre et al., 2016; van de Ven et al., 2005). Such approaches can be compared to fishing with a matched spinner for one particular type of fish, which is nonetheless part of a complex ecosystem. Thus, model-based methods are confirmatory methods, which provide information on expected patterns, but these should be complemented by exploratory methods that allow for the discovery of unexpected (yet relevant) findings. In the fishing analogy, we would ideally want to employ a method that allows us to drain the pond without losing important species (e.g. noise reduction) to uncover the entire ecosystem (all neural events within the brain), after which we can select all species (neural events) that affect the presence of our main fish of interest (i.e. neural activity that is directly related to the conscious experience of AVH). In this paper, we present such a method, and use it to discover the chain of events that lead up to the conscious experience of AVH. The clinical relevance of these findings is shortly discussed.

Our method involves the use of a so called 'model-free analysis' of functional brain connectivity concomitant with AVH, based on fMRI data obtained from 85 hallucinating patients who were diagnosed with a schizophrenia spectrum disorder. Bayesian network analyses (Mumford & Ramsey, 2014) allowed to test assumptions regarding the direction of the causal influence of implicated brain regions on each other. Using a minimum of a priori assumptions about the nature of event-related brain activity, we provide i) a systematic account of the circuits mediating AVH in the patient group, and ii) a perspective on the mediation of AVH that is complementary to that of model-based studies. The challenge here is to *search*, among the vast number of available hypotheses, for the hypothesis that explains the data best, and - preferentially - also facilitates therapeutic interventions.

2. Materials and methods

2.1. Participants

A total of 85 right-handed patients experiencing frequent AVH (i.e., at least three episodes per 15 min) were recruited at Parnassia Psychiatric Institute and the University Medical Center Utrecht. Exclusion criteria included the presence of neurological disorders, IQ < 80, structural brain deficits, and coarse scanner artefacts upon initial inspection of the fMRI data. Of all patients, 56% were male; mean age was 38 (SD 11.0) years, and average time spent on education was 12.5 (SD 2.5) years. All patients were diagnosed in accordance with the DSM-IV-TR criteria as suffering from Schizophrenia (77%), Schizoaffective Disorder (3%) or Psychotic Disorder Not Otherwise Specified (20%). Diagnostic interviews had been carried out by independent psychiatrists using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). There was a large range in the number of years since the onset of hallucinations, with a mean duration of 14.5 (SD 12.5) years. Total PANSS-score averaged 68 (SD 15.5). The majority of participants used antipsychotic medication (89%), with a mean chlorpromazine-equivalent dose of 413 (SD 318) mg/d (Woods, 2003). Of the medicated participants, 36% used clozapine, 34% other second-generation antipsychotics, 26% first-generation antipsychotics, and 4% a combination of these. As these figures indicate, a substantial number of our subjects was treatment-refractory with respect to their AVH. After the participants had received 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. Looijestijn et al. (2013) previously reported on a subset of the fMRI data of these patients (52 of the 85 subjects), presenting the results of a model-based analysis of AVH perceived inside the head (internal AVH) versus those perceived as coming from outside the head (external AVH).

2.2. Image acquisition

Functional neuroimaging maps were obtained with a Philips Achieva 3 Tesla Clinical MRI scanner using a fast 3D PRESTO SENSE sequence, achieving full brain coverage within 0.609 s (Neggers et al., 2008). PRESTO (PRinciple of Echo Shifting with a Train of Observations) makes optimal use of the time lapse between excitation by the radiofrequency pulse and readout, by applying the next excitation well before signal readout. The acquisition speed was further enhanced by combining PRESTO with parallel imaging techniques (sensitivity encoding; SENSE), thus allowing for a readout of fewer lines in K-space (Pruessmann et al., 1999). Scanning resulted in 800 3D images, depicting BOLD contrast acquired at the following parameter settings: 40 coronal slices, TR/TE 21.75/32.4 ms per slice, flip angle 10°, FOV $224 \times 256 \times 160$ mm, matrix $64 \times 64 \times 40$, voxel size 4 mm isotropic. The total functional imaging time per patient was approximately 8 min and 7 s. During the scanning sessions, participants were instructed to squeeze a balloon whenever they experienced AVH and to release it when the hallucinations subsided. A high-resolution anatomical scan with parameters TR/TE 9.86/4.6 ms, $1 \times 1 \times 1$ mm voxel size, flip angle 8°, was acquired to improve localisation of the functional data.

2.3. Preprocessing

The FMRIB software library (FSL, Oxford, http://www.fmrib.ox.ac.