Schizophrenia Research 127 (2011) 202–214

Contents lists available at ScienceDirect

Schizophrenia Research

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

Review

How can the brain's resting state activity generate hallucinations? A 'resting state hypothesis' of auditory verbal hallucinations

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ARTICLE INFO

Article history:
Received 18 May 2010
Received in revised form 16 September 2010
Accepted 8 November 2010
Available online 13 December 2010

Keywords:
Auditory verbal hallucinations
Schizophrenia
Resting state
Auditory cortex

ABSTRACT

While several hypotheses about the neural mechanisms underlying auditory verbal hallucinations (AVH) have been suggested, the exact role of the recently highlighted intrinsic resting state activity of the brain remains unclear. Based on recent findings, we therefore developed what we call the 'resting state hypotheses' of AVH. Our hypothesis suggest that AVH may be traced back to abnormally elevated resting state activity in auditory cortex itself, abnormal modulation of the auditory cortex by anterior cortical midline regions as part of the default-mode network, and neural confusion between auditory cortical resting state changes and stimulus-induced activity. We discuss evidence in favour of our 'resting state hypothesis' and show its correspondence with phenomenological accounts.

1. Introduction

Auditory verbal hallucinations (AVH) refer to the experience of perceiving speech in the auditory modality without corresponding external stimuli. Up to 60–80% of patients with schizophrenia suffer from AVH which can also occur in conditions other than schizophrenia as for instance in drug-induced psychosis or even healthy subjects. This has led to several hypothesis including cognitive-based top–down, sensory-based bottom–up (Javitt, 2009; Jones, 2008; Langdon et al., 2009), combined bottom–up and top–down models (Allen et al., 2008; Fletcher and Frith, 2009; Hugdahl, 2009), and social (Hoffman, 2007; Hoffman, 2008) hypotheses about the neural mechanisms underlying AVH.

Recent investigations point out the crucial relevance of the brain's resting state activity in various networks of the brain including the so-called default-mode network (DMN). The DMN includes various regions like the anterior and posterior cortical midline structures as well as the lateral parietal cortex and the hippocampus (Buckner et al., 2008; Raichle et al., 2001). While the resting state activity level seems to be particularly high in the DMN, its exact impact on stimulus-induced activity remains unclear though (Northoff et al., 2010). This raises the question for the determination of the terms resting state and DMN.

The term resting state can be defined operationally as the absence of specific stimuli as for instance during eyes closed (Logothetis et al., 2009). This applies to all regions in the brain and is therefore not limited to a specific network as the DMN. One may though distinguish a meaning of the term resting state other than the operational definition. This pertains to a more neuronal definition that relates the term resting state with neural activity that is generated by the brain itself and thus intrinsic (See Llinas, 2002) as distinguished from extrinsic, e.g., stimulus-induced activity (see also (Northoff et al., 2010) for these definitional issues). Hence, one may distinguish the operational definition of resting state as it is presupposed in the experimental context from the neuronal determination that refers to the brain's intrinsic activity. It is the latter meaning of the term resting state, the neuronal one referring to the brain's intrinsic activity that is presupposed here when we speak of resting state in our resting state hypothesis.

Conceptually, the DMN describes a set of region that includes anterior and posterior midline regions, the bilateral parietal

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doi:10.1016/j.schres.2010.11.009

cortex and often also the hippocampus (Buckner et al., 2008; Raichle et al., 2001). These regions show a specific temporally coherent network pattern in the resting state (Calhoun et al., 2008). While showing high activity in the resting state (Raichle et al., 2001), many of the DMN regions show negative signal changes in fMRI, so-called task-induced deactivation (TID), during stimulus-induced activity (Buckner et al., 2008; Gusnard et al., 2001; Raichle et al., 2001). Recent studies in schizophrenia report indeed abnormalities in the DMN showing abnormally high resting state activity level and hyperconnectivity to other regions (Broyd et al., 2009; Whitfield-Gabrieli et al., 2009).

In addition to the DMN, high resting state activity as well as neuronal fluctuations or oscillations have been observed also in other regions like the auditory cortex (Hunter et al., 2006; Uhlhaas and Singer, 2010). Furthermore, patients with AVH have been observed to show abnormally high resting state activity in auditory cortex before or during the onset of their hallucinations (Dierks et al., 1999). This raises two questions. First, how does the abnormally increased resting state activity in auditory cortex impact subsequent stimulus-induced activity and auditory perception? Second, what is the origin of the apparently abnormally increased resting state activity in auditory cortex during AVH — could it be related to resting state activity changes in other regions as for instance the DMN?

The general aim of this paper is to develop a neural hypothesis that focuses specifically on the possible role of the brain's resting state activity in generating AVH. We call such hypothesis the 'resting state hypothesis of AVH'. The specific hypothesis is three-fold. First, we hypothesize that there is abnormally elevated resting state activity within the auditory cortex itself. Second, we hypothesize that the abnormal increase of resting state activity in auditory cortex may be due to abnormally elevated resting state activity in the default-mode network and particularly in anterior cortical midline structures; we thus assume abnormal rest–rest interaction between DMN and auditory cortex which may induce abnormal auditory perception. Third, we hypothesize that the abnormally elevated resting state activity in auditory cortex may lead to reduced modulation of auditory cortical resting state activity by incoming exteroceptive stimuli resulting in what may be described as reduced rest–stimulus interaction.

We first discuss the current findings and the main theories about the neural mechanisms underlying AVH. We then present our own resting state hypothesis in three steps, abnormal resting state activity in auditory cortex, abnormal rest–rest interaction between auditory cortex and DMN, and reduced rest–stimulus interaction in auditory cortex. This serves to formulate our resting state hypothesis including its predictions in more detail and to point out their implications for auditory perception. We conclude the paper by discussing some convergence between our neural resting state hypothesis and recent phenomenological accounts (Parnas, 2003).

1.1. Current theories of AVH I: brain imaging studies of AVH

Recent brain imaging explored the structural and functional neural underpinnings of AVH (Allen et al., 2008). Structural studies observed altered (most often reduced rather than increased) grey matter reductions in the superior temporal gyrus (STG), the planum temporale and the Heschl's gyrus (and other regions like the lateral prefrontal cortex and the thalamus) in schizophrenic patients with AVH when compared to those without AVH (Allen et al., 2008; Lin et al., 2006; Shin et al., 2005). Since these regions include both the primary and secondary auditory cortices, these findings are consistent with the lesion studies showing alterations in sensory regions in hallucinations (Braun et al., 2003). More specifically, Braun et al. (2003) investigated patients with focal brain lesions that caused isolated hallucination be it visual, auditory or somatic (Braun et al., 2003). They observed that the lesion was located in all patients in the respective sensory pathway. This lead to, as the authors say, "compensatory overactivation of tissue in the nearby brain sensory pathway" with full awareness of a specific sensory experience, e.g., hallucination. Hence, this study lends support to the assumption that the auditory cortex itself may be altered in AVH with the latter resulting from secondary compensatory neuronal mechanisms.

In addition to the structural studies there have been many functional studies testing for neural activity in schizophrenic patients with AVH during some task as for instance inner speech (i.e., imagining to speak particular sentences) or verbal imagery (i.e., imagining sentences spoken in another person's voice). Patients with AVH showed reduced activity in various regions involved in the inner monitoring of speech like the middle temporal gyrus (MTG) (Kumari et al., 2010; McGuire et al., 1996; Shergill et al., 2003, 2004), thalamus (Kumari et al., 2010), parahippocampal gyrus (Shergill et al., 2003), left or right inferior frontal cortex (including Broca's regions on the left) (Kumari et al., 2010; Raij et al., 2009), the parietal cortex (including Wernicke's area) (Shergill et al., 2003) and the SMA (McGuire et al., 1996) during verbal imagery tasks where spoken sentences of other persons are imagined (or word generation tasks). As demonstrated in healthy subjects (Fu et al., 2006; McGuire et al., 1996) these regions are crucially involved in verbal self-monitoring; the reduction of activity thus suggest a deficit in the monitoring of inner speech, i.e., verbal self-monitoring, in AVH.

1.2. Current theories of AVH II: cognitive-based top–down approaches — theory of self-monitoring and predictive coding

These results have been taken as support of the theory of impaired self-monitoring in schizophrenia as put forward by Frith (Frith and Done, 1988; Frith et al., 1992; Stephan et al., 2009). Due to impaired inner monitoring of the own cognitive processes, the schizophrenic patient is not aware that he himself initiated the thoughts and the verbal sentences and assumes consecutively that somebody else from the external world makes his thoughts and actions and monitors his intentions. In the case of AVH, the deficit in verbal self-monitoring of the internally generated speech cannot be recognized as such, i.e., as internally generated, and is consecutively misattributed to some external person (Frith, 1992; Fu and McGuire, 2003).[2]

[2] Frith argues that such deficit in self-monitoring can explain a particular group of schizophrenic symptoms namely those that are characterized by a confusion between self and others. These symptoms include auditory hallucinations as well as delusions of control and the so-called passivity phenomena where the own actions, emotions and thoughts are experienced estranged from and not belonging to oneself as if they are made by somebody else (see also Schneider 1959 who subsumed them under the concept of first-rank symptoms).