



Review

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

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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.

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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 (Northhoff 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 (Northhoff 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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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 led 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; Raji 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).

The theory of impaired inner speech monitoring, i.e., verbal self-monitoring, has however aroused some criticism since it neither explains why one experiences a particular external author during AVH nor the involvement of other regions including the auditory cortex in AVH (Allen et al., 2007a, 2008; Jeannerod, 1999; Pacherie et al., 2006). Using a speech-monitoring task where subjects had to decide the source of prerecorded speech, Allen et al. (2007a, 2007b) observed that patients with AVH were more likely to attribute their own speech externally than patients without AVH. Such misidentification of self-generated speech in patients with AVH was accompanied by altered activity in the STG and the anterior cingulate cortex (ACC) (Allen et al., 2007a, 2008; Mechelli et al., 2007).

More specifically, disturbance in what is called corollary discharge or predictive coding is assumed in schizophrenia. A self-generated movement goes along with signals to the sensory cortex from motor regions informing it about the intended movement; this in turn allows the sensory regions to predict the possibly incoming sensory signals as the sensory consequences of that movement. This signal has been called 'corollary discharge' or 'efference copy' (Stephan et al., 2009; Wolpert, 1997) which allows to coordinate sensory and motor processing in a fine-tuned way. In schizophrenia, many authors assume disconnection between sensory and motor processing and thus abnormal corollary discharge with a consecutive mismatch between the predicted or anticipated auditory consequences of self-generated speech and the actual auditory experience (Bennett, 2008; Feinberg and Guazzelli, 1999; Ford et al., 2002, 2007, 2008).

The assumption of abnormal corollary discharge may be considered a specific case of the more general assumption of altered predictive coding (Friston, 2005; Frith et al., 1992; Stephan et al., 2009). Predictive coding provides the general framework to minimize predictive errors when comparing the predicted or anticipated signal with the actually occurring incoming stimulus. Imagine the case of an abnormal balance between anticipated predictions and actually occurring sensory input with for instance too much emphasis on the anticipated input, e.g., the expectation of a particular person speaking.

The actually incoming sensory input is then perceived and experienced only in the light of the anticipated prediction, i.e., the predicted source and thus the speaker, while leaving no room for the actually occurring source or speaker which is then no longer perceived as such (Friston, 2005; Stephan et al., 2009), see also Fletcher and Frith, 2009 for the detailed application of the theory of predictive coding to hallucinations and delusions in schizophrenia (Fletcher and Frith, 2009).

The theory of impaired inner monitoring has been criticized for remaining unable to explain that AVH are usually associated with a particular external author (Allen et al., 2007b, 2008; Pacherie et al., 2006). While it can explain that AVH are not associated with the own person, as traced back to impaired inner self-monitoring, it cannot explain why AVH are associated with another person in general and a specific person in particular; this is so because the former does not imply the latter. Hence, the attribution of the source to another particular person remains unexplained in impaired inner monitoring.

This is also the point where the theory of predictive coding falls short. The hypothesis of predictive coding claims that the anticipated predictions, the possible source of the anticipated auditory signal, is the determining factor that outbalances the actually occurring input in generating AVH. Since however the anticipated auditory signal is generated by the own person, the subsequent AVH should be associated with the own person and thus with the First-Person Perspective rather than with another person and hence the Second- or Third-Person Perspective.

This however is not so. AVH are rarely, if at all, related to the own voice thus the person speaking to itself, quasi from the own First-Person Perspective to the own First-Person Perspective as a form of a dialogous monologue. Instead, AVH are usually attributed to another particular person and occur consecutively in Second- or Third-Person Perspective (Fu and McGuire, 2003). This however remains unexplained in the hypothesis of predictive coding which would at least be equally compatible with experience of AVH of the own person in First-Person Perspective.

1.3. Current theories of AVH III: sensory-based bottom-up approaches

The sensory-based bottom-up approach focuses predominantly on early electrophysiological potentials in auditory cortex and neural processing in subsequent regions (Javitt, 2009). One such early electrophysiological potential related to sensory processing in auditory cortex is the Mismatch Negativity (MMN). The Mismatch Negativity (MMN) is an electrophysiological potential that can be measured when an oddball or deviant auditory stimulus occurs embedded in a stream of familiar or standard auditory stimuli. The MMN can be measured in both EEG and MEG as a negative waveform that results from subtracting the event-related response to the standard event from the response to the deviant event.

Elicited by sudden changes in auditory stimuli, the MMN occurs about 100–250 ms after the onset of the deviant stimulus and is strongest over frontal and temporal regions. While the MMN is primarily an auditory potential (Naatanen et al., 2007), it is a matter of debate whether potentials analogue to the MMN also occur in other sensory modalities as for instance in visual and somatosensory modalities (Garrido et al., 2009). In schizophrenia numerous studies demonstrated changes and deficits in the MMN (Garrido et al., 2009; Javitt, 2009). More specifically, these studies demonstrated reduction in the amplitude of the MMN in schizophrenic patients both for frequency and duration deviants in hallucinating schizophrenic patients as compared to non-hallucinating ones (Fisher et al., 2008a, 2008b). Moreover, the MMN in temporal electrodes showed maximal sensitivity to phonetic in hallucinating patients while this was not the case in frontal MMN (Fisher et al., 2008a). Taken together, these studies further underlie the apparently crucial relevance of the MMN as a marker of altered auditory processing and pre-attentive function of AVH in schizophrenia (Fisher et al., 2008a, 2008b).

In addition to the MMN other markers of early sensory processing in auditory cortex have been observed to be altered in schizophrenia. These include reductions in the amplitude of early electrophysiological potentials like P50

and N100 that are elicited by simple repetitive stimuli which distinguishes them from the MMN that is induced by a deviant stimulus after a series of repetitive stimuli. Both potentials are assumed to be generated in auditory cortex including both primary and secondary auditory regions (Javitt, 2009; Tregellas et al., 2009; Turetsky et al., 2007). Taken together, these findings point to deficits in early stages of auditory sensory processing where the stimulus starts to be evaluated.

What do these deficits in early electrophysiological potentials mean in psychological and functional regard? Psychologically, the MMN has been associated with implicit and thus automatic processing since it occurs independent of and thus prior to attention (Garrido et al., 2009). For instance, the MMN is induced when the subjects do not pay attention at all to the stimuli be they standard or deviant or when they perform a task completely unrelated to the stimuli. Hence, preattentive cognitive processes that allow for the detection of the deviant stimulus have been assumed to underlie the MMN. The independence of the MMN from attention is further underlined by its occurrence in sleep and even in comatose patients in vegetative states who have no consciousness (Qin et al., 2008). This strongly indicates that the MMN does not only occur prior to attention but remains also independent of consciousness altogether. Hence, psychologically the MMN seems to mirror the early stage of sensory processing that are prior to attention and consciousness and it is these early implicit and automatic processes that seem to be disrupted in schizophrenia.

These changes in the early automatic sensory processing are not limited to the auditory cortex but are also observed in other sensory systems like the visual cortex. Amplitudes in early visual electrophysiological potentials like the steady-state visual-evoked and auditory-evoked potentials (ssVEP and ssAEP), the N100 and the P100 have been found to be reduced in schizophrenic patients (Javitt, 2009). At the same time, low- and high-frequency visual stimuli induced significantly lower neural activity in primary and secondary visual cortices in schizophrenic patients when compared to healthy subjects (Javitt, 2009). Taken together, these findings indicate deficits in early automatic sensory processing of visual stimuli. Since the other sensory systems (olfactory, somatosensory, and gustatory) also show physiological and phenomenological abnormalities (Javitt, 2009), one may assume a general alteration in early automatic processing of sensory stimuli in sensory cortex schizophrenia.

What remains unclear though is the origin of these early changes and how they relate to the resting state activity in these regions. Moreover, it remains unclear why voices are heard in the absence of any incoming exteroceptive stimulus. Why do these early deficits lead to the generation of voices? Hence the exact step from the abnormal early processing that seems to prevent exteroceptive stimuli from being perceived properly to the generation of internal voices in the gestalt of AVH remains unclear in the sensory-based bottom-up approaches.

1.4. Current theories of AVH IV: combined bottom-up and top-down approach

Based on their own and others results, Allen et al. (2008) put forward a more sophisticated theory of AVH thereby

integrating the assumption of impaired self-monitoring into a wider context (Allen et al., 2008). The often made observation of spontaneous hyperactivity of especially the secondary auditory cortex during AVH (in the absence of any external stimulation and thus during the resting state) may prime the subject to perceive complex auditory objects like words or sentences in a more intense way. Since the secondary auditory cortex may be involved in object perception as distinguished from perception of single aspects like tones as processed in the primary auditory cortex, resting state hyperactivity in this region indicates what Allen et al. (2008) call 'over-perceptualization' (Allen et al., 2008). There may thus be abnormal or increased bottom-up modulation from the auditory cortex to the other cortical regions which lets the subjects experience and perceive their own internal auditory activity in a more vivid sense.

Abnormally strong bottom-up modulation from the auditory cortex may be accompanied by reduced top-down modulation from cortical regions involved in speech and language processing (Allen et al., 2008). These include Broca's and Wernicke's areas underlying the generation and perception of speech as well as regions like the ACC, the SMA and the DLPFC involved in monitoring speech. Hence, Allen et al. (2008) regard the altered balance between reduced top-down modulation and increased bottom-up modulation as crucial in generating AVH (they also include regions implicated in emotion processing in their model) (Allen et al., 2008).

Neurally it remains unclear though why there is abnormal hyperactivity in the auditory cortex and thus where it comes from and whether other regions are also affected. While psychologically the association of the AVH with the Second- or Third-Person Perspective rather than the First-Person Perspective remains unclear. Moreover, the voices perceived are usually attributed to another person thus occurring in Second- or Third-Person Perspective, they are nevertheless perceived as meaningful and important to the own person. And it is this delicate balance between voices from another person and their highly personal meaning and relevance that cannot be explained in either of the theories sketched earlier.

1.5. Resting state hypothesis of AVH I: abnormally increased resting state activity in the auditory cortex

Early functional studies observed an association of hallucinations/delusions as reality distortions with increased resting state activity (e.g., metabolism or perfusion) in the superior or middle temporal lobe that includes the auditory cortex (Gur et al., 1995; Liddle, 1992). Comparing the resting state activity during AVH with the one during the absence of AVH within the same patients, Dierks et al. (1999) observed hallucination-related activity in Broca's area, the temporal gyri and the primary auditory cortex (Dierks et al., 1999). Taken together, these findings lend support to the assumption that especially the secondary (but also the primary) auditory cortex may show increased resting state activity in the acute psychotic state when suffering from auditory hallucinations.

The assumption of abnormally endogenous activity in the auditory cortex during AVH (see Hunter et al., 2006 for investigating resting state activity in auditory subjects in healthy subjects) is further supported by a recent multicenter

study (Hunter et al., 2006). More specifically, the multicenter study by Ford et al. (2009) reported less activation to external tones in left primary auditory cortex in AVH suggesting that the primary auditory cortex is “turned on” already in the resting state by showing increased endogenous activity (Ford et al., 2009). This in turn leads to what the authors describe as “tuned in”, the orientation of perception towards internally-generated activity rather than towards externally-generated activity, i.e., stimulus-induced activity.

One needs to be careful though. The resting state activity measurements do not really reflect a true resting state in a psychological sense since the patients in these studies are asked to mark the beginning and end of their hallucinations. The proclaimed resting state is thus confounded by attention towards the hallucinations. Moreover, there is no true resting state in a physical sense either. This is due to the fact that studies in fMRI cannot detect true resting state activity due to the continuous presence of the scanner noise. This makes it practically impossible to measure true resting state neural activity in the auditory system in fMRI (Logothetis et al., 2009). One may therefore focus on measuring resting state activity in other imaging modalities like the EEG that does not suffer from such methodological shortcomings. Interestingly, electrophysiological studies in schizophrenic patients demonstrate alterations in resting state oscillations (see (Uhlhaas and Singer, 2010) for a recent review). Studies reported an increase in low-frequency activity, e.g., delta (0.9–4 Hz) and theta (4–8 Hz) (Boutros et al., 2008) and reduced in high-frequency activity (30–80 Hz), e.g., the gamma band, in MEG during a true resting state, e.g., eyes closed (Rutter et al., 2009). Another earlier study reported significantly decreased global field synchronization, a measure of resting state connectivity, in the theta band (4–8 Hz) in first-episode schizophrenic patients with positive symptoms (including AVH) indicating loosened functional connectivity among different regions (Koenig et al., 2001).

Taken together, there is solid evidence of abnormally elevated resting state activity in the auditory cortex itself. This though raises two questions. First, where does this abnormal increase in auditory cortical resting state activity come from? Second, how does it affect the neural processing of exteroceptive stimuli so that even in the absence of the latter external voices are heard. These issues will be discussed in the next sections (Fig. 1).

1.6. Resting state hypothesis II: elevated resting state activity in the default-mode network and altered rest–rest interaction

Recent imaging studies in schizophrenia reported indeed abnormal resting state activity and connectivity in the default-mode network. One study demonstrated that the medial prefrontal cortex and the posterior cingulate cortex/precuneus show decreased task-induced deactivation (TID) during a working memory task in both schizophrenic patients and their relatives when compared to healthy subjects (Whitfield-Gabrieli et al., 2009). This is indicative of decreased task-related suppression and possibly increased resting state activity. Furthermore, the very same schizophrenic subjects also showed increased connectivity of the anterior medial prefrontal cortical regions with the posterior regions, the posterior cingulate cortex. Both hyperconnectivity and decreased TID

correlated negatively with each other meaning that the more decreased task-related suppression, the more increased the connectivity. Finally, both decreased TID and increased connectivity correlated with psychopathology, i.e., predominantly positive symptoms as measured with the PANS.

Rotarska-Jagiela et al. (2010) investigated resting state networks; they observed increased connectivity within the regions of the DMN which correlated with positive symptoms severity (Rotarska-Jagiela et al., 2010). However, another recent study (Vercammen et al.) showed rather decreased connectivity of the anterior cingulate cortex with the left temporal–parietal junction and the bilateral amygdala which though regions that are not considered part of the DMN. The TID as indirect measure of the resting state activity level was shown to be decreased in medial prefrontal cortical regions in an earlier study that also investigated working memory (Pomarol-Clotet et al., 2008). Similar to the study described, they let the subjects perform a working memory task and observed abnormally decreased TID in medial prefrontal cortex in schizophrenic patients when compared to healthy subjects. And similar to the other study, they also observed abnormal task-related activation in the right dorsolateral prefrontal cortex in schizophrenic patients. Since the degree of TID also depends on the resting state activity level, decreased TID may be indicative of increased resting state activity. Another study (Mannell et al., 2009) observed also abnormal TID and connectivity between anterior and posterior medial regions and the insula in schizophrenic patients thus lending further support to the other findings (see also Calhoun et al., 2008; Park et al., 2009; Kim et al., 2009; Calhoun et al., 2008; Jafri et al., 2008; Williamson, 2007).

In addition to TID and connectivity, another measure of resting state activity is the temporal features, more specifically fluctuations or oscillations in certain temporal frequencies. For instance, Hoptman et al. (2010) and Rotarska-Jagiela et al. (2010) demonstrated that low frequency fluctuations in the resting state were increased in the medial prefrontal cortex and the parahippocampal gyrus in schizophrenic patients while they were decreased in other regions including the insula (Hoptman et al., 2010). Abnormally increased low frequency oscillations in the medial prefrontal cortex (and posterior medial regions and the auditory network) and their correlation with positive symptom severity were also observed in another study on schizophrenic patients (Rotarska-Jagiela et al., 2010).

Taken together, these, empirical findings demonstrate clear resting state abnormalities in regions of the default-mode network in schizophrenia. More specifically, the findings suggest that the resting state activity in especially the anterior medial cortical regions is abnormally increased as indicated by the observations of decreased TID, increased connectivity, and increased low-frequency fluctuations in schizophrenic patients.

What though remains unclear is how these resting state abnormalities in the DMN affect the auditory cortex. A recent study in healthy subjects (Sadaghiani et al., 2009) investigated tone recognition during implicit and explicit tone recognitions. They demonstrated that those tones that were recognized, e.g., hits, were preceded by higher activity in the DMN prior when compared to those that were not recognized and thus missed. This suggests that the differential resting state activity impacts

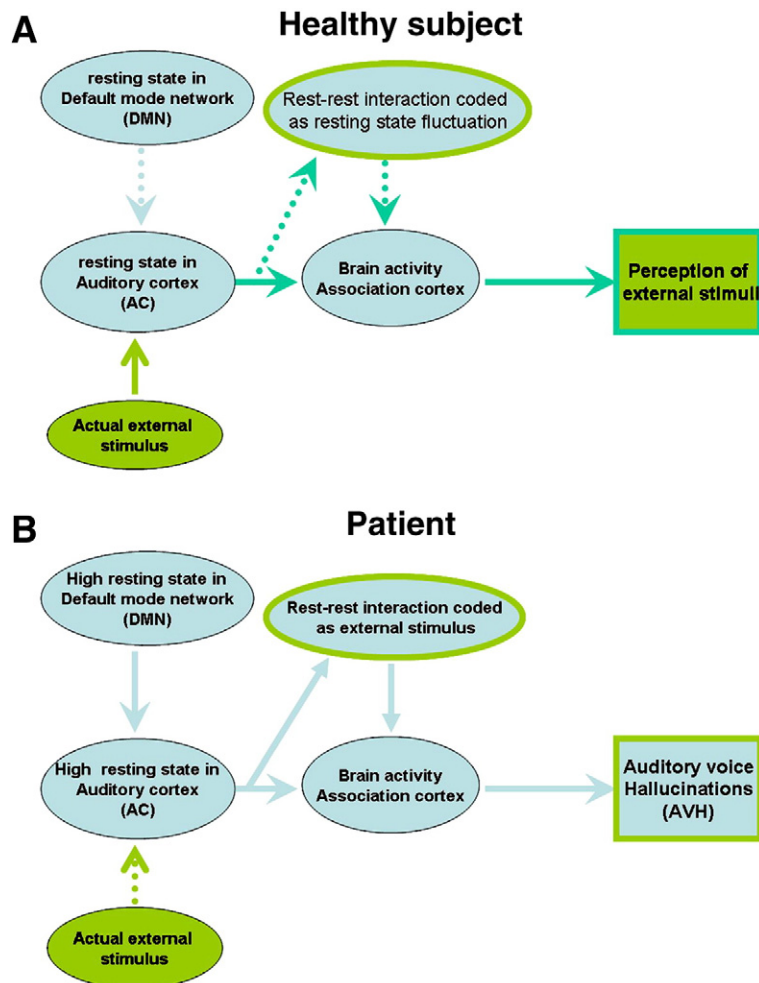


Fig. 1. This figure schematically illustrates our resting state hypothesis of AVH. (A) Healthy subjects: we hypothesize that the external stimuli can induce neural activity in the AC and related association cortex. At the same time, the resting state activity in the AC and other brain regions can interact with each other which the resulting neural difference from such rest–rest interaction being smaller than the one between resting state and stimulus-induced activity, e.g., rest–stimulus interaction. This larger neural difference during rest–stimulus interaction is supposed to generate the perception of the external stimuli. The broken line represents the smaller neural difference in the resting state itself, e.g., rest–rest interaction, when compared to the one between resting state and stimulus-induced activity from the external stimuli, e.g., rest–stimulus interaction. (B) Patients with AVH: we hypothesize that high resting state in default-mode network (DMN) induces high resting state in the auditory cortex (AC). This leads to high and increased larger neural differences during rest–rest interaction in the AC and subsequent auditory pathways. At the same time though such increased rest–rest interaction with larger neural differences diminishes the impact of external stimuli on neural activity in the AC thus leading to decreased rest–stimulus interaction. Rest–rest interaction is thus confused with rest–stimulus interaction which in turn leads to the generation of AVH. The broken line represents the larger neural difference in the resting state itself, e.g., increased rest–rest interaction, when compared to the one between resting state and stimulus-induced activity from the external stimuli, e.g., rest–stimulus interaction. Green indicates the effect of external stimuli, e.g., rest–stimulus interaction, while light blue describes the effects within the resting state itself, e.g., rest–rest interaction.

subsequent auditory cortical stimulus-induced activity and associated behaviour. What remains to be demonstrated though is whether the differential activity in DMN also leads to different connectivity with the auditory cortex in the resting state entailing different rest–rest interactions.

Based on these findings in healthy subjects, one may for instance hypothesize that due to the DMN abnormalities, there may be abnormal rest–rest interaction between the DMN and the auditory cortex. The abnormally elevated resting state activity in auditory cortex may then be hypothesized to be related to abnormal cross-regional rest–rest interaction between DMN and auditory cortex. If this hypothesis holds one would also predict that abnormal

auditory cortical activity during AVH may be preceded by abnormal cross-regional rest–rest interaction with the DMN. This hypothesis as well as its potentially underlying gaba- and glutamergic mechanisms remains to be tested though (Benes, 2007; Benes et al., 2008; Northoff et al., 2007).

How can such abnormal cross-regional rest–rest interaction between auditory cortex and DMN leads to the perception of external voices that are nevertheless perceived as relevant and personally important? The DMN and especially the anterior and posterior medial regions are well known to be involved in processing the degree of self-relatedness or personal relevance of external stimuli (Enzi et al., 2009; Northoff et al., 2006). The strong and often

reported showing of the anterior and posterior midline regions in paradigm probing for self-relatedness has led to the concept of cortical midline structures (CMS) (Northoff and Bermpohl, 2004; Northoff et al., 2006). The CMS describe a set of regions in the midline of the brain including the anterior and posterior cingulate cortex, the ventro- and dorsomedial prefrontal cortex, the medial parietal cortex, the precuneus and the retrosplenium (Northoff et al., 2006). Within this set of cortical midline regions one may distinguish between anterior and posterior CMS (aCMS, pCMS); the aCMS include the anterior cingulate and the ventro- and dorsomedial prefrontal cortex while the pCMS encompasses the posterior cingulate, the medial parietal cortex, the precuneus and the retrosplenium. In the following the abbreviations aCMS and pCMS will be used to describe and conceptualize the findings in schizophrenia.

How does the involvement of the aCMS in self-relatedness can account for the often observed highly personalized, derogatory and second- or third-person nature of AVH? Voices in AVH are perceived as external voices and are nevertheless attributed an abnormally high degree of personal relevance, meaning or self-relatedness which though is experienced in second- or third-person. How is this possible?

Let's start with the high personal relevance, meaning or self-relatedness. In the same way any auditory stimulus of external origin is attributed a certain degree of self-relatedness when processed in aCMS, the internally generated auditory stimulus is also assigned self-relatedness and thus personal relevance. Moreover, since the internally auditory stimulus is derived from memory-based auditory experiences of previous external stimuli (see succeeding discussions for details), it may even be assigned an extremely high degree of personal relevance. Hence, the process of self-related processing may account for the high personal relevance, meaning or self-relatedness of AVH.

Why are the AVH experienced in second- or third-person? If they show such high degree of self-relatedness one would assume them to be experienced in first-person rather than second- or third-person. One may assume that despite its high degree of self-relatedness, the internally generated stimuli underlying AVH are treated as an externally generated one; this may be so because it is processed in the auditory cortex which usually receives externally-generated stimuli which are subsequently experienced in second- or third-person. The same now happens to the internally-generated stimuli and they are subsequently coded (or treated by the brain) as externally-generated stimuli, or, to be more precise, "as if externally-generated" stimuli. One may consequently assume neural confusion between internally- and externally-generated neural activities in the auditory cortex with internally-generated activity being treated as externally-generated one. Therefore, the internally-generated neural activity is processed and treated as if it was externally-generated activity and hence experienced in second- or third-person rather than in first-person (Fig. 2).

1.7. Resting state hypothesis of AVH III: reduced rest-external stimulus interaction in the auditory cortex

What does the finding of a seemingly increased resting state activity in the auditory cortex imply for the neural

processing of exteroceptive stimuli and hence for rest-stimulus interaction? The earlier mentioned study in healthy subjects demonstrated also that the level of the resting state activity in auditory cortex predicted the subsequent auditory behaviour, e.g., whether the auditory tone was recognized (hit) or not recognized (miss) (Sadaghiani et al., 2009). If it was recognized that the preceding resting state activity in auditory cortex was higher when compared to the one observed prior to non-recognized tones. Hence, these results suggest that there is some rest-stimulus interaction in the auditory cortex with the level of the resting state activity determining subsequent the level of stimulus-induced activity and associated behaviour.

What does this entail for schizophrenia and AVH? The study by Ford et al. (2009) suggest that there is decreased rest-stimulus interaction in auditory cortex in schizophrenia; this means that the external stimulus elicits less (or no) activity any more in the auditory cortex when compared to its resting state activity level (Ford et al., 2009). Such reduced rest-(external) stimulus interaction leads no longer to the generation of a neural difference between resting state activity level and stimulus-induced activity; this may also account physiologically for the earlier described reductions in the amplitudes of early electrophysiological potentials during stimulus-induced activity.

The assumption of reduced rest-stimulus interaction is empirically supported by the observation of schizophrenic patients showing reduced amplitudes and reduced phase synchronization in the beta and gamma frequency bands during stimulus-induced activity in auditory and visual cortices (Uhlhaas and Singer, 2010). Since especially phase synchronization is supposed to account for the integration of activity within a local cortical network (Uhlhaas and Singer, 2010), impaired phase synchronization could indicate that the stimulus itself is not properly processed in auditory cortex entailing reduced rest-stimulus interaction. Another reason why the auditory stimulus may not be properly processed in the auditory cortex and the neural processing in subsequent auditory pathways and higher regions may be an altered signal-to-noise ratio indicating different stochastic resonance. Using EEG Winterer et al. (2000) observed decreased signal-to-ratio during event-related activity, e.g., an acoustical choice paradigm, in schizophrenic patients (Winterer et al., 2000). The reduced signal-to-noise ratio was due to reduced signal power and increased noise power meaning that spontaneous activity seems to oscillate stronger and larger (see also (Winterer et al., 2004; Winterer et al., 1999) as well as (Jaramillo et al., 2000, 2001)). Moreover, he demonstrated that the augmentation of theta/delta activity during the stimulus did not correlate with signal power in schizophrenic patients. Hence, it seems that noise-related neural activity is decoupled from stimulus-induced activity in schizophrenia leading to reduced rest-stimulus interaction entailing decreased stimulus-induced activity.

The data described earlier in the section about the sensory-based bottom-up approaches are strongly supportive of the assumption of reduced rest-stimulus interaction in auditory cortex; this is so since the incoming stimulus may no longer be gated and filtered and thus be less impacted and modulated by the brain's resting state activity as it may be suggested to underlie the earlier described bottom-up sensory-based

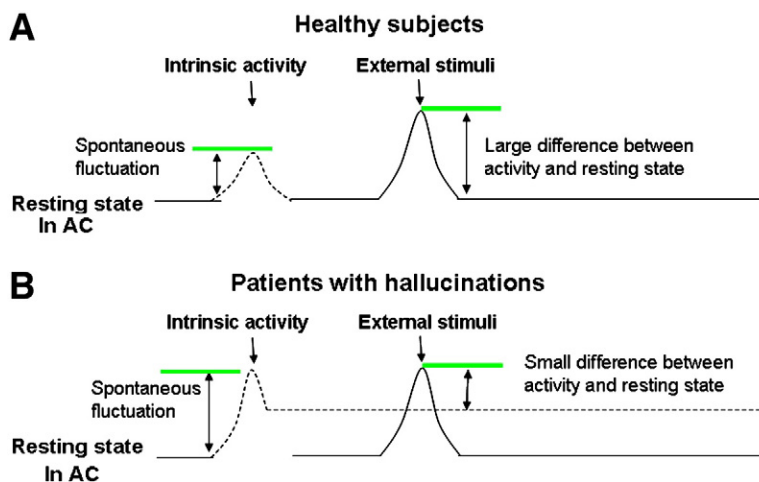


Fig. 2. This figure schematically illustrates the intrinsic activity, i.e., resting state activity and its fluctuations, in relation to extrinsic, i.e., stimulus-induced activity, in auditory cortex (AC) in healthy and schizophrenic subjects. (A) Healthy subjects: We hypothesize that intrinsic spontaneous fluctuations are not as large and are hence treated and coded as resting state fluctuations rather than as stimulus-induced activity. This enables the external stimuli to induce sufficient changes in neural activity, i.e., stimulus-induced activity, as distinct from the level of the resting state activity. (B) On the contrary, in patients with AVH, the intrinsic spontaneous fluctuation is either too large or/and does not return back to the original resting state activity level. The difference between original resting state level, i.e., before occurrence of the intrinsic fluctuation, and the resting state level after the fluctuation may then be as large as the change normally induced by external stimuli; the difference in activity level before and after the resting state fluctuation may then be coded by the brain as if it was induced by an external stimulus which in turn enables and predisposes to perceive it as AVH.

deficits. What does the reduced presence or even complete absence of rest–external stimulus interaction in auditory cortex entail for subjective perception and experience? Why does the schizophrenic patient nevertheless perceive and experience voices, i.e., AVH even though the external auditory stimuli may no longer be processed properly? Where are the stimuli coming from the patient perceives and experiences as voices in AVH?

We may to consider again the auditory cortex. If the auditory cortical resting state activity undergoes a major change ranging beyond the normally occurring neuronal oscillations independent of any external stimulus, this resting state change may be registered as if an external stimulus is coming in. Hence, the auditory cortex may confuse its own (abnormal) change in its resting state activity level with those neuronal changes that are normally associated with an external stimulus. In other terms, abnormal rest–rest interaction is confused with rest–external stimulus interaction. Due to the fact that abnormal rest–rest interaction is taken as rest–stimulus interaction, subsequent stages of auditory cortical processing are activated leading to further processing of what is false positively taken as external auditory stimulus. One may consequently hypothesize abnormal increase in rest–rest interaction within the auditory cortex and its confusion with rest–external stimulus interaction in AVH in subsequent stages of auditory processing.

Is there any empirical evidence in favour of such increased rest–rest interaction in schizophrenia? If there is indeed increased rest–rest interaction in schizophrenia, one would expect increased amplitudes and phase synchronization in the beta and gamma bands that account for the integration of different neural activities within a local cortical network such as the auditory or visual cortex. Interestingly, this is exactly what several studies report when they observed positive symptoms and especially auditory and visual hallucinations

to correlate with enhanced amplitudes and phase synchronization of beta- and gamma-band resting state activity in schizophrenic patients (Lee et al., 2006; Spencer et al., 2008, 2009). More specifically, Spencer et al. (2008, 2009), a deficit in gamma 40 Hz oscillations in auditory cortex in hallucinating schizophrenic patients and also providing evidence for high-frequency synchronization as indicative of cortical hyperexcitability ((Spencer et al., 2008, 2009), also see (Mulert et al., 2010)). In addition to the gamma deficit, Lee et al. (2006) observed increased beta frequencies in schizophrenic patients with AVH that were also decoupled from stimulus-induced activity (Lee et al., 2006). Taken together with the earlier reported increased noise, there is evidence for abnormal neural activity in the resting state with potentially increased rest–rest interaction in the auditory cortex as evidenced by the various electrophysiological measures.

What electrophysiologically is described as enhanced amplitude and phase synchronization may then correspond on the functional level to the neural coding of the differences in the intrinsic oscillations or fluctuations within the resting state activity itself and hence to rest–rest interaction. Instead of integrating resting state activity and external stimulus-induced activity mirroring rest–stimulus interaction, phase synchronization in auditory (and other sensory) cortex integrates now the neural difference between two different resting state activity levels leading to what may be described as abnormal rest–rest interaction within the auditory cortex.

If the onset of hallucinations is assumed to be triggered and preceded by abnormal rest–rest interaction in auditory cortex and subsequent regions of auditory processing, one would hypothesize abnormal neural activity in these regions to prior to the AVH. This has indeed been observed. Activity changes before the onset of AVH (i.e., 6–9 s) were observed in the left inferior frontal cortex, the ACC and the right middle temporal gyrus was evident 6–9 s before the onset of AVH

while during the AVH itself activity was present in the bilateral temporal gyrus (Hoffman, 2007, 2008; Shergill et al., 2000, 2004; van de Ven et al., 2005). There is also ample evidence for altered, i.e., reduced functional/effective connectivity from prefrontal regions like the dorsolateral prefrontal cortex (DLPFC), the ACC and the left inferior frontal cortex to regions in the temporal cortex including the auditory cortex during verbal self-monitoring (Mechelli et al., 2007) or AVH themselves (Hoffman et al., 2007; Raij et al., 2009). This is further corroborated by observation of abnormal structural fronto-temporal connectivity in DTI in schizophrenic patients with AVH (Hubl et al., 2004; Shergill et al., 2007). More specifically, Hubl et al. (2004) and Shergill et al. (2007) reported higher directionality of the arcuate fasciculus in the temporal cortex predisposing for stronger co-activation (Hubl et al., 2004; Shergill et al., 2007). Shergill et al. (2007) observed that AVH were related to increased fractional anisotropy in superior longitudinal fascicule and in the anterior cingulate cortex (Shergill et al., 2007). Taken together, these findings such as the abnormal white matter integrity in the temporal and frontal cortices may alter their interplay and connection during both resting state and stimulus-induced activity.

This though leaves one issue open. How does such abnormal rest–rest interaction transform into the subjective perception and experience of auditory stimuli and hence voices? Since the neural differences in auditory cortex are usually associated with internal–external differences rather than internal–internal differences, the brain takes the latter to be an instance of the former. In other terms, it confuses its current difference, the internal–internal difference, with the usual difference, the internal–external difference, and subsequently infers an auditory stimulus to occur in the external environment resulting in AVH. To put it differently, the brain and more specifically the auditory cortex confuses mere rest–rest interaction with rest–external stimulus interaction.

We assume that mental states in general independent of whether their content is internally or externally generated may be generated by the neural coding of neural differences. These neural differences may be traced back to either neural differences between resting state and stimulus-induced activity, as it normally the case and described here as rest–stimulus interaction. Alternatively neural differences may also be caused by neural differences within the resting state itself, e.g., resting state fluctuations and oscillations, amounting to what we here called rest–rest interaction. The crucial question remaining for the future is thus how large the neural difference must be to be coded as neural difference that is large enough to induce a mental state as for instance AVH. While in healthy subjects rest–rest interaction does not yield neural differences large enough to induce AVH, neural differences in the resting state seem to be increased in schizophrenic patients with the subsequent occurrence of mental states with contents purely internally generated. Since inner speech in healthy subjects is not associated with activity in the primary auditory cortex, abnormally high resting state activity in this region suggests that it may be perceived and experienced as if there is a real external sound. This in turn may prompt the respective subject to infer an external perceptual source thereby turning the perception of one's own resting state activity into what we as external

observers call hallucination (Dierks et al., 1999; Frith, 1999; McGuire et al., 1996).

This assumption may be supported by considering deaf people. Being deaf they cannot hear anything as related to external stimuli. They though are able to develop auditory hallucinations (Atkinson, 2006; Atkinson et al., 2007). The auditory hallucinations of deaf people with experience in hearing speech were very similar to the prior individual auditory experience. This supports our assumption that the rest–rest interaction may functionally imply the recruitment of previous memory-based auditory experiences stored in the auditory cortex and subsequent pathways. The previous auditory experiences thus serve as functional template for the current rest–rest interaction. In contrast, hallucinations in deaf people born deaf map closely onto nonauditory factors of which they had prior experience (Atkinson, 2006; Atkinson et al., 2007). This suggests that rest–rest interaction within the auditory system must be somehow present since otherwise deaf people born deaf could not develop hallucinations. If so one would expect hyperactivity in auditory cortex during auditory hallucination even in deaf people and that is exactly what a recent case report described (Naccache et al., 2005). Even deaf schizophrenic patients can show AVH (Schonauer et al., 1998) which further supports our assumption of rest–rest interaction being central in generating AVH.

Why though do the patients hear external voices, i.e., voices from other people, rather than internal voices, e.g., voices from the own person, in AVH? This may be so because they associate a neural difference in auditory cortex coded in rest–rest interaction with a previously heard auditory stimulus, e.g., of previous auditory objects encountered in his very past. Based on the inference and recruitment of his previous mental auditory (and higher) cortical representations of past verbal utterances, the patient hears verbal voices and hence what we as observers describe then as AVH. Resting state activity in auditory cortex and those regions implicated in subsequent auditory processing may psychologically be associated with the representation of past voices from other people, e.g., of past exteroceptive stimuli. Increases in both resting state activity and rest–rest interaction may then lead to the reactivation of those past voices within the current context. If so this means that the increased oscillatory activity in auditory cortex and the subsequently increased rest–rest interaction may reflect the read-out of stored experiences as internal or mental representations of voices encountered in the past.

Another question concerns the fact that AVH often refer to new voices or, as one may also say, 'do novo conversations or commands'. How is it possible that completely new hitherto unknown voices are generated in AVH? While being unable to ultimately answer this question, one may at least a preliminary tentative hypothesis within the here presupposed framework. We hypothesized increased rest–rest interaction in the auditory cortex and the subsequent auditory pathway in AVH. Such increased rest–rest interaction in the auditory system may imply the reactivation of previous memory-based auditory experiences. Unlike in the case of a specific stimulus inducing 'normal' stimulus-induced activity, this reactivation of previous memory-based auditory experiences may occur unguided and non-systematic (because of the lack of an external stimulus). This in turn may lead to the recombination of different previous auditory experiences

which then may trigger a novel hitherto unknown voice with the resulting AVH being a de novo command or conversation. While admittedly tentative at this point, future studies relating previous memory-based auditory experiences in conjunction with the current content in AVH and the respective neural patterns in the auditory pathway may shed further light on the here proposed mechanisms.

1.8. Resting state hypothesis IV: convergence with phenomenological accounts – a neurophenomenal hypothesis

Phenomenological approaches do not aim to explain neurobiological mechanisms in scientifically objective terms but on the personal significance and meaning of the patient's subjective experience, i.e., their phenomenal states (Blankenburg, 1969; Lysaker and Lysaker, 2008; Minkowski, 1987; Parnas, 2003; Parnas and Handest, 2003; Parnas et al., 1998; Sass, 2000, 2003; Sass and Parnas, 2001). This has led the phenomenological approaches to focus also on the schizophrenic patients' self and their phenomenal states in the prior stages before the outbreak of acute symptoms, the subtle alterations in the to-be schizophrenic patients' subjective experience of their own self, other selves and the world (see Parnas, 2003; Sass, 2003; see further discussion for details). Hence, there has been exploration of the subjective experience of the self in the presymptomatic stages of schizophrenia of which the underlying neuronal mechanisms remain unclear though.

The phenomenological account focuses for instance on the subjective experience of the objective stimulus from the perspective of the experiencing person. It consecutively describes how we subjectively experience incoming sensory stimuli as exteroceptive auditory stimuli or interoceptive stimuli from our own body in a subjective way and thus how we can relate them to our own self. The linkage of sensory stimuli to the own self in subjective experience thus concerns what phenomenological accounts (Bin Kimura, 1997; Blankenburg, 1969; Parnas, 2003; Parnas, et al., 2003; Parnas, et al., 1998; Sass, 2000; Sass, 2003; Sass and Parnas, 2001) describe as 'attunement'. The concept of 'attunement' describes, most broadly, the relation of the self to the world, e.g., how the self adjusts and adapts to the various objects, events and other persons in its respective environment.

Most specifically, phenomenologists point out that 'attunement' in this sense operates already on a prereflective, implicit or preconceptual level which Parnas (2003) and Sass (2003) describe as pre-reflective or preconceptual attunement. In the following I will use the concept of attunement to describe such pre-reflective, pre-conceptual and implicit adaptive processes which corresponds well to the concept of self as relational as presupposed here (Parnas, 2003; Sass, 2003).³ Taken together,

³ I am aware that the concept of self would need extensive definition and discussion by itself which however would be beyond the scope of this paper. There are different concepts of self discussed ranging from a bodily- proto-self over a mental self to an autobiographical self (see Northoff et al., 2006 for an overview). I here presuppose a very basic, precognitive self that is based primarily on sensory processing and strongly affectively coloured and, as I claim, establishes a basic relation to the environment so that I also speak of a 'relational self' (see queryNorthoff and Panksepp 2008; queryPanksepp and Northoff 2009). The pre-cognitive and sensory and relational nature of the concept of the relational self complements well what phenomenologically is described as attunement (see below).

psychosis may phenomenologically be characterized by disrupted attunement which makes it impossible for the psychotic patient to relate to his environment in a subjective-experiential way.

Phenomenological accounts assume that the attunement in this pre-conceptual and pre-reflective way is disrupted in schizophrenia. The patients are no longer attuned to their environment and the incoming exteroceptive stimuli, they can no longer relate to them in a subjective-experiential way. I hypothesize that such disruption in attunement may be related to the reduced impact of the external stimulus on the brain's resting state activity and hence to reduced rest-stimulus interaction in for instance the auditory cortex.

One though needs to be more specific. If the incoming external auditory stimulus no longer induces neural activity changes in auditory cortical activity, mirroring reduced intra-regional rest-stimulus interaction, it can neither be processed further any further nor induce subjective perception and experience. Reduced auditory cortical rest-stimulus interaction may thus decouple the subject from the external auditory stimulus in particular and the environment in general. This in turn may provide the basis for what phenomenological accounts describe as disrupted attunement as the disruption of the relationship between subject and environment. My neurophenomenal hypothesis would thus be that reduced rest-stimulus interaction in sensory cortices like the auditory cortex (and also other sensory regions like the visual cortex (Javitt, 2009)) may be related to the phenomenological feature of disrupted attunement.

2. Conclusions and predictions

We here present a novel hypothesis about the neuronal mechanisms underlying AVH, the resting state hypothesis of AVH. Our resting state hypothesis integrates the latest data on the relevance of the brain's resting state activity for subsequent stimulus-induced activity. In contrast to the three main current approaches, cognitive-based top-down, sensory-based bottom-up and combined bottom-up and top-down, our starting point is not so much with the stimulus-induced activity itself but rather what must happen prior to it during the brain's resting state activity in order to enable and predispose AVH.

How does our resting state hypothesis relate to the current theories with regard to top-down and bottom-up modulations? While one may assume the modulation of the auditory cortex by the DMN to be a top-down modulation, it is distinct from current top-down theories in that it occurs in the resting state, i.e., as rest-rest interaction. Moreover, one may also diagnose bottom-up elements in our hypothesis as manifest in the abnormal auditory cortical processing as related to reduced rest-external stimulus interaction. Unlike the bottom-up approaches who diagnose the disturbance within the auditory cortex itself, we trace this back to the abnormally elevated resting state and the consecutive reduction of rest-stimulus interaction. Hence, our focus shifted from stimulus-induced activity to the resting state activity in auditory cortex and the DMN and how it must be altered in order for AVH to be possible.

Thereby, we postulate two core assumptions which shall be briefly recounted in the following including predictions for

future experimental testing. First, we hypothesize abnormally elevated resting state activity and reduced rest–stimulus interaction in auditory cortex. While elevated resting state activity in this region is supported by the data, abnormally increased rest–rest interaction remains to be demonstrated. The assumption of abnormally increased rest–rest interaction entails reduced rest–external stimulus interaction during for instance verbal stimuli which has indeed been hypothesized though not yet experimentally demonstrated (Allen, et al., 2008).

This leads to testable predictions in the future. (i) Neuronally, one may want to investigate resting state activity fluctuations or oscillations which may be abnormally great and/or less synchronized before the onset of AVH corresponding to abnormally increased rest–rest stimulus interaction. (ii) Psychologically, one may want to investigate whether such abnormal rest–rest interaction goes along with the increased retrieval of mental representations of past auditory stimuli in auditory (and higher regions) cortex in AVH. (iii) Psychologically, one may want to investigate the psychological correlates of the apparently abnormally increased resting state activity in auditory cortex which may be related to what has been described as “listening attitude” or heightened auditory attention (Hoffman, 2010).

Second, we hypothesize that the abnormal rest–rest interaction may be confused (or taken) by the brain with rest–external stimulus interaction thereby inferring externally located voices which in turn leads to the AVH. This inference of external voices may neurally be related to subsequent stages of auditory processing, e.g., ‘upward consequences’ as we called them earlier, which may be supported by the abnormalities in the higher cortical regions observed during AVH (see previous discussions). In terms of neural timing, one would thus expect abnormal rest–rest interaction to precede the involvement of higher cortical regions which in turn may occur prior to the onset of AVH which is at least in part in accordance with the previously described findings.

This leads to predictable predictions in the future. (i) Neuronally, one may want to investigate the auditory pathway before and during AVH in even further spatial and temporal details. If this second part of my hypothesis is correct, one would expect to disrupt AVH by disruption of subsequent auditory processing in the higher auditory regions following the auditory cortex. While we admit that this is difficult to investigate, one may employ in the future TMS that is more refined to tap into specific regions and then interrupt the respective pathways. One could also do corresponding animal experiments with lesion-induced changes in specific regions and pathways and see whether the effects correspond to the findings obtained in humans. (ii) One may also want to investigate deaf patients and their hallucinations in both EEG and fMRI and see whether they show the same functional changes concerning the resting state with increased rest–rest interaction as schizophrenic patients do. This may lead further support to our hypothesis of the neural difference between different resting state activity levels being crucial for inducing the mental states and thus AVH. This may also contribute to determine the degree or amount of neural difference that is necessary to induce a mental state whatever the origin of its content. (iii) Psychologically, one may want to investigate the

relationship of both increased auditory cortical resting state activity and the neural confusion between rest–rest and rest–stimulus interactions with social factors and more specifically social withdrawal and isolation (see Hoffman's social deaf-differentiation hypothesis (Hoffman et al., 2007, 2008)). Hoffman et al. (2007) observed that social withdrawal and isolation relative to the individual level may induce and trigger changes in auditory cortical resting state activity (Hoffman, et al., 2007). Hence, put into the present context, social withdrawal may predisposes one to reduced rest–external stimulus interaction, increased rest–rest interaction and subsequent neural confusion between rest–rest and rest–stimulus interactions. AVH may then be related to a specific constellation between social environment and auditory and DMN resting state activity levels which may eventually also account for the occurrence of AVH in healthy subjects.

The crucial impact of the social context also sheds a light on our resting state hypothesis. We assume resting state abnormalities to be necessary though not sufficient conditions of AVH. Only if combined with the described social withdrawal and the consecutive absence of external stimuli, rest–rest interaction may yield large enough neural differences to induce mental states and thus AVH. If, in contrast, there is a high continuous social input and thus external stimuli, rest–rest interaction even if increased is much more likely to be suppressed by the demands of the external stimuli and its induction of stimulus-induced activity, e.g., rest–stimulus interaction. This means that increased rest–rest interaction may be considered a necessary though non-sufficient condition of possible AVH; increased rest–rest interaction may enable and predispose AVH and may therefore be described as neural predisposition rather than as neural correlate that pertains to the sufficient conditions of AVH.

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Contributors

Dr. Georg Northhoff generated the main structure of this paper and wrote the paper. Dr. Pengmin Qin improved the structure and wrote the paper.

Conflicts of interest

There are no conflicts of interest.

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