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The "paradoxical" engagement of the primary auditory cortex in patients with auditory verbal hallucinations: A meta-analysis of functional neuroimaging studies

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ABSTRACT

The existing literature on neuroimaging studies of auditory verbal hallucinations (AVHs) in patients with schizophrenia contains an apparent "paradox" in that the same areas in the auditory cortex seem to be both activated and deactivated in relation to AVHs, depending on whether an external auditory stimulus is present or not. We performed meta-analyses of neuroimaging studies examining patients with schizophrenia during the processing of auditory stimuli and in individuals experiencing hallucinations in the absence of auditory stimuli to examine whether the auditory cortex shows the paradoxical decrease/increase pattern across studies. Databases PubMed and ISI Web of Knowledge were queried with the combination of the keywords "auditory verbal hallucinations", "auditory hallucinations", "fMRI", "PET", "imaging", yielding 11 studies involving comparison between schizophrenia and control group during external auditory stimulation, and 12 studies of hallucinating subjects experiencing AVHs and resting in the absence of auditory stimulation. The data were analyzed using Activation Likelihood Estimation method. The results showed overlapping increased activation in the absence of an external stimulus, and decreased activation in the presence of an external auditory stimulus in the left primary auditory cortex and in the right rostral prefrontal cortex, confirming the "paradoxical" brain activation in relation to AVHs. It is suggested that the "paradox" may be caused by an attentional bias towards internally generated information and failure of down- and up-regulation of the default mode and auditory processing networks, respectively, with the consequence that the spontaneous activation in the absence of an external stimulus shuts down the perceptual apparatus for further processing.

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1. Introduction

Auditory verbal hallucinations (AVHs) are subjective experiences of "hearing voices" in the absence of corresponding external auditory stimulation. A characteristic feature of AVHs is the perceptual quality of the "voice", which is typically experienced as a real person speaking with distinct perceptual qualities like accent, emotional valence, and timbre, as if in direct interpersonal communication. AVHs are reported by patients with various psychiatric and neurological disorders, most commonly schizophrenia (Choong, Hunter, & Woodruff, 2007), but can also be present in non-psychiatric populations without any accompanying psychotic symptoms (Johns & van Os, 2001; Sommer, Daalman et al., 2008). The fact that AVHs may occur in the general population suggests that AVHs should be studied not only in the context of a diagnostic category, but as an independent phenomenon which can present itself in a variety of situations (Hugdahl, 2009), in turn suggesting a dimensional view of schizophrenia (see e.g., David, 2010).

The similarities between experiencing AVHs and perceiving real auditory stimuli highlight the necessity of understanding the role of the auditory cortex in AVHs. Neuroimaging studies of hallucinating patients while they are experiencing AVHs suggest that auditory cortex is showing increased activation compared to alternating periods when no hallucinations are present (Dierks et al., 1999; Shergill, Brammer, Williams, Murray, & McGuire, 2000; van de Ven et al., 2005). This finding could be interpreted as increased spontaneous neuronal activity, or hyper-excitability of the auditory cortex. Spontaneous fluctuations of activation in sensory cortices have been shown to affect stimulus processing (Boly et al., 2007; Hesselmann, Kell, & Kleinschmidt, 2008; Northoff, Qin, & Nakao, 2010), with increased pre-stimulus activation in auditory cortex being associated with enhanced stimulus detection (Sadaghiani, Hesselmann, & Kleinschmidt, 2009). A straightforward prediction from these studies would be that stimulus-induced activations should also be *increased* in individuals with AVHs, if there already is spontaneous hyper-excitation caused by the

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hallucinations, together with enhanced or better cognitive processing of an auditory task. However, the available empirical evidence seems to indicate the opposite: AVHs are associated with *reduced* neuronal activation to external stimulation in the auditory cortex (David et al., 1996; Hugdahl, Løberg, & Nygård, 2009; Woodruff et al., 1997), and also reduced efficiency of speech processing in behavioural tasks (Green, Hugdahl, & Mitchell, 1994; Løberg, Jørgensen, & Hugdahl, 2004). A similar paradox can also be observed in electrophysiological studies. Hallucinations have been found to result in reduced N1 amplitude to concurrently presented auditory stimuli (Hubl, Koenig, Strik, Garcia, & Dierks, 2007), whereas ongoing hallucinations produce increased coherence measures across bilateral temporal electrode sites (Sritharan et al., 2005). We propose that this discrepancy, with reduced processing capacity to exogenously presented auditory sounds visible in physiological measures and co-occurring with impaired behavioural performance, and enhanced activation in the same brain areas for endogenously induced "voices" is an apparent paradox in the existing literature. If auditory hallucinations are associated with neuronal hyper-excitation in the absence of an external stimulus, leading to spontaneously increased activation, one would then expect further *increase* in activation when an external auditory stimulus is presented. This paradox could suggest either a "refractory" effect in the auditory cortex, such that external stimuli are not capable of producing further activation sufficient to overcome the ongoing, spontaneous neural activity (Hugdahl et al., 2009), or an aberrant attentional bias, such that the prefrontal top-down control mechanisms do not bias the auditory cortex sufficiently towards external stimuli. However, an un-systematic reading of the literature is not enough to establish whether the brain regions typically showing reduced activation during external auditory stimulation in patients who experience AVHs in fact are overlapping with the brain regions which have been found to increase in activation during AVHs in the absence of external stimulation because of small and differing sample sizes and variation in methods and data analysis (Wager, Lindquist & Kaplan, 2007). For this reason we performed a systematic search through the literature, and conducted a meta-analysis, comparing neuroimaging studies of AVHs reporting endogenously driven (in the absence of an external auditory stimulus) versus exogenously driven (in the presence of an external auditory stimulus) activations. We have labelled the first kind of studies "endogenously evoked processing", and the second kind of studies "exogenously evoked processing". We expected to see converging effects of both increased and decreased activation in the same brain regions in patients who experience AVHs if our initial unsystematic observations were correct.

Meta-analytical methods are gaining rapid popularity in the field of functional neuroimaging, providing a powerful tool for detecting consistent patterns across several different studies(Wager et al., 2007). While traditional meta-analyses are focused on the size of an effect across multiple studies in order to establish whether an effect is reliably present, in neuroimaging the interest is predominantly concentrated on the distribution of activation peaks in the brain volume (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009). In the present meta-analysis we aimed to systematically review available functional neuroimaging studies for the evidence that the paradox actually exists, and consequently the implications this may have for theories and models of the neuronal underpinnings and mechanisms behind AVHs. If neuronal activations are opposite in overlapping and converging brain areas, in particular in the auditory cortex to endogenously evoked versus exogenously evoked processing in AVH patients, this would have implications for interpretations of "state versus trait" effects of AVHs (cf. Kühn & Gallinat, 2011). Identifying a discrepant pattern of activation in endogenous and exogenous processing modes would also have implications for the understanding of how AVHs originate in the brain. We have restricted the search to functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies since these methods are based on hemodynamic changes related to neuronal activity. We employed the activation likelihood estimation (ALE) method for the meta-analysis, which allows to estimate the spatial convergence of reported activation peaks across multiple studies (Eickhoff et al., 2009).

2. Materials and methods

2.1. Selection of studies

For the meta-analysis of endogenously evoked processing, the studies were selected by searching the databases PubMed and ISI Web of Knowledge with the combination of the keywords "auditory verbal hallucinations", "auditory hallucinations", "fMRI", "PET", "imaging".

The resulting articles were reviewed to include the studies which compared brain activation during auditory hallucinations with non-hallucinating state within the same individuals. For the meta-analysis of exogenously evoked processing, the keywords "auditory", "schizophrenia", "fMRI", "PET", "imaging" were used. The resulting articles were reviewed to include studies which compared brain activation during auditory stimulation in healthy control subjects and hallucinating schizophrenia patients. The inclusion criteria for both analyses were: reporting of the results from the whole brain and using a standardized coordination system. The number of studies and patients as well as other characteristics of the individual studies in the analysis are provided in Tables 1a and 1b.

2.2. Activation likelihood estimation (ALE)

The meta-analyses were performed using the ALE method (Eickhoff et al., 2009) implemented in GingerALE toolbox (http://brainmap.org/ale). First, for each individual study all the reported activation foci were modelled as three-dimensional Gaussian probability functions, each peaking at the reported focus. The full width at half maximum of the probability function was determined as a function of the number of subjects in the study. For the auditory stimulation studies, involving comparison between two groups, the number of subjects was taken from the smaller group to yield a more conservative estimate. As a result of this procedure, each voxel in the brain volume was assigned a value expressing the probability that activation is reported at these coordinates. These probability maps, representing individual studies, were combined to yield a final ALE map representing the convergence of activation likelihoods across studies. A mask included in the GingerALE toolbox was used to confine the analysis to grey matter regions. To find areas where the convergence across the studies was statistically significant, a reference distribution was constructed, representing a random (null) association between the studies. The significance threshold was set to achieve a false discovery rate (FDR correction) of $p < .05$. A cluster size threshold of 200 mm^3 was used. To find the intersection between the two meta-analyses, the ALE maps, each thresholded at $p < .1$ (FDR correction) were multiplied to reveal areas where both analyses show convergent activations. To localize the activations, cytoarchitectonic atlas was used (Eickhoff et al., 2005; Morosan et al., 2001) as implemented in the SPM Anatomy Toolbox (http://www2.fz-juelich.de/inm/inm-1/spm_anatomy_toolbox).

3. Results

3.1. Endogenously evoked processing

The areas of significant convergence of increased activation when experiencing auditory hallucinations (Table 2, Fig. 1) included a cluster in the superior temporal gyrus (BA 42), corresponding to left primary auditory cortex, extending to parietal operculum.

Additional clusters were found in the left insula (BA 13), extending to BA 44, left posterior hippocampus, right middle temporal gyrus (BA 21 and 22), right inferior parietal lobule (BA 40), opercular part of right inferior frontal gyrus (BA 44) and rostral portion of right superior frontal gyrus (BA 10). Significant converging activations were also found in left primary sensory/motor cortex (BA 2), likely attributable to the fact that the instructions in the included studies commonly required the subjects to signal their hallucinatory status with button presses. Finally, a cluster of convergence was found in the right cerebellum.

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