Brain functioning when the voices are silent – Aberrant default-modes in auditory verbal hallucinations

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Abstract

More than a decade of functional brain imaging has shown that auditory verbal hallucinations (AVH) in schizophrenia correspond with increased brain activity in a wide variety of different brain areas. However, these localized changes in brain activity are likely the end result of a more profound and fundamental aberration in brain dynamics that ultimately lead to the perception of hallucinated voices. In a sense, AVH may result from ongoing brain activity at times when the voices are silent. Recent advances in functional brain imaging may allow insight into these previously unobserved, intrinsic functional brain dynamics. Pioneering studies have shown that intrinsic brain states possess a rich and complex functional architecture that closely resembles brain dynamics observed during many different kinds of cognitive and sensorimotor tasks. Further, intrinsic brain states may prove to be of importance to goal-directed brain activity, and ultimately to our perception and performance, that is, of importance to our behavior. Recent studies provide the first indications that intrinsic brain states may play an important role in AVH and other psychotic symptoms in schizophrenia. This chapter describes the main findings and advances in measuring intrinsic brain states in humans in vivo, and discusses how intrinsic brain states can contribute to our understanding of the aetiology and experience of AVH in schizophrenia.

Introduction

Auditory verbal hallucinations (AVH) constitute an intriguing, often bizarre and almost always distressing manifestation of schizophrenia, and are considered one of its prominent diagnostic features (American 1994). Many hallucinating patients describe their auditory hallucinations being of a derogatory nature, containing offending commentary or harmful commands (Nayani and David 1996). More than a decade of functional brain imaging studies has shown that the online experience of AVH is associated with increased brain activity in areas of auditory perception, speech processing, memory and affective processing (Jardri et al. 2010; Stephane et al. 2001a; Weiss and Heckers 1999; Woodruff 2004). These findings may be closely associated with the phenomenological or emotional experience of AVH in these patients.

However, these activity changes may constitute the tip of the iceberg of functional brain dynamics that give rise to hallucinations. The human brain's rate of energy consumption far exceeds the metabolic demands that would be required for processing task-based performance. A large proportion of the brain's metabolism appears to be spent on moments when it is idle or resting, when it is not involved in processing particular sensory or cognitive states (Raichle and Mintun 2006). Recent advances in brain imaging have introduced novel experimental paradigms that aim to investigate the brain's intrinsic dynamics, which could be associated with self-referential or inner reflections that are unperturbed by intervening events (M. D. Fox and Raichle 2007; Gusnard and Raichle 2001). These paradigms have received a rapidly growing amount of attention from various brain imaging disciplines in a relatively short time (see Figure 1). Findings from these studies indicate that the brain's intrinsic dynamics comprises a rich and complex functional architecture, which may influence current and future, goal-directed processing. These findings provide the starting point for the compelling suggestion that the brain areas that are involved in the experience of AVH are not silent when the voices are silent, and that intrinsic brain dynamics in schizophrenia contribute to the experience of hallucinated voices. Moreover, it could be possible that the pathophysiological mechanism in schizophrenia alters intrinsic brain dynamics, which in turn leads to hallucinatory perceptions.

This chapter considers the novel paradigms in studying the intrinsic brain states that may be relevant for AVH in schizophrenia. The chapter starts with an introduction to the measurement of intrinsic brain states and why the observation of these brain states may be generally relevant in understanding brain function. This section also describes the somewhat different analytical and theoretical approaches that are used in the measurement of intrinsic brain states, compared to the more commonly used approaches in task-related studies. The second part of the chapter describes the 'default-mode network' (Gusnard and Raichle 2001; Raichle et al. 2001). This network has received particular interest because it shows decreased activity when the brain is engaged in task performance, compared to resting baseline. Thus, this network appears to support cognitive functions that are relevant when the brain is at rest, and may possibly be engaged with self-referential processing. The third part of the chapter discusses how disrupted intrinsic brain states could give rise to AVH in schizophrenia. The evidence that is available so far suggests that AVH may be associated with impairments in intrinsic brain states of particular networks, including the default-mode and auditory processing networks. The fourth and final part of the chapter briefly discusses outstanding issues and controversies that need to be resolved before we can learn how AVH arise from the ever-active brain. The field of intrinsic brain measurements in mental disorders is rapidly expanding and many of these issues will be addressed in the near future, and will indicate if intrinsic brain states have a clinical as well as fundamental relevance in understanding the pathophysiological mechanism of AVH and other symptoms in schizophrenia.

Measuring the resting brain

Most functional brain imaging studies measure brain activity while participants perform a task or perceive a stimulus, and the observed changes in activity are interpreted in the context of the parameters of the task or stimulus. Task performance commonly induces changes in brain activity up to 5% from a resting baseline that is typically considered to reflect random fluctuations unrelated to information processing (Boynton et al. 1996; Ogawa et al. 1992; Raichle and Mintun 2006). However, the resting brain poses a metabolic demand of up to 20% of the total body's energy consumption, which stands in stark contrast to the brain's

relative weight of 2% of the whole body (Raichle and Mintun 2006). Assuming that the brain does not waste energy, it appears that the bulk of the brain's processing is spent not at times when it is occupied with task-related performance, but at times when the brain appears at rest. Recent findings indeed suggest that behaviorally relevant processing occurs during 'resting' states, with the quotation marks indicating that during resting baseline measurements the brain is not actually at rest. Moreover, measurement of idle brain states indeed may shed light on the intrinsic workings of the brain, and how these brain states can influence consecutive task performance. Thus, changes in brain activity observed during the experience of hallucinations may constitute the tip of the iceberg of disrupted brain activity that is nevertheless manifested even during times when the voices are silent. Such altered intrinsic brain activity may become trait markers of mental disorders, in which brain activity remains abnormal during symptom-free intervals, possibly comparable to interictal spikes in the encephalogram recordings of epileptic patients.

Observing the resting brain with functional magnetic resonance imaging (fMRI) – the main contemporary technique in studying intrinsic brain states – requires the use of some theoretical and analytical concepts that are different from those commonly used in task-related fMRI studies. Most apparent is the fact that in task-free measurements brain activity cannot be explained in terms of task parameters. An immediate consequence is that functionally relevant brain areas cannot be localized in terms of task-related changes in signal amplitudes, i.e., changes in the brain's *activation* levels. Not controlled by imposed task parameters, brain activity is left free to fluctuate in an apparently spontaneous manner that, on eyeballing, appears devoid of meaningful temporal information (see Figure 2). Instead, brain activity during idle states is investigated in terms of *functional connectivity*, the spatial distribution of synchronously co-activated brain areas (K.J. Friston 1996; K.J. Friston et al. 1993; Rogers et al. 2007). In other words, intrinsic functional brain states are described in terms of the organization of brain networks of synchronously activated, functionally specialized brain areas (see Figure 3). A number of different analytical techniques are now commonly used in analyzing intrinsic brain states, including univariate methods, such as seed-correlation (B. Biswal et al. 1995; M.D. Fox et al. 2005; Xiong et al. 1999), and multivariate methods, such as principal component analysis (PCA) (K.J. Friston 1996), independent component analysis (ICA) (Damoiseaux et al. 2006; M.J. McKeown et al. 1998; van de Ven et al. 2004) or cluster analysis (CA) (Cordes et al. 2002; Mezer et al.

2009). While possibly different in their workings, these methods are based on some formalization of co-activation between brain areas (with the notable exception of ICA, in which functional connectivity is not explicitly formalized but inferred). Excellent reviews about these methods and their applications to resting state data and other paradigms of functional brain imaging are available elsewhere (Calhoun et al. 2009; M. J. McKeown et al. 2003; Rogers et al. 2007).

A pioneer in measuring intrinsic brain states, Bahrat Biswal and colleagues showed that the resting brain contained a high degree of spatiotemporal organization, in which a motor network could be distinguished that was remarkably similar to the spatial distribution of brain activity observed motor tasks (B. Biswal et al. 1995), and included cortical as well as subcortical brain structures. Biswal's group, as well as other research groups, showed that the signal fluctuations of resting state networks were driven largely by oscillations at very low frequencies below 0.1 Hz, i.e., signal fluctuations with periods of 10 seconds or longer (B. Biswal et al. 1995; B. B. Biswal et al. 1997; Cordes et al. 2001; van de Ven et al. 2004; Xiong et al. 1999). These fluctuations could be further distinguished from signal oscillations associated with non-neurophysiological events, such as heart or respiratory rate, head movements of the participant, and artifacts induced by the scanner (Cordes et al. 2001; Xiong et al. 1999) (Figure 3). Over the past decade, many studies have reported intrinsic functional organization in brain networks of motor (B. Biswal et al. 1995; Cordes et al. 2000; Xiong et al. 1999) and sensory (Cordes et al. 2001; Cordes et al. 2000; van de Ven et al. 2004; van den Heuvel et al. 2008) domains, as well as lateralized fronto-parietal networks (Damoiseaux et al. 2006; M.D. Fox et al. 2005; van de Ven et al. 2004; van den Heuvel et al. 2008), a bilateral fronto-temporal network that has been associated with language processing (Hampson et al. 2002), at least one network revolving around insular cortex (Damoiseaux et al. 2006), and a network of medial frontal and parietal cortex, which has been termed the 'default mode' network, or DMN (Damoiseaux et al. 2006; Fransson 2005; Greicius et al. 2003a; Raichle et al. 2001; van de Ven et al. 2004; van den Heuvel et al. 2008) (Figure 3). Especially the DMN has received increasing attention from various neuroimaging disciplines because it may be relevant for understanding pathological mechanisms in clinical disorders. The DMN will be discussed in more detail later in this chapter.

Although its exact source is still unknown, there are a number of proposals to link the spontaneously fluctuating signals in resting state fMRI to known neurophysiological effects. Spontaneous firing rates of neural cells contribute to the formation of synaptic connections and neural systems during brain development, and interruption of spontaneous activity can impair development of neural systems (Chang et al. 2005; Shatz 1996; Zhang and Poo 2001). Also, recent neurophysiological studies have further extended on the role of spontaneous cell firing in preparing for or anticipating functionally relevant states of processing. For example, within cat visual system, primary visual cortex shows oscillating patterns of distributed activity in the absence of visual stimulation, which follow the columnar organization of orientation specificity in primary visual cortex (Kenet et al. 2003). These spontaneously occurring states are very similar to patterns of distributed activity when the cat views visual stimuli at particular orientations. Further, spontaneous firing may synchronize activity across long-range cortical distances, which may lead to functional coupling of different functional systems (Fries et al. 2001). Spontaneous activity may also play an important role in memory consolidation well after training of the stimuli or behavior (Buzsaki et al. 1990; K. L. Hoffman and McNaughton 2002; Wilson and McNaughton 1994). This latter finding has recently been shown in human fMRI studies, in which intrinsic brain states were associated with memory performance at a later time (Hampson et al. 2006; Lewis et al. 2009; Tambini et al. 2010; Vincent et al. 2006). One fMRI study measured brain activity during a resting period after an episodic memory task that involved the learning of pictures of faces or scenes (Tambini et al. 2010). During the period of rest after the memory task, hippocampal regions showed a strong coupling with extrastriate visual cortex that was behaviorally relevant during the memory task. This coupling was less strong between the hippocampus and extrastriate cortex that was not relevant for the memory task, and was absent in a resting period before participants started with the memory task. In another fMRI study of working memory, Hampson et al. (Hampson et al. 2006) showed that the degree of intrinsic brain connectivity between medial frontal and parietal regions correlated with performance on a working memory task. These and other findings illustrate that intrinsic brain states may be behaviorally relevant for information processing during and beyond moments of task performance.

A default-mode of brain processing

In the resting state literature, the DMN has reached a status of particular interest (see blue line of Figure 1). The identification of the DMN resulted from repeated observations in task-related studies that particular medial frontal and parietal brain areas showed decreased activity during task performance (Shulman et al. 1997), which suggested that brain activity in these areas was higher during resting baseline. In a landmark study, Raichle and colleagues synthesized these findings and demonstrated that metabolic rate in these medial brain areas indeed increased during resting or idle states, and decreased when participants engaged in task performance (Gusnard and Raichle 2001; Raichle et al. 2001). The investigators coined the term 'default-mode' to indicate the hypothesis that this network of brain areas subserved some intrinsic and ongoing function that was temporarily halted when attending (i.e., reallocating brain resources to) some new task at hand. This report sparked a surge of brain imaging studies to map the DMN, which has produced a strong consensus that the network includes anterior and posterior parts of the cingulate cortex, precuneus and lateral inferior parietal regions, as well as hippocampal structures (Damoiseaux et al. 2006; Fransson 2005; Greicius et al. 2003b; van de Ven et al. 2004; van den Heuvel et al. 2008) (Figure 3). Importantly, the DMN can be found in task-related imaging data (Esposito et al. 2009; Greicius et al. 2003b; McKiernan et al. 2003; van de Ven et al. 2009), as well as in task-free conditions (Damoiseaux et al. 2006; M.D. Fox et al. 2005; Fransson 2005).

An accurate description of the DMN's cognitive functions is lacking, but there is growing evidence that the DMN is particularly associated with self-referential processing (Beer 2007; Gusnard et al. 2001; Jardri et al. 2007; Mason et al. 2007; Ochsner et al. 2004; Schilbach et al. 2008; Vogeley et al. 1999) and memory functions (Esposito et al. 2009; McKiernan et al. 2003; Spreng et al. 2009; Vincent et al. 2006). For example, activity of the DMN may be associated with processing of self awareness of self-initiated actions, such as speaking. Online speech production, but not passive listening to pre-recorded speech, decreased DMN activity in healthy participants (Binder et al. 1997; Jardri et al. 2007; van de Ven et al. 2009), regardless of whether speech production was covert (Binder et al. 1997; Jardri et al. 2007) or overt (van de Ven et al. 2009). Also, DMN deactivations may be associated with memory load or task difficulty, in which the

magnitude of deactivation may increase with increasing memory loads (Esposito et al. 2009; Mayer et al. 2010; McKiernan et al. 2003; van de Ven et al. 2008). However, rather than being a singular functional entity, the DMN appears to incorporate functionally distinct subparts of anterior and posterior network nodes that respectively contribute to self-referential and memory functions.

The anterior subpart includes ventral medial prefrontal cortex (MPFC), which has been associated with affective processing (Amodio and Frith 2006; Gusnard et al. 2001; Schilbach et al. 2008). Importantly, the ventral MPFC is distinguished from the dorsal MPFC, which is not commonly found within the DMN, and which has been associated with cognitive and action performance monitoring (Botvinick et al. 2004; Ridderinkhof et al. 2004; Steele and Lawrie 2004). In a classic study of DMN functionality, Gusnard et al. (Gusnard et al. 2001) reported that self-referential judgments decreased brain activity in the ventral MPFC, compared to a resting baseline, whereas attention-demanding processing increased activity in dorsal MPFC. Other studies have found decreased brain activity of ventral MPFC, compared to rest, during assessment of one's own mood state (Harrison et al. 2008), perspective-taking and self-other judgments (Beer 2007; Lindner et al. 2008; Ochsner et al. 2004; Vogeley et al. 1999), and assessment of agency in self-generated actions (David et al. 2006).

At the same time, the posterior part of the DMN, including posterior cingulate cortex (PCC), precuneus and hippocampal regions may be associated with semantic and memory functions (Binder et al. 1999; Esposito et al. 2009; Hampson et al. 2006; McKiernan et al. 2003; Spreng et al. 2009; Vincent et al. 2006). Functional coupling between ventral MPFC and PCC was found to correlate with performance on a working memory task (Hampson et al. 2006). Hippocampal and posterior parietal regions of the DMN showed strong functional connectivity in a resting state dataset, but also showed increased activity for successful recollection memory trials in a number of recognition memory tasks (Vincent et al. 2006). A recent meta-analysis showed that many posterior DMN regions were associated with autobiographical memory tasks (Spreng et al. 2009).

Finally, the posterior lateral parts of the DMN, including inferior parietal regions and posterior parts of the middle temporal gyrus, have been associated with processing of agency (Farrer et al. 2003; Farrer and Frith

2002; Ruby and Decety 2001). Farrer and Frith (Farrer and Frith 2002) had participants move a dot on a screen using a joystick. At some point, participants had to move the joystick in one of two ways and the dot would either move in correspondence to the joystick move (self-control) or not (alien control). The authors found increased activity of inferior parietal cortex when participants were aware that they were not in control of the perceived movement, but someone else was (alien control).

In general, DMN may be relevant for generating, monitoring and updating self-referential images, which is possibly based on affective and autobiographical knowledge. These functions constitute an ongoing process in which the internal and external world is monitored for information that may be particularly self-relevant (Gusnard and Raichle 2001). When stimuli are encountered that require a high degree of attention, the ongoing processes are momentarily halted in order to reallocate processing resources in favour of the new stimuli. This notion is further supported by reports suggesting that engaging in more internal or self-referential processing, such as 'day-dreaming' or 'mind-wandering' may *increase* DMN activity (Mason et al. 2007).

The putative functions of the DMN appear very relevant to the generation of psychotic hallucinations because AVH are thought to be associated with impaired monitoring or attribution of agency. However, it is unlikely that one particular region or network node of the DMN is impaired (i.e., as in a lesion or localized damage of a functionally specialized brain area). Instead, AVH may be the result of a disrupted communication between multiple nodes of the DMN, and possibly with auditory or speech-related brain areas, as will be discussed in the next section.

A 'default state' of hallucinations: Disrupted intrinsic connectivity as a pathological mechanism?

From early times since Bleuler introduced the concept of 'fragmented mind' coined the term 'schizophrenia' (Bleuler 1911), different neuropsychological theories have suggested that AVH result from biases in auditory or speech perception (Bentall 1990; Stephane et al. 2001b), aberrant or uncontrolled auditory mental imagery (Bentall 1990; Mintz and Alpert 1972; Seal et al. 2004), and a failure in correctly

monitoring internally generated speech events (Frith 2005). Central to many of these theories is the notion that AVH result from impaired or otherwise altered communication between sensory, motor or cognitive modules. Recently, this concept has been re-introduced and phrased in terms of aberrant brain connectivity, or dysconnectivity, which leads to impaired integration of functionally specialized brain areas and an imbalanced brain architecture in which information processing is distorted (Andreasen 1999; K. J. Friston 1998; Stephan et al. 2009). The prefix *dys-* in dysconnectivity, rather than *dis-*, indicates that disrupted communication between brain areas could result from decreased as well as increased brain connectivity. This hypothesis has recently received empirical support from a growing number of clinical neuroimaging studies. Impaired working memory performance, which has been suggested to be a core pathological factor or endophenotype of schizophrenia (Braff et al. 2007; Gottesman and Gould 2003), may be the result of decreased functional connectivity of prefrontal cortex in schizophrenia, compared to healthy controls (A. Meyer-Lindenberg et al. 2001; A. S. Meyer-Lindenberg et al. 2005). Another study reported aberrant functional connectivity of auditory cortex, which appeared to be independent of performance on an auditory oddball task (Calhoun et al. 2004). However, the implication of this finding for symptoms and impairments in schizophrenia are unclear. Complementary results have recently been found in the *intrinsic* functional organization of patients, showing widespread decreases in functional connectivity (Bluhm et al. 2007; Liang et al. 2006; Y. Liu et al. 2008; Rotarska-Jagiela et al. 2010; Zhou et al. 2007). Impairments of functional connectivity may furthermore be associated with widespread decreases of anatomical connectivity (Hubl et al. 2004; Kubicki et al. 2007; Kubicki et al. 2005; Rotarska-Jagiela et al. 2009; Shergill et al. 2007). Interestingly, a few studies observed that severity of AVH correlated with increased anatomical connectivity of pathways that connected language perception and production areas (Hubl et al. 2004; Rotarska-Jagiela et al. 2009; Shergill et al. 2007), illustrating that brain organization in schizophrenia may be different, rather than only impaired. With respect to psychotic symptoms, the predisposition to hallucinate may be associated with impaired functional connectivity between frontal and temporal brain areas (Lawrie et al. 2002), which appears in line with the suggestion that AVH arise from impaired monitoring or misattribution of internally generated speech events, which in the healthy brain entails the communication between motor planning, performance monitoring and speech perception areas

(Frith 2005). The following sections describe the contribution of intrinsic brain states to AVH in schizophrenia, and their possible associations with available empirical results and contemporary neuropsychological theories of AVH in schizophrenia.

Impairments in DMN connectivity may play a role in the pathological mechanism of schizophrenia. One report suggested that differences in global integrity of the DMN might aid in classification of schizophrenia patients from healthy controls and bipolar disorder patients (Calhoun et al. 2008). However, schizophrenia may be associated with impaired connectivity of particular nodes within the DMN (see Figure 4).

Schizophrenia patients have shown decreased PCC connectivity with other parts of the DMN, compared to healthy controls (Bluhm et al. 2007; Garrity et al. 2007; Rotarska-Jagiela et al. 2010). Interestingly, this effect was found while participants performed a task (Garrity et al. 2007), as well as during task-free measurements (Bluhm et al. 2007; Rotarska-Jagiela et al. 2010), suggesting that the result is a general or task-independent feature of the disorder. However, other studies reported increased DMN connectivity in schizophrenia (Whitfield-Gabrieli et al. 2009; Zhou et al. 2007), or no difference in DMN connectivity between diagnostic groups (Repovs et al. in press), which illustrates that the nature of aberrant DMN connectivity in schizophrenia remains to be resolved. Nonetheless, disrupted PCC connectivity could play an important role in the putatively impaired functional integration in the brain. Anatomical connectivity studies in healthy participants showed that the PCC could be a central node or hub within the DMN, to which many brain areas connect to and share information with (Greicius et al. 2009; Hagmann et al. 2008). An impairment of the functional architecture at the level of the PCC could then lead to a widespread impairment of communication – within the DMN as well as between different networks, which could result in a wide array of different symptoms and impairments of cognitive functioning.

Further, one study reported that reduced functional connectivity between hippocampal regions and the DMN correlated with increased severity of hallucinations (Rotarska-Jagiela et al. 2010) (Figure 5). This finding fits to previous reports of a contribution of the hippocampus to the experience of psychotic symptoms (Kang et al. 2009; Weiss and Heckers 1999; Weiss et al. 2004). For example, Weiss et al. (Weiss et al. 2004) reported that impaired connectivity of the hippocampus could be associated with impaired

source monitoring in hallucinating schizophrenia patients. Kang et al. (Kang et al. 2009) demonstrated aberrant task-related hippocampal activity in relation to psychotic symptoms. In addition, symptom mapping studies in hallucinating schizophrenia patients showed increased hippocampal activity during auditory (Dierks et al. 1999; Shergill et al. 2000) as well as visual hallucinations (Oertel et al. 2007).

Finally, intrinsic functional connectivity of lateral inferior parietal regions within the DMN may be decreased in hallucinating patients (Rotarska-Jagiela et al. 2010; Vercammen et al. 2010). Inferior parietal cortex has been associated with perspective-taking and processing of agency of observed actions (Farrer et al. 2003; Farrer and Frith 2002; Ruby and Decety 2001), the functions of which are commonly associated with hallucinations and delusions in schizophrenia.

These findings suggest that in schizophrenia the DMN may show an aberrant functional architecture, which may contribute to misinterpretations of agency or impairments of memory. Misinterpretations of agency of internally generated auditory images or speech could in turn lead to AVH, which suggests that AVH may result from impaired integration of agency processing of the DMN and auditory or speech processing systems (Wible et al. 2009). Direct evidence for the involvement of the auditory system in AVH comes from symptom mapping studies, which have reliably shown increased activity in auditory perception areas during the experience of auditory hallucinations (Dierks et al. 1999; Lennox et al. 2000; Shergill et al. 2000; van de Ven et al. 2005). Further, AVH has been associated with impaired acoustic processing in a bottom-up fashion, leading to impaired or 'noisy' auditory perception (Bentall and Slade 1985; McKay et al. 2000). These psychophysical findings may have a neural correlate in auditory cortex. At the same time, a number of theories have proposed that the auditory perception system could be involved in a top-down manner, in which AVH results from impaired generation or monitoring of auditory imagery (Bentall 1990; Frith 2005; P. K. McGuire et al. 1995).

There is growing evidence that intrinsic activity of the auditory system may be involved in AVH (Figure 6). Hunter et al. (Hunter et al. 2006) used a resting state measurement to study the intrinsic activity in auditory cortex of healthy participants, and reported that intrinsic activity could spontaneously synchronize within primary and secondary auditory cortex, with signal fluctuations that were similar or larger than those

observed during the processing of acoustic material. This finding showed that it may be possible that the auditory system spontaneously generated auditory perceptions in the absence of acoustic stimulation, which could lead to AVH in pathological cases. Recent clinical neuroimaging studies investigated this notion and measured intrinsic activity in healthy controls and hallucinating schizophrenia patients (Gavrilescu et al. 2010; Rotarska-Jagiela et al. 2010). These studies found contrasting results. One study showed that functional connectivity between left and right auditory cortex decreased with increasing severity of hallucinations (Gavrilescu et al. 2010), which fits with the suggestion that the auditory cortex may be involved in AVH in a bottom-up manner. Evidence for a top-down involvement of auditory cortex in AVH comes from the other study, which reported increased connectivity between bilateral auditory cortex and (pre-)supplementary motor area (SMA) (Rotarska-Jagiela et al. 2010). SMA may be involved in monitoring of speech, in which the area may supply a copy of motor commands during speech intentions or actions to sensory areas and thereby decreases activity in sensory areas in response to perceived speech feedback (Ford et al. 2001; Ford et al. 2010; P.K. McGuire et al. 1996; Paus et al. 1996; van de Ven et al. 2009). In this sense, abnormal functional connectivity between SMA and auditory areas could result in increased activity of superior temporal areas, which may lead to misinterpreted intentions or speech percepts that are experienced as hallucinatory perceptions (Ford et al. 2001; Frith 2005).

A final point in the investigation of the intrinsic neural correlates of AVH can be made about the low-frequency oscillations that appear so characteristic of resting state networks. Intrinsic low-frequency oscillations of the DMN appear to be associated with the severity of hallucinations, but the limited results on this issue are contradictory. Garrity et al. (Garrity et al. 2007) found that the amplitude of low-frequency oscillations of the DMN decreased with hallucination severity, whereas Rotarska Jagiela et al. (Rotarska-Jagiela et al. 2010) reported increased DMN amplitude with increasing hallucination severity. An important difference between the two studies is that the first presented an auditory task to the study's participants, whereas the second measured brain activity in the absence of a task. Low frequency amplitude of the auditory network may also be increased with increasing AVH severity (Rotarska-Jagiela et al. 2010). Finally, Hoptman et al. (Hoptman et al. 2010) reported increased amplitude of low-frequency oscillations in DMN regions and decreased amplitude in occipital and temporal regions, but these differences did not correlate

with positive symptoms. The associations between symptoms and very-low frequency oscillations of DMN and AC largely confirmed those between clinical parameters and functional connectivity. It has been proposed that spontaneous activity may be associated with continuous information processing and consolidation of the integrated network (Achard and Bullmore 2007; Achard et al. 2006; Buzsaki and Draguhn 2004; Uhlhaas and Singer 2006), and that aberrant oscillations may lead to cognitive impairments and symptoms in mental disorders (Achard et al. 2006; Uhlhaas and Singer 2006). If AVH result from impaired communication between brain areas, aberrant oscillations may be an indicator of how a network's malfunctioning influences the severity of psychotic symptoms. This notion appears in line with electroencephalography (EEG) studies that showed altered intrinsic coherence in schizophrenia patients (Higashima et al. 2007). Replication and further extension of these results will be required to further understand how temporal network dynamics are associated with symptoms in schizophrenia.

Outstanding issues

This chapter has described novel paradigms for measuring the intrinsic functional organization of the human brain, and has summarized the preliminary but rapidly developing insights that intrinsic brain measurements may give about how hallucinations arise in the brain. The first, pioneering results appear to coincide with the suggestion that AVH result from an impaired processing of agency of speech-related images or intentions. These impairments likely rest within or arise from a disrupted functional architecture, in which the communication between specialized brain areas is impaired. Aberrant brain activity during the online experience of hallucinations may form the observable consequences of a more profound pathology of intrinsic, ongoing brain functioning, which may not only give rise of hallucinations but to many other symptoms and cognitive impairments. In this sense, aberrant intrinsic organization could be an important endophenotype of schizophrenia (Braff et al. 2007; Gottesman and Gould 2003) that could possibly be used as a biological marker in patients as well as at-risk populations. In turn, treatment or coping efforts to alleviate AVH severity or frequency could perhaps target particular facets of the intrinsic functional architecture in schizophrenia. One promising example of such an approach is treatment of psychotic

hallucinations using brain stimulation protocols delivered to the brain at periods outside of psychotic episodes. In one such treatment, repetitive transcranial magnetic stimulation (rTMS) is used to deliver a train of magnetic pulses at a particular frequency to target cortical areas over the course of several days or weeks. RTMS alters cortical excitability of targeted areas – or even networks of brain areas – for an extended period of time (Pascual-Leone et al. 2000), which in turn may alter brain states and could lead to improvement from AVH. Indeed, a growing number of studies has shown decreased hallucination severity or frequency after delivery of rTMS over auditory or speech perception areas, in which the therapeutic effect lasted for several weeks post-treatment (Aleman et al. 2007; R. E. Hoffman et al. 2007; R. E. Hoffman et al. 2003). These results suggest that understanding the intrinsic brain dynamics may be clinically relevant in studying and treating AVH in schizophrenia.

New advances in studying the default states of hallucinations aim to assess the genetic basis of the aberrant intrinsic architecture, which can be investigated by measuring populations that are genetically at risk to develop schizophrenia, such as non-clinical siblings or other relatives of patients (H. Liu et al. 2011; Whitfield-Gabrieli et al. 2009). Also, it will be increasingly important to map aberrant functional architectures onto anatomical substrates, and to investigate how structure and function influence each other during the critical neurodevelopmental epochs in which prominent dysfunctions in schizophrenia arise. These and other issues will be the target of studies of intrinsic brain states in schizophrenia in the near future, and may provide insight into pathophysiological mechanisms hidden within the brain, but that can culminate into the bizarre and distressing experience of hearing voices of people who are not there.

Figures

Figure 1. Scientific interest in resting state and default mode connectivity. The graph shows the increase in number of functional brain imaging studies of resting state and default mode network since the paper by Biswal and colleagues in 1995 (red diamonds). The default mode network was introduced in 2001, and has since drawn much interest from various brain imaging fields (blue circles). The investigation of resting state and default mode connectivity in schizophrenia has only recently begun (black squares). Results were obtained from queries in PubMed, using the keywords “default-mode network”, “fMRI”, “resting state” and “schizophrenia”.

Figure 2. Brain activity during a task and rest. Shown are brain activations for bilateral auditory cortex (in blue) during task performance (Christoffels et al. 2007; van de Ven et al. 2009) and during rest (Rotarska-Jagiela et al. 2010). The images show that the cortical regions respond systematically to task sequences, but show no apparent pattern of activity during rest.

Figure 3. Intrinsic functional connectivity of 'default-mode' network. In the most straightforward functional connectivity analysis of resting state data, a time series is sampled from a seed region, in this example left PCC. The seed time series is then correlated with all other resting state time series. The correlation can be further corrected for nuisance variables, such as fMRI signal from ventricles and white matter, and head movement parameters. The result is a spatial distribution of time series correlated with the seed, which can be interpreted as a functional network of brain areas with synchronous activity during rest.

Figure 4. Resting state functional networks. Shown are six networks obtained from resting state data. These networks have proved reliable across multiple studies and participants (Cordes et al. 2000; Damoiseaux et al. 2006; Fransson 2005; Hampson et al. 2002; van de Ven et al. 2004).

Figure 5. Default-mode network intrinsic impairments in AVH in schizophrenia. A: Functional connectivity of PCC with other DMN networks is decreased in schizophrenia patients, compared to controls. B: Decreased functional connectivity in lateral parietal cortex and hippocampus is negatively correlated with severity of hallucinations. C: Contribution of low frequencies to the DMN time series correlated positively with severity of positive symptoms, including AVH. Results reproduced, with permission, from Rotarska Jagiela et al. (Rotarska-Jagiela et al. 2010).

Figure 6. Auditory cortex intrinsic impairments in AVH in schizophrenia. A: Functional connectivity between left and right auditory cortex is decreased in hallucinating patients (right panel), compared to non-hallucinating patients (middle panel) and healthy controls (left panel) (Gavrilescu et al. 2010) (Reproduced with permission). B: Increased functional connectivity between SMA and auditory cortex correlates with hallucination severity (Rotarska-Jagiela et al. 2010) (Reproduced with permission). C: In healthy participants, monitoring of self-produced overt speech requires the functional coupling of SMA and auditory cortex, in which auditory cortex activity is suppressed during self-produced speech (van de Ven et al. 2009) (Reproduced with permission).

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