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Voor mijn ouders

CONTENTS

Science may be described as the art of systematic over-simplification.

Karl Popper

Chapter 1

General introduction

During the night, when attuned to our domestic surroundings, we might be convinced that our cat is meowing in the garden or our child is mumbling across the hallway, whereas only moments later we might wonder whether we have been imagining these things.

A combination of both our outside world and our internal expectations generate our subjective experience. While, initially, it may seem puzzling that an internally derived brain process can be experienced as a voice from the outside world, there are convincing reasons it is remarkable that we so often experience a strict division between our internal and external world. Perceptions are constructions. The senses provide input and, while we make representations of our outside world, the information is associated with our internal world, categorized, tested for similarity with the external stimulus, and reprocessed backwards and forwards. If perception occurs with constant reciprocal communication between the mind and environmental factors, then it is not surprising that mix-ups about the origin of our experiences seem inevitable; evolution may not be able to fix that. From an evolutionary perspective, the goal of perception should be to build-up an experience of the environment that effectively detects threats and rewards and thereby guides our behavior [1].

A close-to-the-truth experience is important, but is not necessarily the essence. Internal representations of possible danger are waiting and willing to occupy our attention. Being prone towards quickly recognizing (for example) a brown bear might be more effective than a detailed perception of the leaves behind which brown eyes are lurking. A perception close-to-the-truth is in competition with the speed and low-energy consumption needed for survival [2]. As Hoffman states: "*Take your perceptions seriously. But this does not logically require that you take them to be literally true.*" [1] Our perception of the world might not be as objective as one might experience in daily life and, in line with this, the perceived origin of our experiences might not always be robust.

This thesis aims to provide insight into the neural correlates underlying verbal auditory hallucinations (VAH), with an emphasis on VAH having a broad context of interacting factors that lead to the conscious experience by the patient. The following sections provide a theoretical background to the research questions by discussing 1) verbal auditory hallucinations, 2) brain function using functional MRI, and 3) the opportunities offered by network science.

1.   VERBAL AUDITORY HALLUCINATIONS

VAH have been reported throughout the ages. For example, Socrates allegedly heard a voice warning him about imminent mistakes, and it has been argued that Homerus was inspired by voices [3]. Freud writes that he heard his name repeatedly called out while

'staying in a strange city' [4]. Gandhi describes recurring interventions by a voice when he was experiencing an internal struggle. In fact, there are numerous accounts about 'the voice of God speaking' with (probably, most famously) Saint Joan of Arc joining the army and battling against the English inspired by a 'godly' voice. It might be said that the hearing of voices is embedded in our culture. However, this thesis does not deal with metaphysical sources of VAH, but focuses on underlying brain functions. Starting from the 19th century, the concept of hallucination was introduced as a generic category by pioneers of French psychiatry (most notably by Jean-Etienne Esquirol) [5]. Subsequently, there has been a medicalization of psychotic experiences and behavior, and alongside VAH, they have increasingly been depicted as aberrant and as a sign of disturbed brain function [5]. Esquirol wrote that the person who suffers from hallucinations has a '*profound conviction of having perceived a sensation, when in reality no external object entered through the senses*' [6]. In the most comprehensive definition of hallucinations to date, David defined a hallucination as 'a *sensory experience which occurs in the absence of corresponding external stimulation of the relevant sensory organ, has a sufficient sense of reality to resemble a veridical perception, over which the subject does not feel s/he has direct and voluntary control, and which occurs in the awake state*' [7]. In VAH a person experiences sound, representing language, which has no origin in external space. This contrasts with distorted experiences that do have a discernible origin in external space, which are commonly termed illusions (e.g. hearing a voice in the white noise of your radio). Another typical characteristic of VAH is that the person experiences limited control over their presentation, often adding to a debilitating impact. A few decades ago, hearing voices was regarded as being strongly indicative of a diagnosis of schizophrenia [8] and, to some extent, it still is [9]. However, a relatively large range of conditions frequently display VAH and they are present in about one in ten of the general population [10].

1.1 Prevalence and characteristics

VAH are symptoms frequently found in schizophrenia, major depressive disorder, bipolar disorder, borderline personality disorder, schizotypal personality disorder, dissociative identity disorder and post-traumatic stress disorder, although VAH can occur in the context of any psychiatric disorder [11]. Additionally, hallucinations occur regularly in a wide range of neurological conditions.

1.1.1 Schizophrenia

According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) classification, besides delusions and disorganized speech, the frequent and persisting presence of hallucinations is one of the main symptoms that indicate schizophrenia. Among the different psychiatric disorders, the prevalence of VAH is highest in patients

diagnosed with schizophrenia; there is reasonable consensus on this, with a reported prevalence ranging from 60 % to 75 % [12-14]. In patients with schizophrenia, most auditory hallucinations have a verbal content and are experienced in the second or third person. They can be heard ranging from an unclear whisper or mumble up to a well-defined shouting voice, but are often relatively short messages. There is no clear manifestation with respect to their origin (self or external) and localization (inside or outside the head). In schizophrenia, the most unifying characteristics of VAH are their derogatory content and the very limited control over their occurrence [15, 16]. The voices 'come and go' and it is difficult to alter the experience by will, often making VAH intrusive and overpowering.

1.1.2 Mood disorders

For affective disorders the prevalence is best understood per disease episode, with VAH mostly occurring in the acute phase. Baethge et al. studied the prevalence of hallucinations on admission to hospital and reported that 55 % of the bipolar patients with a mixed or manic episode were having VAH [17]. In bipolar depression 59 % of the patients heard voices, and in unipolar depression 40 % experienced VAH. Generally, in mood disorders, VAH are less severe than in schizophrenia [17, 18]. One study provided a detailed comparison of VAH characteristics between schizophrenia patients and patients with affective disorders [19]. The authors found that VAH were less frequent and briefer, more often localized in the head, and had a less emotionally negative content. However, the VAH were experienced as more distressing by patients with affective disorders than by patients with schizophrenia. Lastly, mood congruence of psychotic symptoms is proposed to be indicative for a diagnosis of an affective disorder, rather than of schizophrenia; however, the evidence for this is somewhat limited [20, 21].

1.1.3 Trauma-related disorders

It has been argued that voices are a dissociative phenomenon related to childhood trauma and occur in the context of post-traumatic stress disorder, dissociative disorder as well as psychotic disorders [22]. This stimulated research to establish whether there are differences in the VAH between these trauma-related disorders, psychotic disorders and the general population. Honig et al. found that VAH in patients with dissociative disorders had more negative content and were more frequent and intrusive than in the general population [15]. The authors also stressed the similarity in characteristics between VAH in schizophrenia and dissociative disorders and that, in both these groups, VAH could (retrospectively) be linked to a start after childhood trauma, or an experience that led to reactivation of trauma. A study by Dorahiy et al. focused on the characteristics of VAH in dissociative disorders and included patients suffering from schizophrenia with and without childhood trauma [24]. The authors found that, in

dissociative disorders, VAH more often started before age 18 years (90 %), that they consisted of both adult and children's voices, and often issued commands.

1.1.4 Personality disorders

Prevalence rates of VAH are reported to range from 21 % to 50 %, with a larger prevalence for hallucinations in general [25-27]. In a study by Slotema et al., no differences were found in the phenomenological characteristics of VAH and the distress they caused between schizophrenia and borderline personality disorder, except for the increased experience of disruption of life in individuals with borderline personality disorder [28]. Niemantsverdriet et al. reported that the presence of hallucinations is related to both childhood trauma and comorbid post-traumatic stress disorder [26]. For schizotypal personality disorder, it is important that the diagnosis is increasingly recognized to appear in a continuum between the general population and schizophrenia, and that differences in the symptoms are quantitative, and not qualitative [29, 30].

1.1.5 Neurological disorders

The occurrence of hallucinations in neurological disorders is referred to as 'organic psychosis'. Generally speaking, visual hallucinations are more prominent. VAH have been described in neurodegenerative dementias and epilepsy, but are also reported in relation to (among others) migraine, stroke and brain tumors. In epilepsy, individuals with a low age of onset are more prone to hallucinations; also, an association has been found with temporal lobe epilepsy, with prevalence rates up to 14 % [31]. Auditory hallucinations can occur both during a seizure and interictal; however, interictal auditory hallucinations are more often with verbal content in contrast with the fragmented sounds of ictal auditory hallucinations. Inzelberg et al. studied VAH in Parkinson's disease and found VAH to exclusively occur in persons also reporting visual hallucinations [32]; in their sample, of the 37 % reporting visual hallucinations in Parkinson's disease, 29 % also had auditory hallucinations. In contrast to psychiatric disorders, the content of VAH was incomprehensible in 50 % and had no affective component [32]. In Alzheimer's disease, there is a prevalence of 4 % to 76 % of hallucinations and 1 % to 29 % of VAH, mainly depending on the extent of cognitive deterioration [33]; moreover, auditory hallucinations were found to be more prevalent in Alzheimer patients with hearing loss.

1.2 Treatment of verbal auditory hallucinations

Currently, the treatment of VAH is mainly based on the use of antipsychotics and (if available) expanded with cognitive-behavioral therapy. Principally, antipsychotic medications block dopamine receptors, although second-generation antipsychotics block other neurotransmitters (e.g. serotonin and histamine receptors) to a greater

extent. The introduction of the drug clozapine has considerably improved treatment effectivity [32] with response estimates of up to 90 % [34]. However, a major concern of current medication is the substantial number of side-effects, including sedation, motor impairment (extrapyramidal symptoms), metabolic disorder, and agranulocytosis. These side-effects can have a considerable impact on a patient's health and functioning and often require prolonged care [35]. Another major concern is the high rate of patients not adhering to prescribed medication, frequently leading to a relapse in symptoms [36]. A negative attitude towards medication is a major risk factor for non-adherence [37] and is indicative of the experienced inconvenience when using antipsychotics. Therefore, although current pharmacotherapy in VAH has advantages, they are also detrimentally a-selective in targeting psychopathological processes. In addition, there is a significant proportion of treatment-resistant patients. An alternative treatment strategy is the use of local intervention techniques, such as transcranial magnetic stimulation or deep-brain stimulation. Repetitive transcranial magnetic stimulation (rTMS) has been used to reduce brain activity in hypothesized VAH-related brain regions and, in general, had promising results [38]. However, due to the considerable individual variation in effectiveness [39, 40] this technique requires further improvement in order to optimize personalize treatment [41].

1.3   Major models

Brain imaging has provided evidence for several hypotheses to explain the occurrence of VAH in schizophrenia. Most theories on VAH incorporate language networks and/ or memory networks, and propose either increased or decreased connectivity between the implicated subparts of the interacting networks [42]. The four models described below show conceptual overlap and studies seeking to confirm these models have reported both similarities and discrepancies. The interactions in these networks might be more complex than currently realized; nevertheless, they provide the basis for a more comprehensive view.

1.3.1   Memory recollection

In Hoffman's hypothesis, hallucinations arise from 'unintended' recollections of memory due to impairments in verbal working memory [43]. As a result of the phonetic ambiguity of speech and the need to assess communication, there is a continuous process of creating linguistic expectations. In persons with schizophrenia, these linguistic expectations are thought to be perceived as external percepts, i.e. they have VAH. In variants of this model, there is an emphasis on inhibitory deficits that contribute to the failure to control the content of memories [44-46]. The model can also explain the association found between childhood trauma and the experience of VAH. If disrupted

memory recollection is underlying the origin of VAH, then impairment would be expected in the interaction between the hippocampus and the putamen.

1.3.2 Source monitoring

When a person is in the process of thinking, this is often done with an experience of 'inner speech'. When this inner speech is not correctly identified as being self-generated, it can lead to the experience of a voice coming from 'someone else'[47]. Frith and Done highlighted feedback mechanisms where one's own actions provide an efference copy for monitoring regions in order to rapidly predict errors[8]. If the efference copy of inner speech derived from Broca's area is not adequately received, this will impair distinctions between self-other and lead to the experience of VAH.

1.3.3 Language lateralization

In a variant of disrupted source monitoring, Sommer et al. proposed that diminished left lateralization of language in the brain is the source of misinterpreted language[49]. Language input from Broca's right-sided homologue is thought to function in the production of high-valence emotional content, often with low semantic complexity; this is in line with the reported characteristics of VAH in schizophrenia. Individuals with schizophrenia can display decreased lateralization of language functions, although not necessarily correlated with VAH[50, 51].

1.3.4 Unbalanced top-down and bottom-up

Based on the study of regular perception, top-down and bottom-up hypotheses imply a disturbed balance between sensory regions and prefrontal cognitive control networks[52]. They often extend on source-monitoring deficits and attempt to capture disrupted networks and related computational concepts in a more concrete way[53-55]. Bottom-up refers to the incoming sensory information from external stimuli, top-down refers to the mental predictions on the perceived stimulus based on memory and priorities. Top-down cortical areas receive sensory data and send their prediction on the source of the sensation back to the bottom-up cortical areas. This prediction is based on prior knowledge on the perceived stimulus and likely occurrences in the sensory environment. In turn, bottom-up areas resolve differences between the prediction and the actual sensation (prediction error) and return these data back to the top-down areas. Together, these processes provide the experience of our environment[56]. Dissociation of these reciprocal connections could lead to the experience of VAH through disinhibited bottom-up areas producing auditory experience from random fluctuations. In the case of overactive top-down processes, imagery might be underconstrained by their bottom-up (sensory) counterpart and give rise to VAH[52, 57, 58]. In brain imaging this is reflected

in an influence of higher-order cognitive regions (prefrontal networks or associations cortices) on auditory regions in top-down VAH, or vice versa in bottom-up VAH.

2. MEASURING BRAIN FUNCTION WITH MRI

Magnetic resonance imaging (MRI) is capable of measuring both brain structure and brain function. Functional MRI (fMRI) employs the different magnetic properties of oxygenated and deoxygenated blood to measure the level of neuronal activity in the different areas of the brain. In activated neurons, the increased use of energy due to rapid firing is directly followed by an increase in blood flow in the surrounding microvasculature. The delivered oxygen overcompensates the use of oxygen, leading to a locally increased presence of oxygenated hemoglobin. The magnetic properties of oxygenated hemoglobin lead to an increase in measured MRI signal in areas where neurons activate. This is referred to as the Blood Oxygenation Level Dependent (BOLD) fMRI signal and provides an indirect measure of neuronal activity in the studied areas of the brain [59-61]. By repeatedly scanning the brain, a three-dimensional map is created that displays the relative activation of brain areas over several minutes. The advantages of fMRI include the unparalleled spatial resolution (millimeters) with reasonable temporal resolution (seconds), and its non-invasiveness for the subject being scanned. A main setback of fMRI is the susceptibility to noise from the scanning procedure and possible movement of the subject. Conventional fMRI studies measure brain activity related to a brain's function by the contrast between rest and a cognitive task. Typically, the person is instructed to perform a task (e.g. listening to sentences, or watching projected faces) in repeated blocks whilst alternating between performing a cognitive task, and not doing this task. After the scanning experiment, for each voxel (3-dimensional pixel) in the brain, it is tested to what extent the BOLD time series matches the onset and offset of the task. Conventional MRI has a relatively strong power and provides information on the functions and dysfunctions of the brain, presented in separate units. However, it is not suitable for measurement of brain function that is organized through a network of communicating brain areas.

2.1 Model-free fMRI studies

Imagine a large murmuration of starlings swarming and swaying through the air. To understand how this is possible, we cannot solely focus on the behavior of two starlings flying next to each other and then make generalizations. Starlings in the lead group have more influence, while others struggle just to remain with the group. Therefore, we need to consider the structure of communication throughout the flock to grasp how this behavior emerges. In a similar way, the separate parts of the brain cannot

fully account for the functioning of the mind; we need to also consider the functions emerging from the complex interactions between the various multiple units. Resting-state studies measure the functional connectivity between brain regions without an activation model derived from a task for reference. If the BOLD signal of two voxels is synchronized, they are thought to represent a shared function, i.e. to have functional connectivity [62]. Accordingly, the whole brain can be mapped for the functional connectivity between its regions. Typical resting-state studies have a person at rest during scanning, with no instruction other than to try and relax. Spontaneous activity in the brain is measured throughout the scan and, afterwards, tested for functional connectivity. Several resting-state networks have been consistently found, the most well-known being the default mode network (DMN). The DMN deactivates in response to the demands of externally-oriented activity and is attributed to processes such as musing, future thinking, and autobiographical memory [63-65].

2.2   Independent Component Analysis

One approach to test for functional connectivity is to employ Independent Component Analysis (ICA) [66]. ICA is a solution to the so-called 'cocktail party problem' [67]. When five people in a room are talking simultaneously, and this is recorded by five microphones, all microphones will register a different mixture of the set of five voices. ICA estimates the five source signals (i.e. the voices of the speakers) separately from the mixtures (i.e. the microphone recordings). Similarly, the voxels in fMRI contain a mixture of signals derived from multiple sources. The recorded time series represent neurons that co-activate in multiple functional networks, each having their own temporal course. ICA estimates the different source signal (functional networks) present in the brain. When source signals have been estimated, voxels can be tested for synchrony and a spatial map of the brain can be constructed, representing the relative degree of synchrony with the source signal per voxel. Thus, the Independent Component (IC) consists of a time series plus its activation map. All the ICs together represent the brain's functional modules. Since the ICA is a study method that applies minimal assumptions on the functioning of the brain with maximal exploitation of data, it may help to provide a comprehensive view of brain networks.

3.   NETWORK SCIENCE

The study of hallucinations is complicated by the considerable number of factors that determine the occurrence and phenomenological characteristics of these phenomena. Until recently, it was not possible to develop a 'global view' of the events that govern their existence. However, advances in network science allow graphical representation

and modeling of a large number of interacting factors [68] which may bring a global view within reach. By the mid-20th century, network science began to take shape as a separate discipline, thanks mainly to Paul Erdős (1913–1996) and many other physicists and mathematicians. In the 1950s, biological organisms were generally considered to be too complex to be described in terms of mathematical formulas. All that changed in the 1960s, when computers became available that allowed for complex simulation of almost anything, ranging from molecules to cells, organs, individuals, and markets. Classical network theory was born, which earned a serious reputation when it produced successful explanations and descriptions of complex phenomena such as the crystallization of atoms, phase transitions in matter, and navigation (e.g., the traveling-salesman problem). However, it took until the 1990s before a number of important discoveries enabled a revolution in network science, the consequences of which are still being felt in modern medicine and current neurosciences.

A network is a mathematical concept that describes interactions between agents that can be identified separately in space [69]. These agents may themselves be in a certain state, which can be transferred from one agent to another in the course of time. It was Albert Einstein (1879–1955) who first remarked that all natural phenomena can be described in terms of events (states) that take place in space and time [70]. Since the addition of 'scale' as a final descriptor, the central thesis has become that states can interact with one another on different spatial and temporal scales. This type of representation is so general that it allows most natural phenomena to be described in terms of networks.

3.1   Network graphs

The graphic representation of a network is called a network graph. Network graphs contain 'nodes' and 'links' which together determine network structure. States traveling between the nodes along the links in the course of time reflect network function. Classical network theory was based on the assumption that nodes were randomly connected to other nodes. Biological systems turn out to violate this rule completely, and are best represented by networks in which many nodes have relatively few connections, whereas the remaining nodes have many connections. Those richly connected nodes are called 'hubs.' Hubs connect many different nodes within the network, thereby forming clusters of tightly interconnected nodes that are called 'modules.' Hubs interconnect the modules, which themselves can serve as nodes to form superclusters at ever higher levels of spatial organization. Viewed in this way, life can be characterized as an endless variation of multimodular-hierarchic network structures which collectively display a so-called small-world topology. In such structures, states can travel from one node to any other node in the network along very short routes. It turns out that every human being is part of various communities and hierarchies, and connected to any

other human being through an average of only six degrees of acquaintance (or six degrees of separation). Using network analyses, brain structure and function are also found to comply with a multimodular and hierarchical organization that is independent of spatial scale [71]. This insight has prompted neuroscientists to study symptoms and disorders in the context of interacting factors across multiple scale levels.

4.   OUTLINE OF THIS THESIS

The aim of this thesis is to gain further insight into brain functions involved in the occurrence of VAH in patients with psychotic disorders. Individuals that are actively hallucinating are studied using functional MRI (fMRI) to determine the brain regions and their interactions that mediate VAH. Then, network models are used to acquire a comprehensive view on brain function and to guide the treatment of VAH.

Chapter 2 provides a case report on the fMRI findings of metamorphopsias and VAH in an individual with the Alice in Wonderland Syndrome. The treatment of symptoms with repetitive transcranial magnetic stimulation (rTMS) is discussed in relation to the fMRI findings.

Chapter 3 presents a model-based fMRI study on the occurrence of VAH, and the difference between patients hearing their voices either inside their head or in extracorporeal space. The rationale for this study emerged from the long-standing debate on the clinical significance of making a distinction between these types of VAH, and aims to establish whether the phenomenological differences can be substantiated neurophysiologically.

Chapter 4 reviews the use of network science to explain psychotic symptoms. A new model is introduced which aims to elucidate VAH based on the premise that the brain is a biological network that functions on multiple scale levels and is influenced by multiple endogenous and environmental factors.

Chapter 5 investigates the mediation of VAH using a minimum of a priori assumptions about the nature of brain activity. Functional MRI data are decomposed into functional networks using independent-component analysis and examined for the interacting circuits that underlie the occurrence of VAH. The aim of presenting a mechanistic account of brain functions is to improve the treatment of VAH and provide a complementary perspective for model-based studies.

Chapter 6 discusses the findings emerging from these studies and makes some recommendations for future research.

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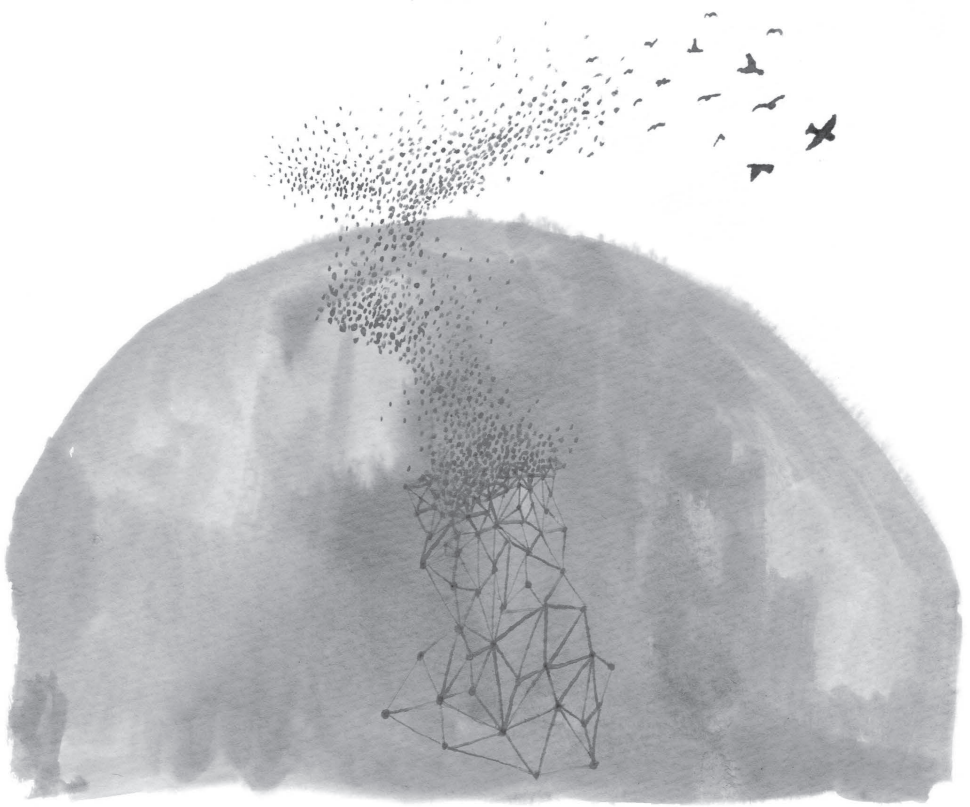
Chapter 2

Treatment of Alice in Wonderland syndrome and verbal auditory hallucinations using repetitive transcranial magnetic stimulation: a case report with fMRI findings

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ABSTRACT

Background The Alice in Wonderland syndrome (AIWS) is a rare cluster of CNS symptoms characterized by visual distortions (*i.e.*, metamorphopsias), body image distortions, time distortions, and déjà experiences. Verbal auditory hallucinations (VAHs) are the most prevalent type of hallucination in adults with or without a history of psychiatric illness. We report the case of a woman with an AIWS, long-lasting VAHs, and various additional perceptual and mood symptoms. **Methods** Semi-structured interviews were used to assess symptoms, and functional magnetic resonance imaging (fMRI) was employed to localize cerebral activity during self-reported VAHs. Treatment consisted of repetitive transcranial magnetic stimulation (rTMS) at a frequency of 1 Hz at T3P3, overlying Brodmann's area 40. **Results** Activation during VAH experience was observed bilaterally in the basal ganglia, primary auditory cortex, association auditory cortex, temporal poles and the anterior cingulated gyrus. The left and right inferior frontal gyri (Broca's area and its contralateral homologue) were involved, along with dorsolateral prefrontal cortex. Interestingly, synchronized activation was observed in the primary visual cortex (areas V1 and V2), and bilateral dorsal visual cortex. Higher visual association cortex also showed significant, but less prominent activation. During the second week of rTMS treatment, not only the VAHs, but also the other sensory deceptions and distortions and mood symptoms showed complete remission. The patient remained free of any symptoms during a four-month follow-up phase. After 8 months, when many of the original symptoms had returned, a second treatment phase with rTMS was again followed by complete remission. **Conclusions** This case indicates that VAHs and metamorphopsias in AIWS are associated with synchronized activation in both auditory and visual cortices. It also indicates that local rTMS treatment may have global therapeutic effects, suggesting an effect on multiple brain regions in a distributed network. Although a placebo effect cannot be ruled out, this case warrants further investigation of the effects of rTMS treatment in AIWS.

1. BACKGROUND

1.1 The Alice in Wonderland syndrome

The Alice in Wonderland syndrome (AIWS) constitutes a rare cluster of CNS symptoms characterized by visual distortions (i.e., metamorphopsias), body image distortions, time distortions, and déjà experiences. The term refers to the protagonist of Lewis Carroll's Alice's Adventures in Wonderland. It was introduced into the biomedical literature in 1955 as 'the syndrome of Alice in Wonderland' by the British psychiatrist John Todd (1914-1987), who was inspired by Coleman's earlier description of a woman who "like Alice in Wonderland" would "sometimes feel that she was shorter, sometimes that she was taller than she used to be."[1,2]. Todd employed the term syndrome of Alice in Wonderland to denote a rare group of symptoms that includes subjective feelings such as derealization, depersonalization, and somatopsychic duality, as well as perceptual symptoms such as illusory changes in the size, distance, or position of stationary objects in the visual field (i.e., metamorphopsias such as micropsia, macropsia, macroproxiopia, microtelepsia, teleopsia, porropsia, and plagiopsia), illusory feelings of levitation, and illusory alterations in the passage of time (i.e., the quick-motion phenomenon and other types of time distortion). Todd also included hyposchematia and hyperschematia, i.e., an underestimation or exaggeration of the space occupied by some part of the body, associated with neglect and right-hemispheric lesions. As he observed, the nature of these symptoms suggested that the parietal lobe may be involved in their mediation. Today many of the body schema illusions (such as kinaesthetic hallucinations, proprioceptive hallucinations, microsomatognosia, macrosomatognosia, splitting of the body image, aschematia, and the illusory displacement of limbs) are also included in the operational definition of the AIWS[3,4]. As already noted by Todd, there are few examples of the complete AIWS to be found in the literature. Even today most reports are concerned with one or several symptoms occurring in association with migraine aura, psychic aura, temporal lobe epilepsy, frontal lobe epilepsy, cerebral lesions, delirium of fever, hypnagogic or hypnopompic states, acute labyrinthine vertigo, a clinical diagnosis of schizophrenia, or a history of psychoactive substance abuse (notably the use of hallucinogens such as dextromethorphan, LSD, and mescaline)[1,5,6,7,8]. A few case reports exist of the AIWS in association with depression, bipolar disorder, and obsessive-compulsive disorder[9,10]. In the pediatric literature, the symptoms of the AIWS are mentioned chiefly as early signs of a viral infection such as mononucleosis infection, Epstein-Barr virus infection, and Coxsackie virus B1 infection[10,11,12,13]. The pathophysiology of the AIWS is largely unknown. The prognosis is usually good. Depending on the underlying condition, remission tends to take place - often spontaneously - within several hours to days. A protracted duration of the AIWS is considered indicative of a structural parietal lobe lesion or a focal epileptic state[14].

1.2 Verbal auditory hallucinations

Verbal auditory hallucinations (VAHs) are the most prevalent type of hallucination in adults with or without a history of psychiatric illness [15]. Traditionally, VAHs are associated primarily with psychotic disorders such as schizophrenia, but they also occur in the context of other psychiatric conditions, such as bipolar disorder, depressive disorder, dissociative identity disorder and borderline personality disorder. VAHs may also occur in various forms of neurodegenerative disorder, such as Alzheimer's disease, Lewy Body Dementia, Parkinson's disease, and Huntington's disease. They often accompany metabolic syndromes such as thyroid disease, delirium, delirium tremens, alcoholic hallucinosis, and substance abuse, and may occur as a side effect of pharmacological intervention. Moreover, VAHs are found in narcolepsy, epileptic aura, and the twilight state. The recent occurrence of VAHs is reported by 10 to 15 per cent of all individuals in the general population [16].

In this paper we present the case of a patient with a protracted AIWS and VAHs which responded favourably to repetitive transcranial magnetic stimulation (rTMS) at the temporoparietal junction.

2. METHODS

2.1 Subject

Patient A (fictitious initial, for 'Alice') was recruited in the context of an imaging study carried out by the Parnassia Bavo Group (PBG) and the University Medical Centre Utrecht (UMCU) in the Netherlands among individuals with a schizophrenia spectrum disorder and VAHs [17,18]. The study was designed to obtain functional magnetic resonance imaging (fMRI) data during episodes of VAH activity, and to employ the ensuing cerebral activation maps for an experimental treatment with rTMS. On the day of scanning, the Positive and Negative Syndrome Scale (PANSS) [19] was used to assess the current symptomatology. Detailed characteristics of the VAHs were assessed with the PSYRATS Auditory Hallucinations Rating Scale (AHRS) [20], and the Hallucination Differentiation List (HDL), a semi-structured interview developed at the PBG. All clinical ratings were performed by trained interviewers. The study was approved by the Humans Ethics Committee of the UMCU. After complete description of the study to the subjects, written informed consent was obtained.

2.2 Experimental design and data acquisition

Imaging was carried out on a Philips Achieva 3 Tesla Clinical MRI scanner. Eight hundred blood-oxygenation-level-dependent (BOLD) fMRI images were acquired with the following parameter settings: 40 (coronal) slices, TR/TE 21.75/32.4 msec,

flip angle 10°, FOV 224x256x160, matrix 64x64x40, and voxel size 4 mm isotropic. This scan sequence achieves full brain coverage within 609 msec by combining a 3D-PRESTO pulse sequence with parallel imaging (SENSE) in two directions, using a commercial 8-channel SENSE headcoil [21]. After completion of the functional scans, a high-resolution anatomical scan, with parameters TR/TE: 9.86/4.6 msec, 1x1x1 voxels, and flip angle 8°, was acquired to improve localisation of the functional data. Scanning time for functional imaging was 8 min and 7.2 sec, and 8 min for structural scanning. In their right hand, the subjects held an fMRI compatible balloon (custom-designed for studying hallucinatory activity) which they were required to press at the onset of VAHs (onset of "HALLUCINATION" condition), and to release at the termination of each hallucinatory episode (onset of "REST" condition). The onset times and duration of the balloon presses were recorded, and employed as the basis for model fitting (see below).

2.3   fMRI data analysis

The functional data set of patient A was analyzed using FEAT (FMRI Expert Analysis Tool) Version 5.98, a part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The first 3 volumes of the data set were discarded to account for T1-saturation effects. The following pre-processing was carried out: non-brain removal, motion correction, and spatial smoothing using a Gaussian kernel of FWHM 8 mm, mean-based intensity normalization of all volumes by the same factor, and high and low pass (100 sec, sigma = 50 sec) temporal filtering [22,23]. Functional neuroimages were coregistered to the structural image. Coregistration was carried out using FLIRT, an intermodal registration tool based on the correlation ratio [22,24].

The PRESTO data used in the current study contain a .41 Hz noise artifact as a result of gradient coil wear and tear. This problem was accounted for using a noise model containing 3 separate regressors to code for the artifact. Time-series statistical analysis was carried out using FILM with local autocorrelation correction [25] on a voxel-wise basis on the 4D time series of patient A. Model fitting with local autocorrelation correction generated whole brain (contrast) images in native space of parameter estimates and corresponding variance, representing average signal change during hallucination conditions versus 'rest' conditions. Images were thresholded using clusters determined by Z > 2.3, and a corrected cluster significance threshold of p = .05, based on Gaussian random field theory [26].

3.   CASE DESCRIPTION

Patient A, a 36-year-old, right-handed woman, was referred to the Psychosis Department of the PBG because of an increase of psychotic symptoms. Over the past five years she had been diagnosed successively with borderline personality disorder, cannabis abuse, cocaine abuse (both in remission for the past two years), psychotic disorder not otherwise specified, and attention-deficit/hyperactivity disorder (ADHD). She had no history of somatic disease, and at the time of presentation she had been free from any drug or alcohol abuse for over a year. The prescribed medication consisted of olanzapine 20 mg/day, paroxetine 20 mg/day, methylphenidate (Ritalin®) 10 mg twice a day, methylphenidate (Concerta®) 72 mg/day, and oxazepam 10 mg three times a day. Patient A presented with the introductory remark that thanks to the methylphenidate her ADHD symptoms were under control, and that her main problem now consisted of a variety of perceptual symptoms which had aggravated upon the termination of her relationship one year ago. These perceptual symptoms included VAHs which had been present for five years, consisting of three different voices experienced as coming from inside the head (internal auditory hallucinations). The voices tended to speak alternately, while a second voice sometimes laughed in the background. Patient A described the content of the hallucinated propositional remarks as "sometimes positive, sometimes negative, but on the whole not too bright". The voices often ridiculed her, and gave her incentives and commands. Secondly, patient A occasionally experienced foul odours, especially of feces, in the absence of an apparent source (olfactory hallucinations, cacosmia). Thirdly, she described an intuitive feeling of a 'presence', which made her conjecture that she might be followed around by several ghosts (sensed presence with secondary delusions). Sometimes this intuitive feeling developed into a tactile sensation on the skin of the neck, as if it were touched by a breeze, or as if two hands were folding around it (tactile hallucinations). Occasionally, she had the impression of actually seeing a ghost, in the form of a dark silhouette in the central part of the visual field (cognitive illusion). This sensation occurred mostly at dusk, and lasted no longer than a second. In bed, at night, the experience of a sensed presence was sometimes accompanied by hallucinoid experiences such as a touch in the ribs, or the feeling of waking up in a paralyzed state with a creature sitting heavily on the chest (incubus phenomenon). The latter experience was accompanied by intense feelings of fear, and aggravated by the sleep paralysis and the inability to scream and breathe. In the fourth place, patient A suffered from two types of metamorphopsia which she experienced while awake and with a clear sensorium. They were a regularly recurring phenomenon in which stationary objects appeared to be moving away from her (porropsia, dysmetropsia), and the recurring impression that the rooftops of buildings in her environment became higher and lower in a jerkily fashion (interpreted by us as a

variant of the autokinetic effect). These metamorphopsias had been present for about a year. Finally, patient A described regularly recurring feelings of déjà vu, and a single experience in which her body appeared to take on a miniature format (whole body microsomatognosia).

In addition to these sensory deceptions and distortions, psychiatric examination indicated a severely depressed mood with anhedonia, general anxiety, decreased attention and ability to concentrate, and sleep disturbances. General physical examination, neurological examination, and extensive blood testing revealed no abnormalities. Electroencephalography (EEG) showed a regular pattern, and structural MRI gave no indication of focal CNS pathology. On the basis of these findings it was concluded that patient A met the DSM-IV criteria of schizoaffective disorder, even though she also fulfilled the criteria of at least three additional - but hierarchically lower-ranking - syndromes: parasomnia not otherwise specified (with classic nightmares), substance abuse in remission, and an Alice in Wonderland syndrome. Whether she also met the criteria of ADHD was uncertain at the time of examination, although patient A insisted that without the use of methylphenidate the disorder's symptoms would return within a few days.

4.   RESULTS OF fMRI AND rTMS TREATMENT

General statistics of patient A's VAHs are shown in Tab. 1. Model-based analysis of the fMRI data revealed significant brain activation in several cortical and subcortical areas (see Fig. 1, red areas, and Tab. 2, locations). Apart from left motor cortex and accompanying contralateral cerebellar activation, which were expected because of the balloon presses and releases, activation was observed bilaterally in the basal ganglia, primary auditory cortex, association auditory cortex, temporal poles (superior temporal gyri), and the anterior cingulate gyrus. Left and right superior, middle and inferior frontal gyri (Broca's area and its contralateral homologue) were also involved, along with bilateral dorsolateral prefrontal cortex (superior frontal gyri). Additional activation was observed in posterior cerebral regions including the primary visual cortex, occipital fusiform gyrus, and cuneus. Higher visual association cortex showed less prominent activation. Only little deactivation was observed (see Fig. 1).

Table 1 – VAHs as perceived by patient A

Total number	Avg. Duration	SD	Frequency	Content
19	5.34s	5.21s	2.3 / min	Negative
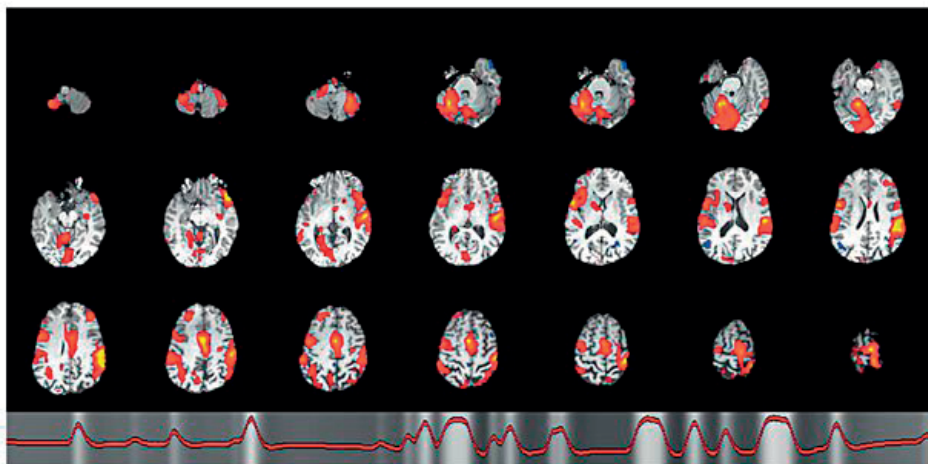
Figure 1 – Brain activation during reported verbal auditory hallucinations
Effects are shown at Z > 2.3, cluster corrected at Z > 2.3. The gray bar shows time series of hallucinations (light grey vertical stripes) versus rest periods (dark grey periods). The red line denotes typical (modeled) signal intensity changes during verbal auditory hallucinations (see table 1 for general statistics of hallucinations; see table 2 for locations of the effects). Left in the image is right in the brain, and vice versa. Top left: brain stem and lower brain areas. Bottom right: upper brain areas. Most effects involve brain activation (red areas). Only a little deactivation is observed (blue areas).

The rTMS treatment was directed at the temporoparietal junction, located at T3P3 (based on the international 10-20 system for placement of EEG electrodes) for five days a week, 20 minutes a day, for three consecutive weeks. In an effort to reduce the frequency and severity of the VAHs, rTMS was given at a frequency of 1 Hz. Meanwhile, the prescribed medication was continued. During the first week of rTMS treatment, not only the VAHs, but also the other sensory deceptions and distortions receded into the background, and during week 2 they vanished completely. The AHRS scores of the PSYRATS dropped from 2-4 at baseline to 0 in week 3, and the PANSS hallucination score dropped from 5 at baseline to 0 in week 3. There were no side effects of the rTMS treatment. During a four-month follow-up phase, all rates remained 0. The depressive symptoms also disappeared, and patient A's ability to focus and concentrate on daily activities was fully restored. After four months the depressive symptoms returned, and after eight months the VAHs returned. When patient A was treated a second time with rTMS, under similar conditions, but for a duration of 5 days, once again all of her symptoms went into remission.

Table 2 – Talairach coordinates and anatomical locations of local maxima of brain activation during VAHs in patient A

Z-score	X	Y	Z	Level 1	Level 2	Level 3	Level 4
9.07	-53.1	-21.4	34.8	Left Cerebrum	Parietal Lobe	Postcentral Gyrus	BA 2
8.96	-56.1	-10.4	43	Left Cerebrum	Parietal Lobe	Postcentral Gyrus	BA 3
8.7	-34.9	-22.1	70.6	Left Cerebrum	Frontal Lobe	Precentral Gyrus	BA 4
8.67	-57.5	-28.6	43.2	Left Cerebrum	Parietal Lobe	Postcentral Gyrus	BA 2
7.71	-50.6	-17.9	11.5	Left Cerebrum	Temporal Lobe	Transverse Temporal Gyrus	BA 41
7.36	1.75	9.87	33.4	Right Cerebrum	Limbic Lobe	Cingulate Gyrus	BA 24
7.21	8.16	9.02	49.1	Right Cerebrum	Frontal Lobe	Superior Frontal Gyrus	BA 6
6.75	-4.75	-3.85	71.4	Left Cerebrum	Frontal Lobe	Superior Frontal Gyrus	BA 6
5.92	-3.72	-6.9	39.3	Left Cerebrum	Limbic Lobe	Cingulate Gyrus	BA 24
7.64	32	-60.3	-32.4	Right Cerebellum	Posterior Lobe	Cerebellar Tonsil	*
7.25	14.7	-53	-21	Right Cerebellum	Anterior Lobe	*	Dentate
5.43	1.73	-54.4	-7.61	Right Cerebellum	Anterior Lobe	Culmen	*
7.24	55.2	10.3	-2.42	Right Cerebrum	Temporal Lobe	Superior Temporal Gyrus	BA 22
7.12	56.9	9.66	14	Right Cerebrum	Frontal Lobe	Inferior Frontal Gyrus	BA 44
9.44	-50.3	13.6	-9.02	Left Cerebrum	Temporal Lobe	Superior Temporal Gyrus	BA 38
6.37	-35.8	-65.7	-36.8	Left Cerebellum	Posterior Lobe	Inferior Semi-Lunar Lobule	*
6.97	54.4	6.1	37.3	Right Cerebrum	Frontal Lobe	Middle Frontal Gyrus	BA 6
5.42	3.13	-87.8	-14.2	Right Cerebrum	Occipital Lobe	Lingual Gyrus	BA 18
5.85	-69.3	-28.7	23.1	Left Cerebrum	Parietal Lobe	Inferior Parietal Lobule	BA 40
5.15	-65.9	-31.3	12.4	Left Cerebrum	Temporal Lobe	Superior Temporal Gyrus	BA 42
6.15	-34.6	48.2	22	Left Cerebrum	Frontal Lobe	Superior Frontal Gyrus	BA 10
5.53	61.9	-20.9	38.8	Right Cerebrum	Parietal Lobe	Postcentral Gyrus	BA 3
5.45	58.9	-22.5	12.4	Right Cerebrum	Temporal Lobe	Superior Temporal Gyrus	BA 41
5.08	-25	-9.77	65.4	Left Cerebrum	Frontal Lobe	Precentral Gyrus	BA 6
6.47	32.4	52.4	21.4	Right Cerebrum	Frontal Lobe	Superior Frontal Gyrus	BA 10
5.22	41	22.4	-9.34	Right Cerebrum	Frontal Lobe	Inferior Frontal Gyrus	BA 47
5.08	62.8	-27	51.5	Right Cerebrum	Parietal Lobe	Postcentral Gyrus	BA 2
5.13	63.9	-30	19.3	Right Cerebrum	Temporal Lobe	Superior Temporal Gyrus	BA 42
5.09	2.09	-84.7	17.9	Right Cerebrum	Occipital Lobe	Cuneus	BA 18
5.05	-0.667	-93.7	-0.909	Left Cerebrum	Occipital Lobe	Cuneus	BA 17
5.1	21.9	-88.5	-16.9	Right Cerebrum	Occipital Lobe	Fusiform Gyrus	BA 18

Z-scores, Talairach coordinates, and anatomical locations of local maxima of brain activation during verbal auditory hallucinations in patient A. Effects are cluster corrected using a cluster significance threshold of Z > 2.3. Effects are shown at Z > 2.3. See also Fig. 1.

5.   DISCUSSION

Our patient experienced an AIWS with VAHs, and various additional perceptual and mood symptoms. Although she formally met the DSM-IV criteria of schizoaffective disorder, especially the chronically recurring symptoms of the AIWS were considered indicative of structural CNS pathology, as suggested by the literature [5].

Functional MRI showed brain activity in the left motor cortex and contralateral cerebellum, which served as a positive control for detection of brain activation in relation to the balloon squeezes that patient A executed with her right hand. Additional activation was present in the network comprising primary sensory auditory cortex, association auditory cortex, thalamus, basal ganglia, and anterior cingulate gyrus. Involvement of this network is commonly found in activation studies of auditory stimuli with an external source [27]. Primary and higher auditory areas serve to process auditory information, and as such form a network with the thalamus, basal ganglia, and anterior cingulate areas as part of an 'active state' network, involved with cognitive control (*i.e.*, attention regulation, response selection, priority formation, and error monitoring) over incoming stimuli [28]. Activity in Broca's area, which is normally associated with the motor generation of speech, has also been found in studies of VAHs [29]. The involvement of the right homologue of Broca's area is consistent with earlier findings in fMRI studies [18,30]. During the execution of normal language functions such as speaking, listening to speech, and reading, the dominant (left-sided) language areas inhibit their contralateral homologues through reciprocal callosal connections [31,32]. It has therefore been hypothesized that certain subtypes of VAHs may result from aberrant activity of the right homologue of Broca's and Wernicke's areas, due to insufficient inhibition by dominant language areas [33,34]. Some subtypes of VAHs may therefore be seen as lateralization phenomena [35].

Interestingly, signal intensity changes within the auditory network synchronized with those found in the right primary visual cortex (areas V1 and V2), bilateral dorsal visual cortex, and, to a lesser extent, in the higher visual association cortex. From previous fMRI analyses examining single subjects and groups of patients experiencing VAHs exclusively, it would seem that concomitant activation of visual and auditory cortices is quite uncommon to the extent shown in this case report [18,29]. According to the subjective reports of patient A, her VAHs were continuously accompanied by changes within the visual field (metamorphopsias), albeit of a varying nature and intensity. Because of this co-ocurrence of symptoms, it was impossible for her to separate events in the visual and auditory domains within the MRI scanner. We can therefore only assume that the involvement of visual areas reflects brain activity responsible for the mediation of patient A's metamorphopsias. This is in keeping with the results of two single photon emission tomography (SPECT) studies in metamorphopsia, which

showed hyper- and hypoperfusion, respectively, at the right occipito-parietal junction [36,37]. However, other SPECT studies found hypoperfusion of the right frontal, and right fronto-parietal regions [38], and of the left and right temporal lobes [39].

Generally speaking, metamorphopsias may have their origin within lower-level (*i.e.,* retinal) or higher-level (*i.e.,* cerebral) structures. In the case of patient A, a peripheral origin was ruled out because the types of metamorphopsia described by her, along with their sudden disappearance after treatment, are incompatible with any known intra-ocular defects. Long-lasting and permanent metamorphopsias of a more central origin have been associated with discrete lesions and/or aberrant activity within specialized cortical cell columns of visual association areas [14]. This finding is consistent with Hubel and Wiesel's classic thesis on the response selectivity of cortical cell columns [40,41]. The absence of any structural changes, as observed by MRI, or epileptic activity, as observed by EEG, suggests that the symptoms reported by patient A involve a functional rather than structural deficit. The simultaneous activation of visual and auditory cortices suggests a common pathophysiology underlying her VAHs and metamorphopsias. If true, this defect apparently triggered the occurrence of visual and auditory symptoms in a serial fashion, with the visual ones being quintessential for the auditory ones to occur. The nature of such a defect, and indeed of psychotic symptoms in general, is still open to speculation. One attractive hypothesis can be offered by network theory, where psychosis may be viewed as a hyperconnectivity syndrome [42]. In this view, a slight increase in the average number of connections per neuron (*i.e.*, as a result of inheritance, intoxications or medication) may cause a dramatic increase in the inter-connectivity of distributed neural networks, providing a level of connectivity between brain regions beyond that which is considered normal or healthy. Alternatively, it may be hypothesized that the simultaneous mediation of visual and auditory and symptoms stemmed from the disinhibition of a higher cortical centre involved with the integration of information from various sensory modalities. This hypothesis would be in line with the impaired cortical inhibition hypothesis of schizophrenia [43,44].

The positive effect of the rTMS treatment on patient A's sensory deceptions and distortions - and on her mood - was unanticipated by us, especially in the light of the disappointing results of rTMS upon VAHs in a recently published study [45]. Obviously, the possibility of an overall placebo effect cannot be ruled out with certainty. In the context of the elaborate diagnostic and therapeutic procedure to which patient A was subjected, such a strong placebo effect can probably be best designated as a Hawthorne effect, so called after a study of industrial productivity at the Hawthorne plant of Western Electric (1927-1929), where the effect of the investigators' presence and attention on the productivity of the workers was shown to be overwhelming [46]. A similar effect may have been produced by the intensive diagnostic process, the high-tech environment, and the daily attention given to patient A during her participation in our study.

A second possibility is a beneficial effect of the medication, which was continued in unaltered dosages during the rTMS treatment periods. As mentioned above, the only change of medication was the replacement of oxazepam by zopiclon. As zopiclon has a weaker effect upon the seizure threshold, and is less potent than oxazepam in its influence upon the GABA system, we assume that its role in the overall remission must have been minimal. Moreover, considering the fact that both episodes of remission followed upon rTMS treatment, a substantial medication effect would not seem likely.

If we assume a direct relation with the magnetic field pulses induced by the TMS coil, the overall result is open to various explanations. At T3P3, the coil was directed towards Wernicke's area at the left parieto-temporal junction. As demonstrated in seven prior studies, and meta-analyzed by Slotema *et al.* [47], rTMS with a frequency of 1 Hz over T3P3 was until recently considered an effective treatment for VAHs. The same meta-analysis demonstrates that rTMS is effective for depression, but here it should be noted that all of the 34 published studies involved with rTMS treatment of depression targeted the left and/or right dorso-lateral prefrontal cortex, and none involved Wernicke's area. One explanation of the resolution of depressive symptoms after rTMS at T3P3 is that the exact localization of TMS is less important in treating depressive symptoms. However, this is not in line with previous hypotheses considering the working mechanism of rTMS in depression [48]. Alternatively, the mood fluctuations observed in patient A may have been the result of the remaining other (perceptual) symptoms. With the resolution of her perceptual symptoms, her mood may have improved as well.

Due to its local and temporary effects, TMS provides a unique opportunity to study visual perception and awareness [49,50]. But ever since the electrical probing experiments by Penfield and Perot [51], and especially Gloor *et al.* [52], it has been known that stimulation of circumscript cortical areas may induce cerebral activity in structures as deep as the limbic system. Even though the magnetic pulse of TMS is circumscript, and capable of depolarizing local neurons at a maximum depth of 2-3 cm [53], local interventions into brain areas may well have distributed effects on brain activity because of the network structure of the human brain [54]. In biological networks such as the human brain, a few highly connected areas ('hubs') may bind the entire network of less connected regions together, thus facilitating information transfer. In the case of patient A, it may be hypothesized that Wernicke's area functioned as a hub which carried local effects of rTMS treatment to more remote brain areas. This is in line with previous reports of the network structure of both structural and functional networks within the human brain [54]. Whether the effect on patient A's mood should be explained along similar lines, or as a result of the remission of her perceptual symptoms, remains open to debate.

The present case report indicates that metamorphopsias are associated with activation of the visual association cortex and posterior cerebral regions, including the
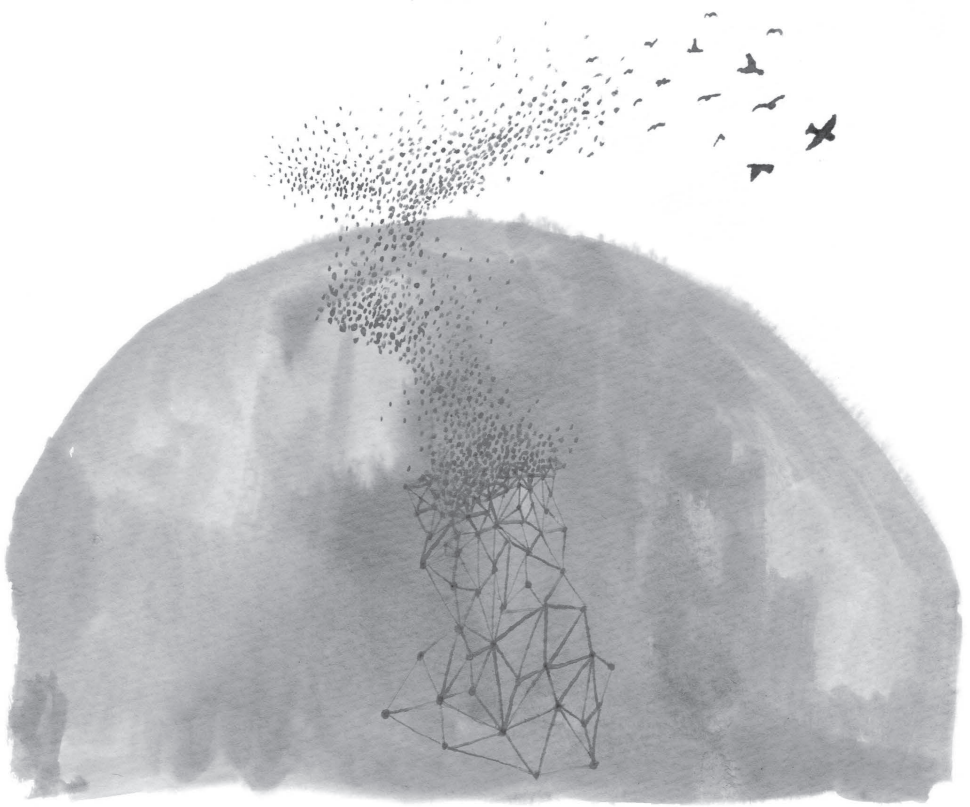
primary visual cortex, occipital fusiform gyrus, and cuneus. It also demonstrates that local rTMS treatment at T3P3 may have widespread therapeutic effects on symptoms attributable to brain regions that lie scattered throughout the CNS, and that the network structure of the human brain allows for a general explanation of the neurophysiological mechanism behind this disseminated effect.

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Chapter 3

The auditory dorsal stream plays a crucial role in projecting hallucinated voices into external space

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ABSTRACT

Introduction Verbal auditory hallucinations (VAHs) are experienced as spoken voices which seem to originate in the extracorporeal environment or inside the head. Animal and human research has identified a 'where' pathway for sound processing comprising the planum temporale, middle frontal gyrus and the inferior parietal lobule. We hypothesize that increased activity of that 'where' pathway mediates the exteriorization of VAHs. **Methods** The fMRI scans of 52 right-handed psychotic patients experiencing frequent VAHs were compared with the reported location of hallucinations, as rated with the aid of the PSYRATS-AHRS. For each subject, a unique VAH activation model was created based on the VAH timings, and subsequently convolved with a gamma function to model the hemodynamic response. In order to examine the neurofunctional equivalents of perceived VAH location, second-level group effects of subjects experiencing either internal (n = 24) or external (n = 28) VAHs were contrasted within planum temporale, middle frontal gyrus, and inferior parietal lobule regions of interest (ROIs). **Results** Three ROIs were tested for increased activity in relation withthe exteriorization of VAHs. The analysis revealed a left-sided medial planum temporale and a right-sided middle frontal gyrus cluster of increased activity. No significant activity was found in the inferior parietal lobule. **Conclusions** Our study indicates that internal and external VAHs are mediated byafronto-temporal pattern of neuronal activity while the exteriorization of VAHs stems from additional brain activity in the auditory 'where' pathway, comprising the planum temporale and prefrontal regions.

Non-standard abbreviations: IVAH - Internal Verbal Auditory Hallucination
                                EVAH - External Verbal Auditory Hallucination

1.   INTRODUCTION

Internal verbal auditory hallucinations (IVAHs) are voices experienced inside the head. They are traditionally distinguished from external verbal auditory hallucinations (EVAHs), which have an apparent source in extracorporeal space [1, 2]. There is a long-standing debate on whether the phenomenological difference between these two types of hallucination is relevant from a clinical and a neurophysiological point of view [3-5]. In conformity with the 19th-century tradition of designating IVAHs as 'pseudohallucinations', it has been argued that these are not actual hallucinations, but rather forms of imagery, or phenomena lying on a continuum between imagery and true hallucinations [6, 7]. As a corollary, IVAHs have been associated primarily with personality disorders and non-psychotic experiences, whereas EVAHs are traditionally regarded as 'hard symptoms' characteristic of schizophrenia and other psychotic disorders [8]. However, other sources have argued that IVAHs are true hallucinations which simply lack an additional characteristic present in EVAHs [9], and which tend to be experienced as equally 'real'[3]. A recent comparison of 111 healthy voice hearers and 118 voice hearers with a psychotic disorder revealed that IVAHs and EVAHs are distributed evenly among both groups [10].

The debate on the clinical significance of the IVAH/EVAH distinction might be pushed forward by increased insight into the neurophysiological correlates of these phenomena. The spatial localization of sounds has been studied quite extensively, but those studies provide only indirect evidence of the mechanisms underlying the exteriorization of endogenously mediated sounds.

The localization of sounds from our environment depends on the interaural time difference (ITD) and the interaural intensity difference (IID). Synaptic input from both cochleas connects to the ipsilateral and contralateral superior olives in the midbrain, where the signal goes through encoding algorithms capable of registering very fine temporal differences [11]. The auditory signal then passes on to the auditory cortices, where additional networks facilitate the localization of sounds, and ultimately the conscious experience of sound location. The experience of internal or external sounds is furthermore dependent on the head-related transfer function (HRTF) [12]. The HRTF describes how bodily characteristics such as ears, head and torso have source-location-specific signal altering effects used for further neural determination in frontal and transversal plane. Within the visual system, optical stimuli are topographically projected onto the primary visual cortex, from where they reach more specific 'what' and 'where' pathways [13]. The existence of comparable 'what' and 'where' pathways has been hypothesized for auditory processing [14], hinting at a sound localization network extending beyond the primary and secondary auditory cortices. Experimental studies in monkeys combining anatomical and functional research have indeed shown that the

localization of sounds takes place in posterior temporal regions and the dorsolateral prefrontal cortex [15]. Research in humans implicated similar brain regions to play a role in auditory localization in humans [16-20]. A meta-analysis of functional imaging studies in healthy humans, designed to identify the 'where' pathway, indicates that the posterior temporal lobe, middle frontal gyrus (MFG) areas along the superior frontal sulcus, and the inferior parietal lobule (IPL) function within this stream [21].

Other studies focused on the role of the planum temporale (PT), part of the posterior temporal lobe, in sound localization, designating it as the probable junction of the 'what' and 'where' pathways [22]. Hunter et al. [4] used headphone stereotactic stimulation in healthy subjects with incorporation of the HRTF. Normal appliance of sounds through headphones creates an internal experience of sounds, whilst modification of the spectrotemporal patterns simulating the HRTF successfully externalizes sounds. They showed that the localization of exogenous sounds (as opposed to auditory imagery) is associated with increased left PT activity. A study that focused on the anatomical differences underlying EVAHs and IVAHs found opposed white-matter and sulcus displacements in the right temporoparietal junction, with intermediary scores for a control group [5].

The aim of this paper is to investigate whether the phenomenological differences between EVAHs and IVAHs can be substantiated neurophysiologically by differential activation within the acoustic 'where pathway'. We used blood-oxygenation-level-dependent (BOLD) functional MRI in 52 hallucinating subjects to test the hypothesis that within our regions of interest the planum temporale, the middle frontal gyrus, and the inferior parietal lobule, externally experienced voices are characterized by significantly more activity than internally experienced voices.

2. METHODS

2.1 Subjects

Fifty-two right-handed psychotic patients experiencing frequent VAHs (at least three episodes per 15 minutes) were recruited from the Parnassia Group, The Hague, and the University Medical Center, Utrecht, the Netherlands. A minor portion of these patients (33 %) has been described in a prior publication [23]. Exclusion criteria were the presence of neurological disorders, structural brain deficits, a frequency of less than three hallucinations per scanning session, and having more > 25 % ambiguous VAH-responses (see Scanning Paradigm). We chose not to include healthy controls in our study design, as this could not be expected to provide any additional information in relation to our research question. Patients had a mean age of 38.2 years, with thirty-two patients (62 %) being male. All patients were diagnosed in accordance with

DSM-IV criteria as suffering from schizophrenia (77%), schizoaffective disorder (4%), psychosis not otherwise specified (13%), or personality disorder (6%). Interviews were carried out by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) [24]. The mean duration of VAHs was 136 seconds during scanning sessions (i.e., 28% of total fMRI acquisition time). All patients were on stable dosages of antipsychotics. After the subjects were provided with a complete description of the study, written informed consent was obtained in accordance with the Declaration of Helsinki. The study was approved by the Human Ethics Committee of the University Medical Center Utrecht.

2.2 Phenomenological data

The localization of VAHs was determined using the Dutch version of the Psychotic Symptom Rating Scales-Auditory Hallucinations Rating Scale (PSYRATS-AHRS), an eleven-item structured interview assessing the phenomenological characteristics of auditory hallucinations [25]. On the day of scanning, complete interviews pertaining to the experience of VAHs during the past three months were carried out by trained interviewers. Subsequently, cases were divided into two subject groups, depending on the perceived location of VAHs (see table 1). The first group consisted of subjects experiencing internal VAHs, equaling a PSYRATS-AHRS location item score of 1. The second group consisted of subjects experiencing external VAHs, as well as subjects experiencing predominantly external VAHs and possibly some internal VAHs (see table 1, location item score 2), equaling a PSYRATS-AHRS location item score of 2, 3 or 4. In addition, the PANSS was used to compare the patients' clinical characteristics.

Table 1 – PSYRATS Auditory Hallucinations Location Item

Location score	Description
0	No voices present
1	Voices are perceived inside the head only
2	Voices are perceived outside the head, but close to the ears or head. Voices inside the head may also be present.
3	Voices are perceived within or close to the ears, and outside of the head, away from the ears
4	Voices are perceived outside the head only

2.3 Scanning paradigm and data acquisition

Functional neuroimaging maps were obtained with the aid of a Philips Achieva 3 Tesla Clinical MRI scanner using a fast 3D PRESTO SENSE sequence, achieving full brain coverage within 0.608 s (to detect brain activity in relation to hallucinations with a relatively brief duration) [26]. Scanning resulted in eight hundred 3D images, depicting

BOLD contrast acquired at the following parameter settings: 40 coronal slices, TR/TE 21.75/32.4 ms, flip angle 10°, FOV 224 x 256 x 160, matrix 64 x 64 x 40, voxel size 4 mm isotropic. After completion of the functional scan, a high-resolution anatomical scan was carried out for co-registration. Activity during hallucinations was measured for a duration of 8 minutes, during which fMRI scans were continuously made. Subjects were instructed to squeeze a balloon when they experienced VAHs, and to release it when the hallucinations subsided. The digital output of the balloon squeezes was vulnerable to inconsistent balloon presses, and sometimes required interpretation. Subjects with over 25 % of ambiguous VAH-responses were excluded. This criterion leaded to the exclusion of nine subjects in the IVAH-group and five subjects in the EVAH-group, resulting in the 52 subjects currently studied.

2.4 fMRI data analysis

The FMRIB software library (FSL, Oxford, http://www.fmrib.ox.ac.uk/fsl) was used for data analyses. Pre-statistical processing consisted of motion correction; non-brain removal; spatial normalization to a standard Montreal Neurological Institute template based on the T1-weighted scans with high anatomical contrast; spatial smoothing using a Gaussian kernel of FWHM 8 mm; and high-pass temporal filtering (sigma = 100s). Time-series statistical analysis was carried out with local autocorrelation correction [27]. For each subject, a unique VAH activation model was created based on the VAH timings, and subsequently convolved with a gamma function to model the hemodynamic response. Registered within-scanner hallucination epochs were contrasted with non-hallucinatory epochs to obtain hallucinatory activity per subject. In order to examine the neurofunctional equivalents of the perceived VAH location, second-level effects of IVAHs (i.e., location item score 1) and EVAHs (i.e. location item score 2, 3 and 4) were subsequently contrasted. Planum temporale, middle frontal gyrus, and inferior parietal lobule regions of interest (ROIs) were used to test our hypothesis, as well as to reduce multiple comparisons. The ROIs were extracted from the Harvard-Oxford probabilistic atlas (distributed within FSL). Significance of statistical images was determined using $Z > 2.3$ to define contiguous clusters. Then a corrected cluster significance threshold of $p < 0.05$ was used for each cluster its Gaussian random field derived significance level [28]. When significant activity clusters were found using this contrast, the mean percentage signal change with regard to the baseline condition (no hallucination) were extracted from these region-of-interest (ROI) locations for all location subgroups (i.e., 1, 2, 3, and 4). The results were plotted to display the actual signal change related to the perceived location in these regions.

3. RESULTS

3.1 Subjects

Our 52 subjects were mainly medication-resistant schizophrenia patients (77%). Table 2 shows the group clinical characteristics per subject group (IVAHs or EVAHs). Statistical testing revealed a significant difference for the beliefs on the origin of the voices, indicating that voices experienced in extracorporeal space are associated with an external origin of the voices. A trend was seen for the VAH timings derived from the balloon presses, suggesting that the EVAH group had a longer total duration of the VAHs during the acquisition of scans.

Table 2 – Summary of clinical data per subject group

		Internal VAH	External VAH	Group comparison p
N		24	28	
Age		36.9 (10.7)	39.2 (10.0)	0.335
Sex	Male	71%	54%	0.258
DSM-IV diagnosis	schizophrenia	17	23	
	Schizoaffective disorder	1	1	
	Psychosis not otherwise specified	4	3	
	Personality disorder	2	1	
Chlorpromazine equivalents		321.2 (284.6)	228.0 (158.8)	0.333
VAH timings (per 480 s scan)	Average duration	7.6 (6.3)	11.6 (13.4)	0.48
	Total duration	162.6 (107.4)	113.8 (96.9)	0.071
PANSS	Total positive score	16.2 (3.6)	18.5 (4.6)	0.081
	Total negative score	17 (5.6)	18.4 (5.6)	0.359
	Total general psychopathology	31.8 (8.0)	35.3 (8.6)	0.133
	Total score	65.3 (14.4)	72.1 (15.5)	0.119
PSYRATS auditory hallucinations	Loudness	1.6 (0.7)	1.9 (1.0)	0.531
	Beliefs on Origin	2.3 (1.2)	2.9 (1.0)	0.035*
	Amount of negative content	2.5 (1.3)	3.1 (0.9)	0.198
	Degree of negative content	2.4 (0.9)	2.8 (0.8)	0.387
	Amount of distress	3.0 (1.2)	3.0 (1.2)	0.641
	Intensity of distress	2.7 (1.1)	2.8 (0.8)	0.092
	Disruption to life	2.5 (1.3)	2.6 (0.9)	0.164
	Controllability	3.0 (1.2)	3.3 (1.0)	0.296

Mean (SD). All per location group characteristics were tested using a independent samples Mann-Whitney U test (scaled variables), or a Chi-square test (nominal variables).

3.2   Verbal auditory hallucination network

Figure 1 shows a whole-group analysis of brain activity during the conscious experience of VAHs using cluster correction at Z-score ≥ 2.3 (cluster threshold) and a p < 0.05 threshold for cluster size. Multiple brain regions were involved, including bilateral inferior and middle frontal areas, bilateral insula, the anterior cingulate gyrus, and predominantly left-sided superior temporal gyrus, as well as a motor network which included left motor cortex and the right cerebellum (most likely corresponding with the balloon presses, see Methods section). The established regions of activity were in conformity with prior fMRI studies on VAHs [29-31].
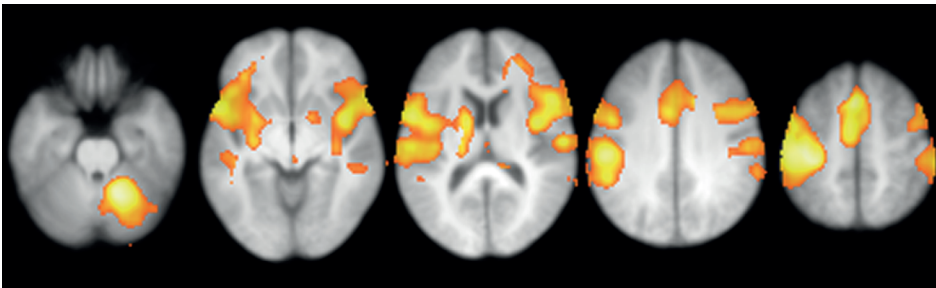

Figure 1 – Brain regions active during the conscious experience of VAHs
Functional maps were created using cluster correction at Z-score ≥ 2.3 (cluster threshold) and p<0.05 (threshold for cluster size). Axial view of mean structural subject brain in standard space at MNI coordinates z = -25, -5, 15, 35, 55. Orange-yellow color coding for VAH activity with lighter color referring towards Zmax .

3.3   Contrast between internally and externally perceived VAH location

Three ROIs were tested for a significantly higher BOLD signal strength in EVAHs as opposed to that in IVAHs (EVAHs > IVAHs), and a reverse contrast (IVAHs > EVAHs) using cluster correction at Z-score ≥ 2.3, with P < 0.05 threshold for cluster size. The EVAH > IVAH contrast produced a cluster of 45 voxels located in the medial left-sided planum temporale, just posterior of Heschl's gyrus, and a cluster of 660 voxels located in the right-sided dorsolateral prefrontal cortex and premotor cortex (see figure 2, table 3). No significant activity was observed in the inferior parietal lobule ROI for the EVAH > IVAH contrast. The three ROIs revealed no significant activity for the negative contrast (IVAH > EVAH). To further differentiate our findings, the VAH-related percentage signal change per cluster per location group was extracted for the observed clusters. Figure 3 demonstrates that the signal change is around zero percent for IVAHs, whereas EVAHs co-occur with signal increases in the listed brain regions. The brain areas not involved in the mediation of IVAHs are recruited during the exteriorization of VAHs. One subject was identified as an outlier in both the planum temporale ROI and the middle frontal gyrus ROI when applying the Chauvenet criteria on the percentual signal change of the EVAH > IVAH activation cluster (figure
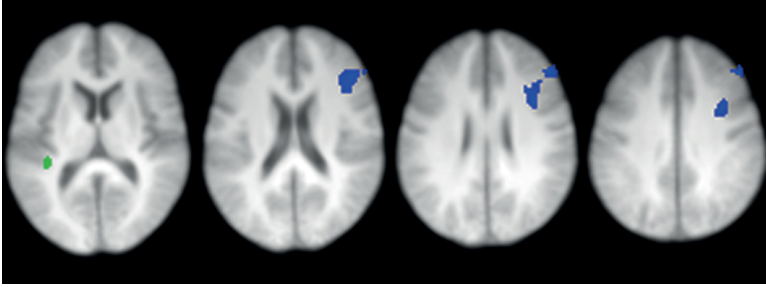
Figure 2 – Brain regions associated with the conscious experience of external VAHs
Functional maps were created at Z-score ≥ 2.3 (cluster threshold) and P<0.05 (threshold for cluster size).
Green color coding for the planum temporale ROI, blue color coding for the middle frontal gyrus ROI. Axial
view of mean subject structural brain at MNI coordinates z = 12, 20, 28, 36.

Table 3 – Brain regions EVAH > IVAH

Brain region	x, y, z	Cluster size	Z-max
L Planum Temporale (BA 22)	-37, -34, 13	45	2.89
R Middle Frontal Gyrus (BA 9)	37, 19, 32	660	3.52

Z-scores correspond to cluster center of gravity, given at stereotactic MNI-coordinates with brain regions
referring to the Harvard-Oxford probability map as distributed within FSL

3). Additional analyses with exclusion of this subject did not alter the results in any
significant manner. The PT activation cluster changed from 45 to 39 voxels, with Zmax
from 2.89 to 2.87 and the MFG activation cluster changed from 660 to 653 voxels, with
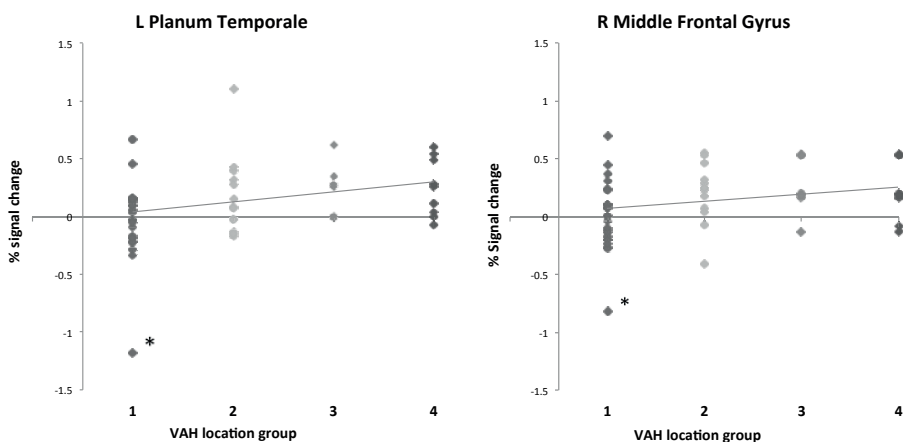Zmax from 3.52 to 3.48.

Figure 3A+3B – Percentual signal change with exteriorization of VAH
The mean percentage signal change per location group per activation cluster displays an increase with more
profound exteriorization of VAHs. Location groups refer to table 1. * outlier data point, see results.

4.   DISCUSSION

Our results demonstrate that, on a group level, external verbal auditory hallucinations and internal verbal auditory hallucinations are mediated by a fronto-temporal brain network, while exteriorization is mediated by additional activity within the auditory system's sound localization or 'where' pathway. This pathway comprises the planum temporale and dorsolateral prefrontal cortical areas [14]. The clusters of activity that we found correspond with those reported in animal [15, 22] and human studies [4, 16, 18-20, 32]. No differences were found in the inferior parietal lobule. The increase in planum temporale activity concomitant with EVAHs occurred solely on the left side, which is in concordance with simulation studies of verbal auditory hallucinations in healthy human subjects by Hunter et al. [4]. This location is congruent with the results of fMRI studies on the localization of sounds [19, 33]. As posterior superior temporal regions are thought to constitute the junction of the 'what' and 'where' pathways of the auditory system [15], we propose that the planum temporale functions as the starting point of the auditory localization pathway. Prior studies report planum temporale activity during sound location changes not dependent on attentive listening or active localization, which supports the notion of a basic spatial encoding function for this structure [16, 19]. The only study on structural brain differences underlying EVAHs and IVAHs suggests an altered anatomy of the right temporo-parietal junction (TPJ) [5]. They used voxel-based-morphometry and found a gradient from decreased white matter volume in EVAH subjects, to intermediary values for healthy controls, and increased values for IVAH subjects. In a secondary analysis they also found gradient-wise superior temporal sulcus displacements nearby the TPJ. The TPJ is in close anatomical relation with the planum temporale. Loss of function might lead to a loss of white matter at the right TPJ, or vice versa. Either way, the diminished white matter at the right TPJ by Plaze et al. [5] and the increased function of the left planum temporale found in our study might reflect the same process leading up to externalization of endogenous sounds. The study by Hunter et al. [4] applied three sound lateralization conditions (left – balanced – right) and found left planum temporale activity in all three outside-head minus inside-head conditions, with the strongest contrast in the right lateralized condition supportive of dependency of left-lateralized activitity of the PT in externalized sounds. Lastly, a recent meta-analysis of voxel-based morphometry studies examining VAHs reports left superior temporal gyrus abnormalities as most consistently associated with VAH severity [34], and altered hemispheric lateralization in those regions has been reported to be associated with schizophrenia [35]. Our results suggest the involvement of the dorsolateral prefrontal cortex (DLPFC) and premotor cortex (PMC) in the mediation of EVAHs. The DLPFC has an essential function in visuospatial working memory in primates and humans, as well as in auditory localization processing [18, 36, 37]. The

ensuing DLPFC activity found in our study may be considered the output part of the 'where' pathway, where information from different 'upstream' modalities projects onto functionally specific prefrontal neuron populations [38]. The retrieved PMC activity can either be attributed to subsequent motor planning in reaction to the perceived EVAHs, or to the representation of the motor code for verbalization of the experienced EVAHs, in conformity with the motor theory of language [36]. Prior studies have indicated that the inferior parietal lobule (IPL) may also be part of the human sound localization network [18, 20, 32, 39], but we were unable to confirm this for VAH. Lowering of the statistical threshold to $p < 0.005$ uncorrected, minimum cluster of 20 did not reveal any differences between EVAHs and IVAHs in the inferior parietal lobule ROI. An elaborated model of the auditory 'where' pathway by Rauschecker [36] postulates the IPL to function in the evaluation of a DLPFC- and PMC-derived efference copy containing motor articulations, and a posterior superior-temporal-region-derived sensory afference copy, thus allowing for an 'optimal state estimation'. In line with this model IPL activity has been found to further increase when localizing moving targets [40]. It might well be possible that prolonged episodes of uninterrupted EVAHs lead to habituation, and hence to a ceasing of optimal state estimations. It has also been argued that IPL activity may be quite specific for active sound localization tasks [16, 33]. As our experiment involved unattended sound location processing, the IPL might not acquire enough contrast.

A comparison of the clinical data revealed a difference in the attributed origin of VAHs between the IVAH group and the EVAH group. Phenomenological surveys are ambiguous on whether the perceived location of VAHs is decisive in determining the attributed origin of the voices, and it has been suggested that the duration of the illness may act as a confounder [2, 3, 41]. In our study, however, the EVAH group had a stronger belief that their voices originated from an external person or entity. The EVAH group showed a trend towards a longer duration of VAHs during scanning (33,9 % vs. 23,7 % of fMRI acquisition time). As the established clusters of activity display around zero per cent increase during the occurrence of VAHs in the IVAH group, with increasing percentage signal changes for more externally perceived VAHs, it is unlikely for said effect to be derived from a diminished power of the rest-versus-hallucination condition on the subject level.

The present study is limited by the relative difficulty to obtain suitable scans, due to interindividual anatomical differences, high within-scanner anxiety levels, and relatively large variations in hallucination frequency, duration, and non-hallucinatory intervals. However, the established group-level VAH network was in concordance with earlier studies [29, 31]. All patients were interviewed on the day of scanning, and requested to indicate the perceived location of VAHs as experienced during the three months preceding the scanning session. As a consequence, their reports may not fully

correspond with the location actually perceived within the scanner. Conversely, the reported location of VAH-related activity tends to be reliable over multiple inquiries [5, 41].
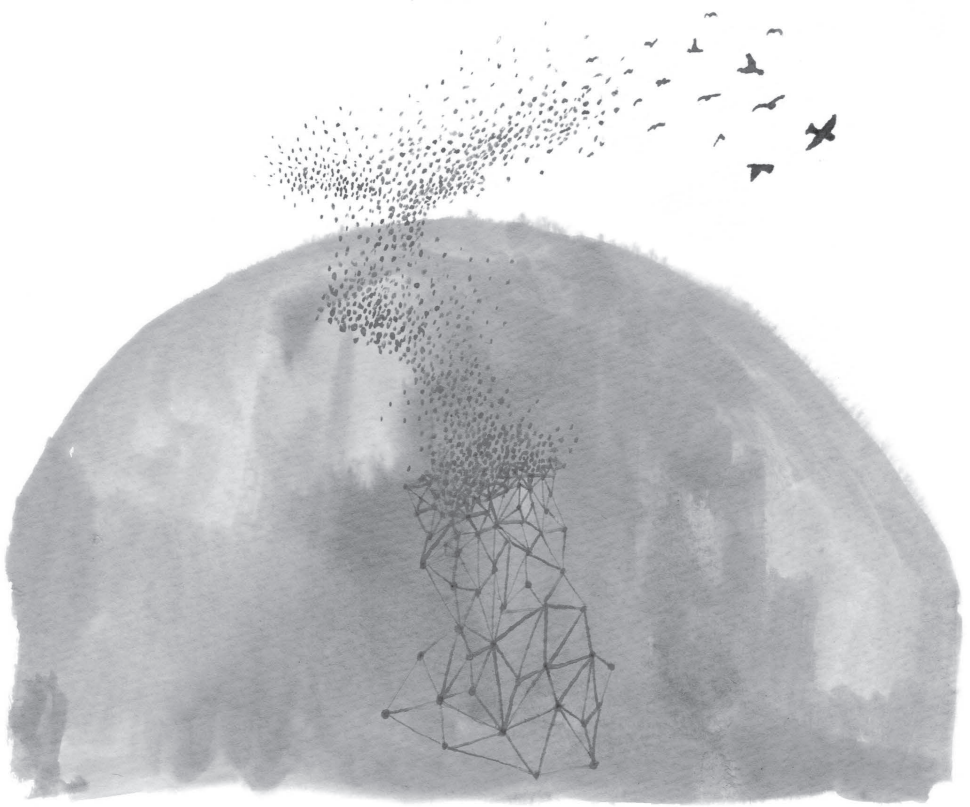
Our results support the thesis that VAHs are mediated by a fronto-temporal pattern of neuronal activity and that IVAHs are neurophysiologically distinguished from EVAHs by their lack of activity within the 'where' pathway. These results indicate that the 'where' pathway plays a crucial role in the projection of hallucinated voices into external auditory space. On the basis of those findings we advise to exert some caution in designating IVAHs as 'pseudohallucinations'. To better understand the relationships and hierarchy within the networks involved in the mediation of EVAHs and IVAHs, a next step might be to establish the functional connectivity between the various brain regions of interest, and to study the timings of brain activity within those regions of interest [42]. The use of transient lesioning with transcranial magnetic stimulation might well be capable to aid in further differentiating the position of the where pathway in the chain of neural events. Finally, we believe that future studies may well benefit from a more sophisticated method of assessing the reported VAH location in individual patients.

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Chapter 4

An integrated network model of psychotic symptoms

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ABSTRACT

The full body of research on the nature of psychosis and its determinants indicates that a considerable number of factors are relevant to the development of hallucinations, delusions, and other positive symptoms, ranging from neurodevelopmental parameters and altered connectivity of brain regions to impaired cognitive functioning and social factors. We aimed to integrate these factors in a single mathematical model based on network theory. At the microscopic level this model explains positive symptoms of psychosis in terms of experiential equivalents of robust, high-frequency attractor states of neural networks. At the mesoscopic level it explains them in relation to global brain states, and at the macroscopic level in relation to social-network structures and dynamics. Due to the scale-free nature of biological networks, all three levels are governed by the same general laws, thereby allowing for an integrated model of biological, psychological, and social phenomena involved in the mediation of positive symptoms of psychosis. This integrated network model of psychotic symptoms (INMOPS) is described together with various possibilities for application in clinical practice.

OUTLINE

1. Introduction
2. Network science
3. Network science and psychosis
4. Network models of psychosis: scale levels of organization
5. Network models of psychosis: the microscale level
6. Network models of psychosis: the mesoscale level
7. Network models of psychosis: the macroscale level
8. Conclusion
9. References

1.   INTRODUCTION

Worldwide schizophrenia is considered the most disabling of mental health conditions [1], even though its etiology, epidemiology, and nosological status are subject of ongoing debate [2-5]. For over a century the schizophrenia concept has provided a conceptual framework for clusters of psychotic symptoms that tend to have a protracted duration, but defy attribution to any known somatic condition. Bleuler [6], who introduced the term, envisaged schizophrenia as a group of disorders rather than a single nosological entity. Nevertheless, during the past century numerous attempts have been made to link this variegated group of neuropsychological symptoms to a single etiological or pathophysiological process that may serve as a common pathway and, thus, confirm schizophrenia's status as a single-disease concept. As a corollary, schizophrenia has been attributed to several biological, psychological and interpersonal mechanisms, including psychophysical degeneration [7], metabolic disorder [8], a hypothetical neurotoxin called Toxin X [9], weakness of association [10], acute infectious disease [11], deficiencies in glucose metabolism [12], double binds in social interactions [13], victimization by the nuclear family and/or society at large [14], abnormal methylation of catecholamines [15], dopaminergic dysfunction [16], genetic vulnerability [17], synaptic slippage [18], atypical language lateralization [19], prefrontal–parietal lobe functional disconnection [20], membrane lipid disorder [21], and disturbances in salience regulation [22]. However, as none of these mechanisms applies to the whole group of individuals diagnosed with schizophrenia, and many additional risk factors (including prenatal stress, maternal famine during pregnancy, cannabis use, urbanization, and social defeat) have been identified, it is now customary to conceptualize schizophrenia in terms of a neuropsychiatric disorder with multiple etiologies, multiple clinical expressions, and an (often) unfavorable outcome. Andreasen [23] summarized this general concept in her Unitary Model of Schizophrenia, and emphasized that the notion of unitarianism hinges on the presumed lathomenology – or common pathway – which connects those multiple etiologies and multiple clinical expressions.

   The repeated failure to find empirical evidence for the existence of such a common pathway has led to increasing doubt about the usefulness of maintaining schizophrenia as a unitary nosological construct (for an overview of the various positions in this debate see Blom [24] and Blom and Van Praag [3]). This has prompted a number of alternative approaches, ranging from pleas to abandon the concept altogether [25-27] to attempts at reconceptualization with the aid of different types of classification [29-30], endophenotypes [31-33] or more modest clusters of symptoms [34, 3]. While the concept's dissection with the aid of intermediate phenotypes is considered promising [35], and a proposal to link genomics to certain neural circuits may be viable in the near future [36], the conceptualization of psychotic symptoms and their interconnectedness has remained an elusive task.

1.1   Aim

Drawing on insights from network science, the present paper seeks to approach the symptoms considered characteristic of schizophrenia in a different way, i.e. by addressing different levels of biological organization through a unifying framework. Recent breakthroughs in network science allow for a mathematical representation of an unprecedented number of interacting factors in a single model [37]. We apply those insights to a substantial number of clinical, neuroscientific, and sociological findings pertaining to the origin and expression of psychotic symptoms. Rather than attempting to solve the 'schizophrenia problem' by seeking to establish its alleged lathomenology, our goal is to define a single mathematical framework and corresponding language with which to describe the large number of (neuro)biological and social factors that contribute to the occurrence of psychotic symptoms as the result of interactions between events that take place at multiple spatial scale levels of organization. The end result will be an Integrated Network Model of Psychotic Symptoms (INMOPS), which can be examined for its ability to explain and predict events that contribute to the occurrence of psychotic symptoms (Fig. 1).
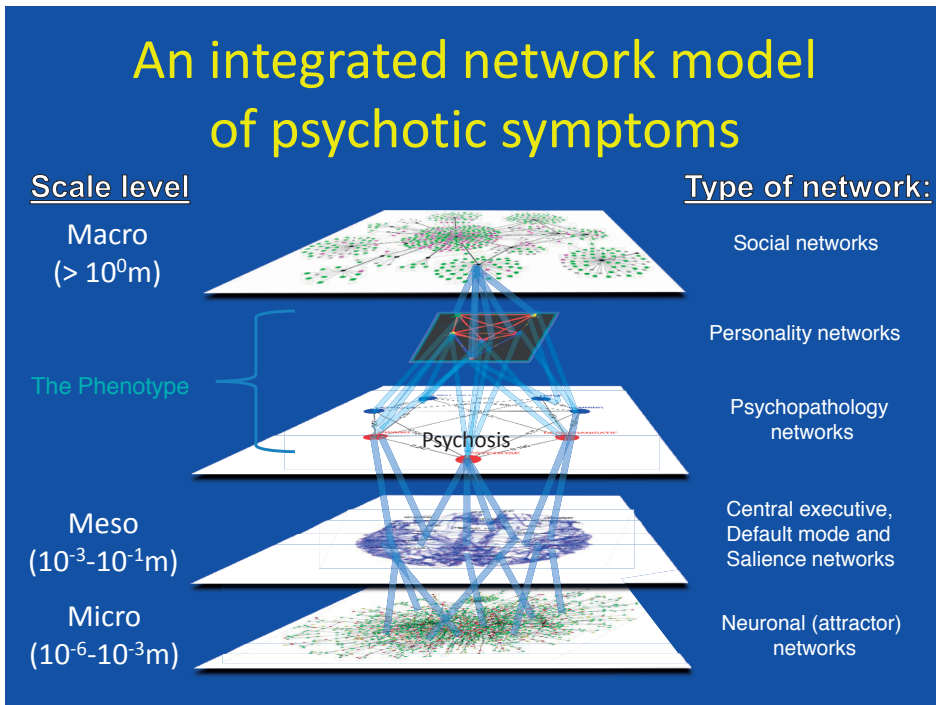

Figure 1 – An integrated network model of psychotic symptoms

An integrated network model of psychotic symptoms. The dynamic interplay between multiple scale levels of organization and their relationship to phenotypical experience is indicated by cross-connections within and between the various levels. Each level is governed by similar mathematical rules, as defined by the multimodular, hierarchic, and scale-free organization of the network as a whole. This allows for the study of psychotic symptoms in different fields of science using a single methodolody and a common (mathematical) language.

2. NETWORK SCIENCE

In mathematics, a network is a set of interconnected agents that can be identified separately in space. Within networks, agents can transfer their properties to other agents within and across different spatial scale levels of organization. Agents may be genes, for example, or proteins, which activate each other through chemical reactions; they may be neurons that fire and transfer their active state onto other neurons; they may be individual people in a social network who share ideas or emotions; or they may be companies that exchange cash flows in a global market [38]. In each case the agents and their interactions are modeled as network structures in which nodes are mutually connected through links that have a certain strength or weight (as expressed, for example, in terms of contact frequency). Throughout the 20th century, mathematicians assumed that all networks consisted of agents that were randomly connected to each other and (on average) had the same number of links. That assumption was challenged when Watts and Strogatz [39] discovered that most nodes in biological networks are not randomly connected but that most of them have few connections, while the remaining few have many (i.e., some 20 % of all nodes 'own' some 80 % of all links). The few richly connected nodes within networks are called hubs. Hubs can be compared to the center of a spider's web from whence direct access is possible to many other parts of the network. Because of the existence of hubs, each node within a network is only a small number of steps away from any other node, even when their physical distance can vary considerably. In social networks, for example, the average number of degrees of separation between all 'nodes' (people) is 5.9 ('everyone is only six handshakes away'). This plain number explains why it is not uncommon for us to meet a stranger in some distant country who turns out to be the best friend of our best friend's wife. Networks with this general topology are called small-world networks, after this peculiar phenomenon. The major hubs that connect large groups of people tend to be public figures such as school teachers, CEOs, politicians, and community center volunteers. Hubs surround themselves with large numbers of nodes and create numerous connections within their network. In this way they promote the formation of 'network communities', which are collections of nodes that are significantly better connected with each other than with all other nodes in the network [38]. Network communities can themselves be viewed as yet another set of nodes in a different network at a higher spatial scale level of organization. Thus networks may have 'superclusters' that represent 'communities of communities' which act as nodes at an even higher scale level of observation, and so on. Small-world network structures are found at all levels of biological organization, varying from molecules to cells, and from neural networks to social networks. Hence, similar network structures and corresponding mathematical rules can be found in small-world networks, regardless of the scale level of observation;

this is why such structures are called 'scale-free' (or fractal-like) network structures [40]. Human beings consist of large collections of molecules, organelles, cells (neurons), tissues, and organs. Therefore, they can be conceptualized as giant, scale-free network structures. Each spatial scale level has nodes or modules that are dedicated to the sensing of incoming information (e.g. receptors, dendrites, sensory neurons, sensory cortices), the evaluation of this information (second-messenger pathways and genes, soma of the neuron, interneurons, brain areas involved in emotional and cognitive (salience) processing), and response formation (e.g. lysosomes, the axon, motor neurons, motor cortex). Each spatial scale level is characterized by its own unique spatial dimensions (e.g. micrometers to centimeters, centimeters to decimeters, etc.) and temporal dimensions (e.g. faster or slower oscillations of activity, etc.). Thus, network science offers a common mathematical framework and language that allows us to explore human (patho)physiology at different scale levels of organization. Below, we approach the positive symptoms of psychosis from the vantage point of this general framework.

3. NETWORK SCIENCE AND PSYCHOSIS

To date, one of the most common ways to identify groups of agents that somehow belong together in a collective is principal-component analysis (PCA). In medicine, PCA allows for the detection of groups of symptoms that have a tendency to co-occur within individuals (called 'principal components'). PCA studies have shown that 'schizophrenia' consists of multiple components of psychopathological symptoms [41]. These components include 'positive symptoms' (such as hallucinations and delusions), 'negative symptoms' (such as retardation and psychomotor inhibition), and 'disorganization' (of speech, cognition, and behavior). In most individuals diagnosed with schizophrenia, these three basic components (or 'syndromes') come to expression to some significant degree. Moreover, they tend to go hand in hand with other symptom clusters, such as affective symptoms (depression, anxiety, anger), neurotic symptoms (obsessive–compulsive symptoms, phobias), cognitive symptoms (memory loss, mental retardation) or motivational symptoms such as mania [42].

Network community detection (a clustering technique based on network analysis) became available about 15 years ago. Similar to PCA, this technique allows to identify groups of symptoms (or network communities) that have a tendency to co-occur within and between patients. In psychiatry, such network communities show a large correspondence (i.e. > 90 %) with the principal components of psychopathology as established with the aid of PCA [42]. However, unlike PCA, network community detection offers an explanation of why those symptoms tend to cluster together: not by proposing an external latent variable (e.g. an etiological or pathophysiological mechanism that

may serve as its long-sought-after lathomenology), but by granting individual symptoms the status of causal agents that facilitate the occurrence of other symptoms [43]. As these causal agents have a tendency to create closed causal loops, all symptoms within a particular causal loop contribute to each other's existence. For example, increased tension levels may contribute to sleeping difficulties, which may induce fatigue, which may lead to concentration difficulties, which may lead to a proneness to errors, which may lead to actual errors, which may lead to a further increase of the tension level, etcetera. This general model of the self-organization of mental disorders is now rapidly gaining field, since it provides an explanation for the preferential connections between groups of symptoms in terms of the emergence of 'vicious circles' (or circularly causal relations) among individual symptoms [44]. A network graph of interacting symptoms of psychopathology contains clusters of densely interacting symptoms that can be readily identified as 'elementary syndromes', such as Psychosis, Retardation and Disorganization [42]. Such basic syndromes consist of vicious circles of individual symptoms of psychopathology. Interestingly, mental disorders at large (such as 'schizophrenia') can be conceptualized as vicious circles between such elementary syndromes. Regarding the elementary syndrome that we call 'psychosis' (a combination of hallucinations and delusions), this syndrome can be seen as a vicious circle in which hallucinations trigger delusional explanations which, in turn, may strengthen hallucination proneness, etcetera. Causal relationships within this syndrome may be bidirectional and involve multiple different pathways, characteristic of the elementary syndrome of psychosis.

In this paper we restrict ourselves to a review of the positive symptoms of psychosis (i.e., the elementary syndrome of 'psychosis') since these constitute the core features of all psychotic disorders. As is shown, positive symptoms and their relationships involve changes in network structure and function across many different spatial and temporal scale levels of organization within the human brain. Current estimates indicate that the human brain has at least 20 different scale levels of neural organization ('from molecules to mind') [45]. As appropriate tools to cover all these scale levels and their mutual interactions have not yet been developed, we limit our discussion of neural correlates to two global levels of organization, which we designate as the micro- and mesoscale levels of organization. Finally, we demonstrate that the principals and mathematical laws that govern events at the neural micro- and mesoscale levels of organization also govern the social level of organization, i.e., the macroscale level of organization.

4. NETWORK MODELS OF PSYCHOSIS: SCALE LEVELS OF ORGANIZATION

At the microscale level, events are described at a spatial scale level of 10^{-6} to 10^{-3} m, which is the level where individual neurons combine into neuronal networks of mi-

crometers to millimeters in diameter. At this scale level, the main task of networks is to represent the (combined) states of networks further 'upstream' in the general flow of information, to separate signal from noise, and to pass on activity to networks located further 'downstream' of the information flow [46]. Thus, a stimulus-evaluation-response network organization can be discerned already at the microscale level of organization. Within these networks, neuronal activity is a result of neurochemical changes (i.e., changes in neurotransmitter signaling pathways), changes in synaptic density and function, and (environmentally-induced) genetic expression profiles [47]. This scale level is difficult to study using in vivo techniques, whereas in vitro techniques have the disadvantage of placing the important actors (network nodes) out of their natural context. To overcome these obstacles, findings from in vivo and in vitro studies can be combined in in silico models of neuronal interaction, e.g. in computer simulations. Based on the principles of computational neuroscience, such simulations help to understand how firing patterns of neuronal populations change when, for example, different receptor types are selectively stimulated or inhibited.

Below, we discuss the ability of such in silico models to cover the correlates of positive symptoms of psychosis at the microscale level of organization.

The mesoscale level of organization has a spatial scale level of 10^{-3} to 10^{-1} m, i.e., a distance of millimeters to decimeters. The main task of these networks is to represent the milieu externe of the organism in sensory cortices, to integrate information from all sensory modalities and information with an emotional or cognitive content, to evaluate these data streams in terms of salience, to develop motivational drive, to facilitate response selection (executive functioning), to execute premotor planning, and to generate motor output. Thus, a stimulus-evaluation-response loop can again be observed at the mesoscale level of organization. Network activity at this level is the net result of events taking place at all lower levels of neurobiological organization. The mesoscale level can be studied in vivo using structural and functional magnetic resonance imaging (MRI and fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). Since MRI has a spatial resolution superior to that of EEG and MEG we focus mainly on MRI findings (although EEG and MEG findings are also briefly mentioned).

Finally, we briefly address the social environment as the macroscale level of organization, since studies on the composition of social networks show that this level is also relevant for the development of positive symptoms of psychosis [48]. Like neural networks, network communities in social networks develop through a process of self-reinforcement and suppression of neighboring communities. Information pertaining to the external world is shared among individuals, evaluated, and acted upon in a way that is similar to the way information is processed at the network's lower levels of organization. We demonstrate that such processes may contribute to psychotic symptoms in their own idiosyncratic ways.

5. NETWORK MODELS OF PSYCHOSIS: THE MICROSCALE LEVEL

Currently, one of the most sophisticated network models of the neurobiological correlates of psychotic symptoms at the microscale level stems from Loh et al. [49]. Their work starts from the central premise that the neural correlates of percepts can be described in terms of firing patterns of individual neurons within perception networks, and that those firing patterns display certain specific frequencies and amplitudes. Taking visual perception as an example, light reflected from an object in the extracorporeal world (say, a tree) activates retinal cells which, after a cascade of intermediary processes, recruit a particular subset of neurons in primary visual cortex that respond selectively to the various subcomponents of this stimulus (e.g. texture, color, movement). In conformity with the adage 'neurons that fire together, wire together', repeated exposure to similar objects leads to a strengthening of the synaptic connections between the cells of this ensemble through long-term potentiation (LTP) [50]. Thus, preferential connections are created between the neurons within this particular subset of neurons in visual cortex, yielding what we might call – in this case – a 'tree network'. Such higher-order representations (leaves, branches, bark, etc.) are formed in secondary visual cortex. When there is no tree present in the percipient's visual field, the tree network is at rest because it receives no dendritic input. When there are only leaves to be perceived, parts of the tree network may become activated (i.e., those involved in the coding for leaves), but the remainder of the network will remain at rest and no tree will be perceived. Only when the dendritic input reaches a critical threshold (i.e. when the input picture comprises essential parts such as bark, branches, and leaves), will the network be triggered in such a way that it mediates the perception of a tree. Incidentally, not all parts of the tree need to be present in the visual field in order for the tree network to respond in its entirety. When the input picture consists of a sufficiently large number of tree-like elements, the remainder of the tree network is activated as a form of 'pattern completion', which facilitates the perception of a tree. As soon as this particular network is activated by dendritic input, it passes its activity on to higher-order processing networks further downstream of the flow of information processing. Meanwhile, excitatory connections that emanate from the neurons of the tree network loop back to themselves and engage in auto-excitation (Fig. 2). Such positive feedback loops help to maintain an active state within the tree network, thus allowing for the creation of a stable percept and facilitating its storage in memory. In addition, the tree network stimulates inhibitory interneurons that connect to neighboring neurons not implicated in the tree network, thus helping to suppress any percepts for which there is insufficient support in the perceptual input picture (i.e., 'noise'). Thus, neighboring perceptual networks are in a constant state of competition to represent external signals (Fig. 2).
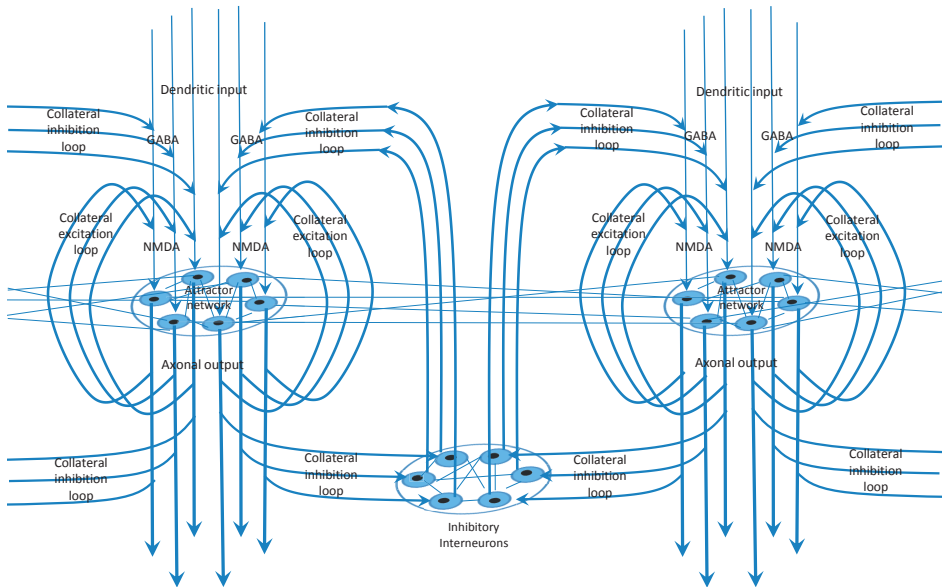
Figure 2 – Network structure of an attractor network

Network structure of an attractor network. Two attractor networks are shown that are interconnected into a larger network. Dendritic input selects a subpopulation of neurons that constitute the attractor network for that particular stimulus. Excitatory (NMDA-related) output loops back onto the dendritic input connections, thus causing a self-perpetuation of attractor activity. Excitatory output also connects to (GABA-ergic) interneurons, which loop back to the dendritic input connections of all surrounding neurons whose activity is subsequently inhibited. Thus, attractor networks compete for activity by promoting the persistence of their own attractor states and suppressing activity in neighboring attractor networks. This is Nature's way of selecting those attractor states for which there is most 'empirical support'. Neuromodulatory neurotransmitters can shift the balance between noise suppression and auto-excitation (change signal-to-noise ratios), thereby allowing biases in the perception of particular stimuli. Dopamine 2 antagonists enhance collateral inhibition (noise reduction) by enhancing GABA-ergic neurotransmission, whereas Dopamine 1 agonists enhance auto-excitation by facilitating NMDA-receptor-mediated neurotransmission, thereby increasing the robustness of the attractor state (or signal). This network model is so generic that it can be used to describe attractor states at multiple levels of biological organization (i.e. the micro, meso and macrolevels described in this paper).

5.1 Attractor networks and energy landscapes

In network science, networks that encode for particular percepts – such as the tree network – are known as attractor networks [49]. Attractor networks are networks characterized by a more or less pronounced attractor state, which is a preferential (low energy) state toward which the network tends to converge by default. Regardless of its initial state, the network will eventually settle for that particular state. The attractor state is a function of the strength of the network's own synaptic connections, formed during prior episodes of learning (synaptic rewiring). In other words, the attractor state represents the information that has been stored in the network (e.g. a percept). Depending on the amount of energy that is applied to the network (e.g. intrinsic noise levels or dendritic stimulation), all brain networks have lower- and higher-energy at-

tractor states. The effect of this can be further clarified by picturing a ping pong ball which has been moved uphill by applying energy to it (Fig. 3). When enough energy is applied to push it to the top, it can settle for a higher-energy stable (attractor) state. When insufficient energy is applied, the ping pong ball has no other option than to settle down in the valley at the foot of hill and assume a lower-energy stable (attractor) state. The tiny amount of energy needed for the network to assume this low-energy 'resting state' is provided by random depolarizations within the network itself (i.e., internal noise) and sustained by the absence of any external signals. Such low-energy resting states are characterized by low-frequency firing patterns that display a certain lability due to the fact that there is only little auto-excitation (Fig. 2). In perceptual networks, that activity may induce weak, fleeting percepts such as those characteristic of daydreaming, hypnagogia or actual dreaming. When more energy is applied in the form of dendritic input, networks will shift from their labile, low-energy attractor states to robust, high-energy attractor states with high-frequency firing patterns and the subsequent formation of robust percepts [49].

5.2 Psychosis at the microscale level of organization

5.2.1 Healthy individuals

In the idiom of network science, positive symptoms of psychosis are conceptualized as the experiential equivalents of robust, high-frequency attractor states that occur in the absence of adequate dendritic input. In other words, positive symptoms arise when perceptual or cognitive networks enter their high-energy attractor state when all they should do is remain in their low-energy attractor state. Several mechanisms have been proposed for this switching from true-negative (low-energy) to false-positive (high-energy) attractor states [51]. To illustrate these mechanisms, Fig. 3 provides a schematic illustration of network activity in an energy landscape. In this scheme, attractor states are represented as valleys or attractor basins in the landscape. When the differences in energy between the resting and active state are less pronounced, i.e., when the attractor basins are shallow, the transition from a low-energy resting state to a high-energy active state is achieved more easily.

The shallowing of attractor basins can occur under various conditions. In healthy subjects, a well-known example is sensory deprivation. As demonstrated in numerous experiments during the 1950s through 1970s, the depatterning and deprivation of sensory information tends to evoke hallucinations in healthy participants within 24 hours [52]. Such an extreme sensory disconnection from the external world corresponds with a lack of dendritic input and, hence, in a low-frequency firing rate of the attractor network and an increased likelihood of that network to roam the resting-state basins of the attractor landscape. Experientially, this is associated with weak perceptions of a fleeting nature since the lack of auto-excitation prevents the formation of strong and
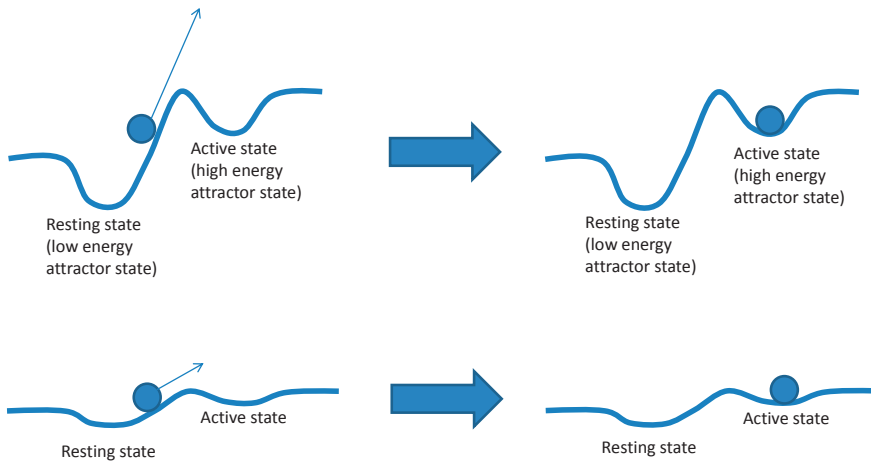
Figure 3 – State transitions in attractor networks, as visualized in an energy landscape
State transitions in attractor networks, as visualized in an energy landscape. When at rest, each network is in a stable, low-energy state (e.g. a pingpong ball at the bottom of the valley, or a coin lying flat on the ground). When energy is applied to the network (i.e. dendritic stimulation occurs, or noise levels rise within the network itself), the network as a whole may enter another stable state at a higher energy level (e.g. a ping pong ball that has has been moved uphilll by some force and settles in a valley at the top, or a coin that is dropped onto the ground and starts to roll on its side). When the valleys in the energy landscape become shallower (lower two drawings, see main text for presumed mechanisms), differences in energy levels between active and resting states decrease, and only little energy (e.g. noise or dendritic stimulation) suffices for the network to make the transition from its resting state (e.g. true-negative perception) to its active state (i.e. false-positive perception or hallucination).

robust firing patterns (and, hence, the mediation of strong and robust percepts). Additionally, a lack of collateral inhibition (due to a lack of competing stimuli) decreases noise suppression and renders the network susceptible to any newly emerging stimuli. Individual neurons and neural networks at large have thresholds to prevent them from being accidentally activated, e.g. by low-intensity noise fluctuations. In the absence of high-energy stimuli, the neurons in the attractor network tend to lower their thresholds (e.g. to adapt to low stimulus intensities in a dark room). This process, known as neural adaptation [53], leads to a shallowing of the attractor basins of the active as well as the resting state. Once this is achieved, even small amounts of energy will suffice to make the network switch from its low-energy resting state ('down in the valley') to a high-energy active state ('further uphill'). In the absence of any external stimuli, the energy needed for this 'uphill' trajectory in the energy landscape can be supplied by random depolarizations of the network itself (i.e., 'noise'), or by low-intensity dendritic input provided by any of the neighboring attractor networks that have crossed their thresholds of activation for similar reasons [54]. As a consequence, robust percepts are formed in the absence of corresponding external stimuli. These robust percepts may induce the activation of other sensitized networks, thus producing a chain reac-

tion of false-positive state transitions. When such state transitions occur in perceptual cortices, the individual experiences hallucinations. Similarly, when these events take place in higher-order cognitive brain regions, they evoke delusions.

5.2.2 Patients with psychosis

In psychotic patients, less extreme conditions than sensory deprivation suffice to produce hallucinations. Rolls et al. [55] explain this by linking the dynamics of attractor networks to deficiencies in gamma-aminobutyric-acid (GABA) and N-methyl-d-aspartate (NMDA) signaling found in patients diagnosed with schizophrenia [56-59]. Biochemically, the dynamics of attractor networks depends on specific neurochemical substances. Their positive feedback loops are created with the aid of NMDA-receptor activation by the excitatory neurotransmitter glutamate (Fig. 2). Reduced NMDA conductance reduces the robustness and firing rate of the active state, thus leading up to a shallowing of the attractor basins for this state [49]. Collateral inhibition and noise reduction depend on GABA-receptor activation by the inhibitory neurotransmitter GABA [60]. Therefore, GABA interneuron inefficacy will yield a decrease in the suppression of competing signals as well as a disinhibition of the resting state, both of which contribute to the shallowing of the attractor basin of the low-energy resting state. Thus, the resting and active state start to resemble each other in terms of energy levels, which facilitates transitions between the two states. As a consequence, a network with these characteristics will display loose and erratic jumps between low-frequency resting states and high-frequency active states [49, 61]. Experientially, these unanticipated state switches in human neocortex translate to the switching on and off of hallucinatory and delusional states.

Further support for the attractor network model comes from the elevated ratios of D2 versus D1-dopamine receptor activity found in prefrontal cortex in groups of patients diagnosed with schizophrenia [62]. Throughout the human brain, basic excitatory and inhibitory signaling is modulated by neurotransmitters such as dopamine, (nor)adrenaline, serotonin, and acetylcholine. In attractor networks, these neurotransmitters shift the balance between NMDA-related and GABA-ergic signaling, thus producing shifts in signal-to-noise ratios (SNRs). Dopamine changes SNRs in favor of noise production by reducing GABA-ergic collateral inhibition, thus promoting the occurrence of hallucinations and delusions. Since chain reactions may occur in labile or sensitized attractor networks and only parts of these networks need to be triggered in order for it to engage in pattern completion, GABA-ergic and glutamatergic changes in patients diagnosed with schizophrenia may principally underlie loose associations. Clinically, this may manifest as 'jumping to conclusions', meaning that patients show a tendency to link the occurrence of one event (e.g. their car breaking down) to another one (a visit from their mother) and, without much delay, assume that, for example, she must have been the one who sabotaged the car.

Similar to dopaminergic activity, noradrenergic stimulation (induced, for example, by stress) induces shifts in the SNR in favor of the false-positive detection of noise. The mechanism behind this involves a decrease in both GABA-ergic collateral inhibition and glutamatergic collateral excitation [63]. A possible reason for this is that stressful conditions require our perceptual and cognitive networks to be biased toward the false-positive detection of rivals, predators, and other threats. From the vantage point of evolution, this type of bias has important benefits for survival since it allows to minimize the false-negative detection of actual threats (e.g. not seeing a tiger when there is actually one there) at the cost of false-positive threats (i.e. hallucinations and delusions). In individuals whose attractor networks are already susceptible to false-positive states, these mechanisms increase the chance of experiencing hallucinations and delusions; this happens to many psychotic patients under stressful conditions.

Thematically, delusions and hallucinations can be valued positively or negatively by the person experiencing them and, in the general population, are indeed valued positively by a significant number of people [64]. However, in clinical populations many of those experiences involve situations of a threatening or otherwise frightening nature. This preference for negative stimuli again seems to involve a detection bias for rivals, predators, and other threats. In that sense, hallucinations and delusions can be regarded as an unfortunate price that is paid by some individuals for a critical survival mechanism [65, 66]. Interindividual variation in this detection bias will cause some people to show an extreme sensitivity to such stimuli, especially under stressful conditions. Normally, alterations in dopaminergic and GABA-ergic functioning reach a climax in early adulthood [67]. Together with the fact that stress levels (and hence noradrenergic activity) peak in early adolescence [68], this may explain why the onset of psychosis-proneness tends to commence at this relatively early age.

5.2.3   Microstructural and genetic changes in psychosis

Apart from neurotransmitter concentrations, the dynamics of attractor networks at the microscale level of organization are also influenced by microstructural changes in the number and quality of synapses. It is suggested that the basis for psychosis-proneness is laid during the gestational period, even though the clinical signs of psychosis tend to become manifest no sooner than in late adolescence [69]. It has been shown that the brains of healthy adolescents undergo massive pruning of (primarily) excitatory synapses (in conformity with the 'use it or lose it' principle) [70, 71]. Due to this process, the loss of excitatory NMDA-ergic synapses tends to be more substantial in adolescents diagnosed with schizophrenia than in age-matched controls [72]. The concomitant decrease in (auto)excitation of attractor networks might contribute to the instability of internal representations, and to the proneness of these individuals to hallucinations and delusions at a later age. Another factor that affects connectivity at the microscale

level is the use of cannabis which, apart from the direct effects of its active compound tetrahydrocannabinol (THC) on neuronal signaling, affects the outgrowth of synaptic terminals [73-75]. The question why some individuals develop psychotic symptoms due to cannabis whereas others do not, is probably best answered with reference to inter-individual differences in synaptic density and expression levels of the cannabinoid receptor. In individuals who have a local excess of synaptic connections, a tipping point may be reached under the influence of THC, thereby increasing the likelihood for psychotic symptoms to set in. Similarly, hallucinogens and other psychotogenic substances may alter neurotransmitter levels in attractor networks in favor of false-positive attractor states, and thus facilitate the mediation of positive symptoms of psychosis.

Another group of factors that may alter connectivity at the microscale level are immunocytochemical changes, which may interfere with neuronal signaling at the receptor level and with synapse formation at the microstructural level [47]. This may tilt the balance of SNRs within attractor networks toward producing false-positive perceptions. A final factor that deserves to be mentioned in this context is histone methylation, the microbiological process that bridges the gap between environmental stress and levels of genetic expression (i.e. epigenetic changes). Extremely stressful events (e.g. psychotraumata) may cause particular genes to switch on or off through histone methylation, leading to more or less permanent changes in gene expression profiles (e.g. profiles compatible with an enhanced alertness to stressful stimuli). In accordance with the hostile environment in which such changes take place, acquired changes in genetic expression levels shift SNRs in attractor networks in favor of the early detection of such threats; again, the experience of positive symptoms is the price that is paid for an increased ability to pick up true-positive threats [65, 66].

5.2.4 Clinical lessons from the microscale level

The number one evidence-based treatment option for psychotic symptoms at the microscale level is the administration of D2 antagonists (i.e. 'antipsychotics'). In psychotic patients these substances increase GABA-ergic currents [76], thus correcting GABA-ergic deficiencies and suppressing noise levels in networks surrounding the attractor network. As a result, attractor networks become more resistant against switches from low-energy (true-negative) resting states to high-energy (false-positive) persistent states. In theory, the administration of D1-receptor agonists (e.g. psychostimulants such as methylphenidate) should be able to produce deeper attractor basins of the persistent state, since these substances increase NMDA-mediated auto-feedback within attractor networks [55]. This prevents the occurrence of state switches from high-energy to lower-energy attractor states and helps produce more robust percepts, which is the basic aim of psychostimulant treatment in patients diagnosed with attention-deficit

(hyperactivity) disorder (AD(H)D). This hypothesis also explains why methylphenidate monotherapy should not be prescribed for AD(H)D patients with comorbid positive symptoms of psychosis, since this might lead to default stabilization of their hallucinations and delusions. Since beta-adrenergic stimulation decreases GABA-ergic noise suppression and facilitates the formation of false percepts in already vulnerable attractor networks, psychotic symptoms may also be reduced by prescribing either direct GABA-ergic agonists (i.e., benzodiazepines) or beta-adrenergic antagonists (beta blockers).

To summarize, a simple model of excitation, inhibition, and modulation within interconnected attractor networks allows to explain various psychotic phenomena, to provide a rationale for conventional anti-psychotic interventions, and to facilitate the exploration of novel interventions. The agents in this model are brought off balance by an array of different processes, globally involving neurochemical, neuroinflammatory, microstructural, and (epi)genetic alterations, whereas therapeutic interventions target these global pathogenetic pathways by shifting SNRs within the attractor networks back from false-positive to true-negative values.

In the following sections, we connect this state of affairs at the microscale level of organization with those occurring at higher-scale levels of organization.

6. NETWORK MODELS OF PSYCHOSIS: THE MESOSCALE LEVEL

6.1 Structural and functional connectivity

Until about a decade ago, voxel-based morphometry (VBM) of structural MRI data was among the most popular in vivo neuroimaging techniques used to localize brain areas in which gray-matter volume (GMV) correlated with some variable of interest (e.g. task performance or positive symptom scores). Similarly, diffusion tensor imaging (DTI) was used to relate local differences in white-matter tract integrity to certain variables of interest [77]. Most functional MRI studies involved the localization of discrete brain areas in which activity markers such as the Blood Oxygenation-Level Dependent (BOLD) response correlated with phenotypical markers. During the past decade, this non-relational approach gradually made place for a relational (network-based) approach. This development was largely made possible by methodological advances and the discovery of small-world networks (outlined above). From the perspective of network science, 'alterations in GMV' can be regarded as 'changes in network nodes', whereas 'local changes in white-matter-tract integrity' can be regarded as 'changes in network links'. Brain connectivity studies traditionally distinguish between two types of connectivity, i.e., structural, and functional connectivity [78]. Structural connectivity can metaphorically be compared to the actual glass-fiber cables that allow for

information exchange across the World Wide Web, whereas functional connectivity is comparable with the links between .html pages on the Internet. Such pages may link directly to each other, even though several servers and routers can be involved in connecting the actual computers on which the pages are stored. Thus, structural-connectivity studies focus on the actual white-matter tracts that run between different areas of gray matter, whereas functional imaging techniques such as fMRI, EEG, and MEG are used to study statistical associations between the neurophysiological states of gray-matter regions that may be located various structural degrees of separation apart from each other. Since network studies examine relationships between brain areas rather than individual brain areas themselves, current neuroimaging studies allow to explore structural and functional correlates of positive symptoms at an unprecedented level of integration.

Previous studies show that both structural and functional connectivity maps are characterized by a small-world and scale-free topology [78]. As a consequence, the human brain at the mesoscale level of organization seems to display the same general network architecture as the attractor networks rendered in Fig. 1. However, a major difference is that, in this case, the neurons in Fig. 1 do not represent single cells but rather substantial clusters of gray matter. The structural connections between these clusters of gray matter are not formed by single axons, but by white-matter fiber tracts that can be visualized in vivo with the aid of neuroimaging techniques. Functional connections, on the other hand, consist of statistical relationships between activity levels in these areas. In comparison with neural networks at the microscale level of organization, connectivity maps at the mesoscale level of organization involve highly integrated and multimodal brain states that correspond to full-blown mental representations. Sensory cortices provide integrated representations of the organism's milieu externe, medial temporal and limbic structures integrate information from the sensory domains with emotional and cognitive information, medial prefrontal (anterior cingulate) and (dorsal) anterior insular regions have a function in salience detection regarding this data stream, striatal structures are involved in developing motivational drive and initiating automatic response patterns, and dorsolateral prefrontal areas are involved in effortful response selection and conscious executive functioning, while the actual planning and execution of motor output takes place in prefrontal (premotor) and motor cortices [79]. Together, these processes are referred to as 'cognitive control'. Three canonical networks can be distinguished within the set of brain regions involved [79]: the central executive network (CEN) is predominantly active during the execution of goal-directed task performances, and relies on dorsolateral prefrontal and posterior parietal areas. As soon as individuals cease to perform in a goal-directed manner and engage in a state of quiet wakefulness (i.e., with eyes closed, but awake), activity levels within the CEN drop to a minimum whereas activity levels in a set of brain

regions comprising the default-mode network (DMN) show a simultaneous increase. The DMN comprises medial prefrontal regions, posterior cingulate, dorsal parietal regions, and mediotemporal regions. Activity within these regions is associated with mind-wandering, fantasizing, musing, autobiographical recollection, daydreaming, and actual dreaming [54]. Finally, anterior cingulate and (dorsal) anterior insular regions are part of a so called salience network (SN), which has a key role in salience detection and in switching between goal-directed CEN activity and reflective DMN activity. The CEN, DMN, and SN appear to be of crucial importance in the pathogenesis of positive symptoms [80]. Below, we discuss the current neuroimaging literature on psychosis from the perspective of structural and functional connectivity studies involving these networks, whereas the results of VBM and DTI studies are discussed only in relation to changes in network nodes and links as reported in connectivity studies.

6.2 Structural connectivity and psychosis

Whole-brain structural connectivity maps of patients diagnosed with schizophrenia show a reduction of values of small-worldness parameters. Some examples include the loss of frontotemporal and insular hubs, the emergence of novel non-frontal hubs [81, 82], a lowering of the clustering coefficient [83-84], the randomization of connectivity [81, 85], increases of path lengths, and the reduction of interregional connectivity [86]. The loss of frontotemporal and insular hubs may correspond with previous VBM findings involving the loss of GMV in medial prefrontal, (superior) temporal, insular, thalamic, striatal, and cerebellar regions [87-94]. Similarly, the emergence of novel hubs may correspond with previous findings of an increased GMV in areas associated with delusion-proneness [95-97]. An increase in the randomness of wiring patterns may explain the inconsistency of previous DTI findings in patients diagnosed with schizophrenia, varying from a global decrease in white-matter-tract integrity associated with 'schizophrenia' [98] to decreases specifically associated with verbal auditory hallucinations, in the white-matter-tract integrity of medial prefrontal areas [99-101], medial temporal areas [102], and the superior and inferior longitudinal fasciculus [103-107]. Most of these findings involve the loss of prefrontal connections, which corresponds with the loss of important hub regions in the same areas found in patients diagnosed with schizophrenia.

Generally speaking, a loss of small-world topology is associated with a decrease in the quality and efficiency of information processing which is, in turn, experienced as a slowing-down of cognitive abilities and processing speed. Regarding alterations in specific brain regions, a loss of frontal hubs seems to be associated with a reduced capacity for integration, abstraction, and creation of overview [82]. Reduced integration is thought to result in the loosening of cognitive associations, a symptom historically marked as a core feature of schizophrenia [6, 20]. The central role of the anterior cingulate and (anterior) dorsal insular region in salience detection has sparked the hypothesis

that decreased GMVs within these frontal areas may lead patients to attribute en-hanced salience to sensory events and erroneously attribute endogenously mediated percepts to external sources [108-110]. The dissolution of higher-order (prefrontal) clusters may reduce collateral inhibition by competing attractor states, thus leading to a disin-hibition of lower-level clusters and, ultimately, the mediation of hallucinations and/or delusions [81]. In addition, a loss of hubs may interfere with the ability to discriminate between stimuli and concepts [111]. Such changes may also promote the aforementioned 'jumping to conclusions', whereas increased randomness of anatomical connections – possibly the result of the excessive pruning of synapses [112] may promote bizarre delu-sions and hallucinations.

Finally, the network structure of psychotic symptoms at the phenotypical level indi-cates that hallucinations may simply trigger delusional explanations of these percepts (a bottom-up genesis of delusional activity). There is also evidence for the reversed causal direction, i.e., delusions triggering hallucinations in a top-down manner. In the latter case, higher-order conceptual regions may enhance selective attention (i.e. alertness) to particular stimuli, such as facial expressions or policemen in the street. Such top-down effects involve increased dopaminergic and adrenergic signaling within primary sensory cortices [65, 66, 113], which may shift SNRs in favor of false-positive at-tractor states.

6.3   Functional connectivity and psychosis

Changes in functional connectivity maps in psychotic disorders resemble those in structural connectivity maps to a considerable degree [37]. Again, a loss of small-worldness parameters can be observed in terms of increased randomness of (frontal) connectivity patterns [114] and a loss of frontal hubs. Since functional connectivity is thought to lie closer (process-wise) to phenotypical experience, the study of functional connectivity may yield important information on the origins of the psychotic pheno-type. Functional connectivity studies typically examine associations between scores on phenotypical markers and connectivity maps calculated across various different brain states that globally involve central executive, salience-related, and default-mode states. As observed above, these global networks are differentially activated during wakeful and sleeping states of the human brain (with a preference for DMN activity during dreaming and CEN during active task performance). Since positive symptoms by definition occur during wakefulness, we limit our discussion of mesoscopic changes in psychosis to functional connectivity maps during the wakeful state.

Due to the scale-free nature of the network that constitutes the human brain, similar rules apply at different scale levels of organization. Starting from that general principle, the CEN and the DMN are conceptualized as giant attractor networks at the mesoscopic level of organization that are in a constant state of mutual competition. The CEN is en-

gaged in auto-excitation during task performance, while suppressing the activity of the DMN through collateral inhibition. The reverse happens when the individual enters a state of quiet wakefulness (not to be confused with the 'resting state' of microscale-level attractor networks), and the DMN in turn gears up from its low-energy resting state to a high-energy active state. In this state, the DMN engages in auto-excitation and in collateral inhibition of the CEN. Crucially, the salience network (dorsal anterior insula and anterior cingulate cortex) is responsible for biasing the competition between DMN and CEN activity levels [79]. In psychotic disorders, both auto-excitation and collateral inhibition are impaired. Comparable to what happens at the microscale level of organization, this leads to the formation of instable percepts during active states and to insufficient suppression of noise in competing (resting state) networks. At the mesoscopic level of organization, this combination of an increase of noise levels and a decrease of the resistance against intrusion by noise, facilitates the mediation of false percepts. Therefore, on the one hand, positive symptoms may be due to insufficient suppression of (noise generated by) the DMN during task performance. Additionally, a decrease in auto-excitation of the CEN will render this network more susceptible to noise intrusions from the DMN. Once DMN activity 'overrules' the already labile CEN, it becomes manifest at the experiential level in the form of clear, consciously experienced delusions and/or hallucinations of a multimodal, integrated, and complex nature. In this sense, psychosis is comparable to a state of 'dreaming-while-awake', or a blending of endogenously and exogenously mediated representations. On the other hand, the activity of the DMN is also labile [115] and, therefore, susceptible to intrusions by insufficiently suppressed noise generated by the CEN. Experientially, such CEN intrusions into the DMN may produce a phenotype where actual events are experienced as unreal or dreamlike, as in derealization or depersonalization. Moreover, noise generated by the CEN that overrules the DMN may provide the neurophysiological correlate of delusions of control.

In summary, insufficient noise suppression and increased susceptibility to noise intrusions within both the CEN and the DMN network may promote the blending of information processing between these two anticorrelated networks and mediate specific positive symptoms of psychosis. We will first discuss evidence for the hypothesis that network states spill over from the DMN to the CEN. After that, we will discuss the evidence for psychotogenic mechanisms in the opposite direction.

Various observations seem to confirm the hypothesis that an excess of DMN noise is responsible for the emergence of positive symptoms. For instance, insufficient suppression of DMN activity during task performance is a common finding in patients diagnosed with schizophrenia [116-119]. This indicates that these patients may be more susceptible to noise intrusions originating from the DMN, experienced by them in the form of hallucinations and/or delusions [115]. Additionally, administration of ketamine

(a NMDA receptor antagonist) induces hyperconnectivity within (i.e. increases the robustness of activity within) the DMN, which is associated with the severity of positive symptoms induced by this substance [120]. DMN hyperactivity is most likely due to a net decrease in GABA-ergic signaling. This decrease may involve an isolated neurochemical deficiency, or a structural loss of fronto-temporal (inhibitory) hubs observed in schizophrenia. Indeed hypoconnectivity of (inhibitory) anterior cingulate and (dorsal) anterior temporal regions is specifically related to hyperconnectivity within auditory cortex in general [101] and the occurrence of verbal auditory hallucinations in particular [121, 122]. Reduced input from speech perception areas, such as Wernicke's, to frontal areas such as Broca's, as established with measures of effective connectivity in hallucinating patients [123], may be analogous (at the mesoscale level of organization) to the sensory-deprivation effect described earlier in this paper. The loss of frontal (inhibitory) hubs in schizophrenia to a large degree involves the salience network, which is responsible for biasing the balance between DMN and CEN activity levels. The salience network (SN) can therefore be conceived as the meso-scale equivalent of the GABA-ergic interneurons shown in Fig. 2, which has a modulatory influence on both attractor networks (CEN and DMN). Thus, a loss of frontal hubs may impair GABA-ergic noise suppression of the DMN, which 'jams' the CEN with noise that is experienced actively and consciously in the form of hallucinations or delusions. The role of the predominantly dopaminergic salience system in appraising and balancing DMN and CEN activity is in line with the dopamine hypothesis for the mediation of psychotic symptoms [124]. A disconnection between prefrontal cortex and hippocampus during (working-memory) task performance has been linked to the severity of positive symptoms [125]. In the latter situation, hippocampal activity is insufficiently suppressed. Such findings have given rise to the memory hypothesis of hallucinations, which states that hallucinations at least partly represent insufficiently suppressed memories [98]. Since hippocampal regions are part of the DMN, the memory hypothesis fits the global picture of insufficient noise-reduction in DMN areas as a precondition for the occurrence of positive symptoms. Moreover, various studies have shown that losses of prefrontal function are associated with increased activity within auditory areas of the temporal lobe and the experience of verbal auditory hallucinations [109]. Since these regions are part of the CEN, such findings fit the notion that aberrant DMN activity eventually overrules the CEN, resulting in the active and conscious perception of hallucinations.

  All the findings discussed so far are in line with the notion of insufficient collateral inhibition of the DMN by the salience network and CEN, as well as with the notion of increased susceptibility of the CEN to noise intrusions due to a lack of auto-excitation and the resulting instability of its neural activity patterns. However, as indicated, the reverse causal direction is also possible, i.e. positive symptoms of psychosis being due to a disinhibited CEN and instability of DMN activity patterns, possibly mediated by

a dysfunctional salience network. Various empirical observations support this mechanism. Jardri et al. [108] studied the spatial and temporal stability of the DMN and association sensory cortices during hallucinatory episodes, and found that instability of the DMN correlates positively with the severity of hallucinations. Similarly, increases in DMN variability have been described by Garrity et al. [116], while a loss of local connectivity within anterior and posterior cingulate subclusters of the DMN correlates with positive symptom scores [126]. Rotarska-Jagiela et al. [101] report reduced internal DMN connectivity (i.e. instability) in right inferior parietal cortex and the left hippocampus in association with hallucinations and delusions. Thus, disinhibition of the CEN also seems capable of mediating positive symptoms of psychosis. So far, however, most studies show hyperconnectivity as well as reductions of path length in the DMN [96, 127, 128], which suggests that the instability of the DMN is less pronounced than that of the CEN. As a corollary, positive symptoms of psychosis may be primarily associated with DMN noise affecting the CEN (a bias that may be the result of impaired functioning of the salience network), which is in conformity with the dreaming-while-awake hypothesis. However, other networks may also be relevant, such as the salience network and the amygdala [129, 130], which deserve more detailed examination in future studies.

In conclusion, the mechanisms that govern the mediation of psychotic symptoms at the mesoscale level of organization seem to resemble those at work at the microscale level of organization. Moreover, at all levels of organization, positive symptoms of psychosis would seem attributable to disorders of salience [22] since eventually they involve non-adaptive changes in signal-to-noise ratios in favor of the conscious perception of noise. Although this hypothesis is in line with the scale-free nature of the human brain as predicted by network science, further empirical studies are needed to test its validity.

6.4   Clinical lessons from the meso level

The attractor network model at the meso level explains why patients often report that hallucinations and delusions decrease when they listen to music, sing, hum, whistle, go for a hike, or talk to others. Activities such as these induce strong active states in the CEN that compete with false-positive active states in the DMN through the process of collateral inhibition. This is an important biological reason why patients should be encouraged to seek a stimulus-rich environment, engage in social and physical exercise, or conduct any other kind of activity that requires executive action. Indeed, cognitive behavioral therapy (CBT) can be seen as a systematic effort in gaining active, verbal, conscious cognitive control over overly intrusive DMN states. The re-evaluation of what is salient and what is not is a crucial aspect of this therapy, since it aims to alter activity in the SN and promote a better balance between CEN and DMN states. So far, behavioral activation and CBT seem to be the most effective interventions that are aimed at the meso level. Evidence that physical stimulation methods such as transcra-

nial magnetic stimulation, transcranial direct current stimulation and electroconvulsive therapy are effective against psychotic symptoms is currently weak [131].

7. NETWORK MODELS OF PSYCHOSIS: THE MACROSCALE LEVEL

The macroscale level of organization takes us beyond the realm of the human brain with its micro- and mesoscale levels, into the world of social networks. As noted above, the same mathematical principles that govern the latter levels of organization are applicable here [132]. Thus, social networks can be analyzed using the same algorithms used to calculate cerebral network clusters and network metrics. Previous studies have shown that social networks form communities in which individuals try to be as similar as possible (referred to as 'copy-cat' behavior, homophily, or mimesis) [132]. Subjects at the center of such social communities tend to be healthier, happier, and more at ease than those residing at the periphery [133, 134]. Comparable to the way attractor networks promote their own activity at the cost of those surrounding them, social clusters are in a constant state of mutual competition. At the macroscale level of organization that may translate to a constant desire of individuals to blend into their own community (the 'in-group') and affirm their common norms and values, whereas individuals living at the borders of the cluster are constantly tested for conformity or otherwise pushed toward another cluster (the 'out-group'), when considered 'different'. As a result, these people are more often exposed to feelings of rejection, social tensions, and habitual paranoia [134]. In the field of psychosis research, this mechanism has been substantiated by the work of Veling et al. [135], who found that the risk for psychotic symptoms tends to decrease as a function of ethnic density. Ethnic density is a measure for the proportion of inhabitants who are members of the patient's own ethnic group, and Veling et al. [135] found that living in a neighborhood with a higher ethnic density is associated with a lower chance to develop psychotic symptoms. In network terms, being part of a community of individuals with a similar ethnic background (an 'in-group') apparently protects against psychosis, whereas the risk for psychosis increases outside such a neighborhood cluster. Since social isolation and rejection rank among the most stressful events, the latter situation increases the likelihood of actual paranoia and psychosis through the process of a stress-induced false-positive identification of threats (false alarms) as described above. Additionally, social deprivation can lead to psychosis in a way that is analogous to sensory deprivation as described in the section on the brain's microscale level of organization. According to the social-defeat hypothesis by Selten et al. [136], prolonged social exclusion promotes enhanced baseline activity and/or sensitization of the dopamine system, thus increasing the risk for psychosis. Indeed, evidence for increased dopamine release in the striata of young people with hearing impairment,

who may be at increased risk for psychosis, has recently been reported [137]. Thus, the macroscale level can be linked to the mesoscale level through studies of social neuroscience in schizophrenia [138]. Stigmatization and social exclusion can create a vicious circle, with social isolation promoting psychotic symtoms and psychotic behavior promoting social exclusion, etcetera. This circle is bound to be more active in people already at risk for developing psychotic symptoms [139]. Therefore, in addition to the micro- and meso-scale levels that are habitually targeted with the aid of antipsychotic medication and CBT, antipsychotic interventions should also target the macroscale community level. Just as community medicine enforces adequate sanitation and hygienic measures at a community level, community psychiatry should focus on psychohygienic measures at the level of families, neighborhoods, villages, cities, states, and countries.

8. CONCLUSION

The Integrated Network Model of Psychotic Symptoms (INMOPS) allows to describe the positive symptoms of psychosis and their neurobiological correlates at three (subsequent) scale levels of organization (Fig. 1). At the microscale and mesoscale levels of organization, it allows for the description of individual psychotic symptoms and their relation with each other, together with descriptions of their mediation by structural and functional alterations in attractor networks. Empirical evidence for the validity of the mechanisms examined is provided by studies describing changes in neurotransmitter signaling pathways, in synaptic density and function, and in (environmentally-induced) genetic expression profiles, as well as by studies of structural and functional neuroimaging. At the macroscale level of organization, the model allows for the description of social mechanisms that influence the risk for psychosis. Starting from the premise that each of these scale levels of organization is governed by small-worldness, and that the network as a whole ('from molecule to mind') is essentially scale-free in nature, the model allows for the application of the same mathematical framework and corresponding language at each of its levels of organization. This allows to indicate at each scale level, and across scale levels, how alterations in network structure and function increase or decrease the likelihood for psychotic symptoms to occur. Rather than attempting to 'solve the schizophrenia problem' by proposing a hypothetical lathomenology to explain the connection between its multiple symptoms and multiple risk factors, the INMOPS attempts to explain the likelihood for various positive symptoms of psychosis to co-occur with reference to the principle of self-organization. Despite the considerable heterogeneity of factors considered characteristic of 'schizophrenia', this opens up a new avenue toward a unified framework for understanding this complex group of symptoms and their mediation.

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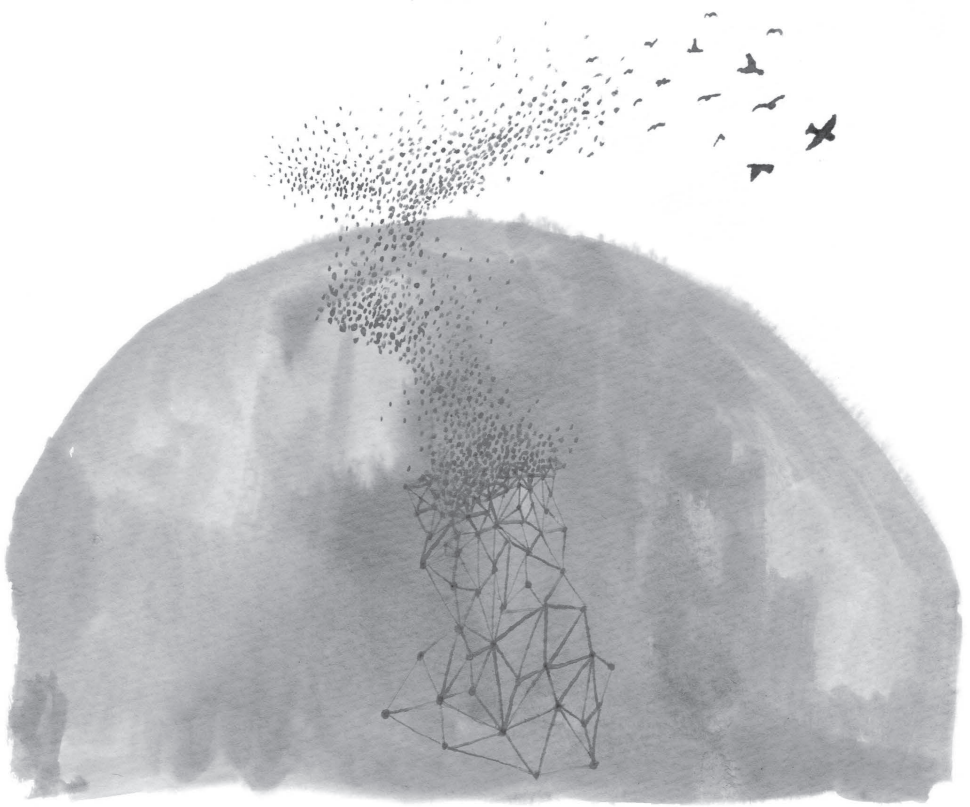
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Chapter 5

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

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ABSTRACT

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

Non-standard abbreviations:

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

1. INTRODUCTION

Auditory verbal hallucinations (AVH) are the most prevalent types of hallucination in individuals diagnosed with a schizophrenia spectrum disorder, as well as in individuals without a diagnosis, psychiatric or otherwise [1]. They have been the object of extensive neuroimaging research over the last 20 years and various hypotheses have been proposed concerning their mediation [2]. As recently summarized by Curcic-Blake et al. [3], the four major hypotheses involve: i) memory intrusion into language processing, ii) disrupted self-monitoring of inner speech, iii) aberrant cerebral lateralization, and iv) unbalanced top-down and bottom-up processing. As all four models overlap somewhat with respect to the brain regions involved, hybrid models for AVH postulate an overflow of default-mode-network-derived information into sensory association cortices or into central executive networks (CEN), with the ensuing noise intrusions being falsely attributed to an external source [4-7]. It is hypothesized that such imbalances between the default-mode network (DMN) and CEN are mediated by a disrupted function of the salience network (SN) when the latter fails to attribute appropriate salience to input from resting-state and active-state (central executive) modi. Alternatively, such noise intrusions are thought to derive from unstable neural networks at a lower spatiotemporal level that erratically switch between their high-frequency active state and their low-frequency resting state [7, 8]. Functional MRI studies have shown that hallucination-related brain activity precedes the conscious experience of hallucinations by as much as nine seconds, which is way before subjects become conscious of the hallucination [9-11]. The experience of hallucinations therefore seems to depend on a chain of neural events that precedes it. The nature of this causal chain of events has so far remained largely unclear, since current methods of functional imaging were limited in their ability to examine this chain of events for several reasons: Most fMRI studies have used model-based methods to identify brain activity, which involves searching the brain for specific patterns of interest. Such approaches can be compared to fishing with a matched spinner for one particular type of fish, which is nonetheless part of a complex ecosystem. Thus, model-based methods are confirmatory methods, which provide information on expected patterns, but these should be complemented by exploratory methods that allow for the discovery of unexpected (yet relevant) findings. In the fishing analogy, we would ideally want to employ a method that allows us to drain the pond without losing important species (e.g. noise reduction) to uncover the entire ecosystem (all neural events within the brain), after which we can select all species (neural events) that affect the presence of our main fish of interest (i.e. neural activity that is directly related to the conscious experience of AVH). In this paper, we present such a method, and use it to discover the full chain of events that lead up to the conscious experience of AVH. The clinical relevance of these findings is shortly discussed.

Our method involves the use of a so called 'model-free analysis' of functional brain connectivity concomitant with AVH, based on fMRI data obtained from 85 hallucinating patients who were diagnosed with a schizophrenia spectrum disorder. Bayesian network analyses [12] allowed to test assumptions regarding the direction of the causal influence of implicated brain regions on each other. Using a minimum of *a priori* assumptions about the nature of event-related brain activity, we provide i) a mechanistic account of the processes mediating AVH in the patient group, and ii) a perspective on the mediation of AVH that is complementary to that of model-based studies. The challenge here is to *search*, among the vast number of available hypotheses, for the hypothesis that explains the data best, and - preferentially - also facilitates therapeutic interventions.

2. MATERIALS AND METHODS

2.1 Participants

A total of 85 right-handed patients experiencing frequent VAH (i.e., at least three episodes per 15 min) were recruited at Parnassia Psychiatric Institute and the University Medical Center Utrecht. Exclusion criteria included the presence of neurological disorders, IQ < 80, structural brain deficits, and coarse scanner artefacts upon initial inspection of the fMRI data. Of all patients, 56 % were male; mean age was 38 (SD 11.0) years, and average time spent on education was 12.5 (SD 2.5) years. All patients were diagnosed in accordance with the DSM-IV-TR criteria as suffering from Schizophrenia (77 %), Schizoaffective Disorder (3 %) or Psychotic Disorder Not Otherwise Specified (20 %). Diagnostic interviews had been carried out by independent psychiatrists using the Comprehensive Assessment of Symptoms and History (CASH) [13]. There was a large range in the number of years since the onset of hallucinations, with a mean duration of 14.5 (SD 12.5) years. The majority of participants used antipsychotic medication (89 %), with a mean chlorpromazine-equivalent dose of 413 (SD 318) mg/d [14]. Of the medicated participants, 36 % used clozapine, 34 % other second-generation antipsychotics, 26 % first-generation antipsychotics, and 4 % a combination of these. After the participants had received a complete description of the study, written informed consent was obtained in accordance with the Declaration of Helsinki.

The study was approved by the Human Ethics Committee of the University Medical Center Utrecht. Looijestijn et al. [15] previously reported on a subset of the fMRI data of these patients (52 of the 85 subjects), presenting the results of a model-based analysis of VAH perceived inside the head (internal VAH) versus those perceived as coming from outside the head (external VAH).

2.2 Image acquisition

Functional neuroimaging maps were obtained with a Philips Achieva 3 Tesla Clinical MRI scanner using a fast 3D PRESTO SENSE sequence, achieving full brain coverage within 0.609 s [16]. PRESTO (PRinciple of Echo Shifting with a Train of Observations) makes optimal use of the time lapse between excitation by the radiofrequency pulse and readout, by applying the next excitation well before signal readout. The acquisition speed was further enhanced by combining PRESTO with parallel imaging techniques (sensitivity encoding; SENSE), thus allowing for a readout of fewer lines in K-space [17]. Scanning resulted in 800 3D images, depicting BOLD contrast acquired at the following parameter settings: 40 coronal slices, TR/TE 21.75/32.4 ms, flip angle 10°, FOV 224 x 256 x 160 mm, matrix 64 x 64 x 40, voxel size 4 mm isotropic. The total functional imaging time per patient was 8 min, 12 s. During the scanning sessions, participants were instructed to squeeze a balloon whenever they experienced VAH and to release it when the hallucinations subsided. A high-resolution anatomical scan with parameters TR/TE 9.86/4.6 ms, 1 x 1 x 1 mm voxel size, flip angle 8°, was acquired to improve localisation of the functional data.

2.3 Preprocessing

The FMRIB software library (FSL, Oxford, http://www.fmrib.ox.ac.uk/fsl/) was used for data analysis. Prestatistical processing consisted of motion correction [18], non-brain tissue removal, and spatial smoothing using a gaussian kernel of 6 mm FWHM. Six initial volumes were deleted to reach steady-state imaging. Temporal band-pass filtering was applied, using a liberal bandwidth (0.007 < f < 0.30 Hz) to maintain a broad range of frequencies, thus allowing for possible high-frequency VAH-related brain activity and upholding non-gaussianity in the data to perform causal searches [19]. This broad temporal range allowed us to delineate a greater number of (subdivided) functional networks [20]. The 0.30 Hz cut-off was chosen to thoroughly remove a scanner artefact settled around 0.38 Hz. Individual fMRI data were denoised in three steps using the novel FMRIB's ICA-based Xnoisefier (FIX), a data-driven automated classifier of signal-versus-noise components [21, 22].

2.4 Denoising

The first step of the denoising process involved *training*. To optimize FIX for the fMRI PRESTO task, we used a subset consisting of the first 33 participants (recruited from an alphabetically arranged list) for hand-training of the classifier. Thus subject-level independent components (IC) from the independent-component analysis (ICA) in FSL [18, 23] were assessed with regard to temporal and spatial characteristics by two raters from our study group and one external rater, all of whom scored the results either as 'signal' or 'noise'. Spatial maps were assessed for noise from i) cardiac pulsation, ii)

movement, iii) susceptibility artefacts, iv) white matter fluctuations, v) the sagittal sinus, and vi) MRI acquisition. During consensus meetings, all IC scoring discrepancies were reviewed and relabeled as either 'signal' or 'noise'. Any ambiguous components were given the benefit of the doubt in order to prevent the loss of valuable information. The ensuing manual classifications were fed into FIX to train the multi-level classifier. The second step involved *classification*. During this stage, the resulting training file was used by the FIX algorithm to classify the ICs of all 85 participants as 'signal' or 'noise'. FIX requires a threshold for classification to be chosen (of 1-100) for the level of signal-versus-noise components. We used a classification threshold of 40, based on the highest true-positive and false-negative rating results of the Leave One Out-testing (LOO-testing) [21], and confirmed these by manually inspecting all signal-versus-noise classification decisions. The third and final step involved *cleanup*, meaning that all noise components were subtracted from the individual fMRI datasets, including motion confounders, yielding 85 preprocessed and denoised fMRI datasets for further analysis.

2.5 Group-level independent component analysis: identification of ICs

During the next stage, we used group-level ICA (GICA) with automatic component estimation in FSL [23]. The preprocessed functional data, containing 794 time points for each participant, were temporally concatenated across patients to create a single 4D data set. The resulting 160 ICs were visually inspected to identify any remaining artefacts using a white-matter/cerebrospinal-fluid mask (WM/CSF mask), based on averaged individual anatomical scans. Whenever the local maxima of IC spatial maps were located inside the WM/CSF mask (or whenever the IC constituted a clear rim artefact), group-level ICs were excluded from further analysis. If there were any doubts regarding the nature of the signal, ICs were not excluded (IC2, IC68). As a result, of the initial 160 ICs, 98 were retained for further analysis.

2.6 Constructing a sparse directed IC network

The following stage involved the construction of a multimodular, directed IC network that would allow to estimate the effective connectivity (e.g., the causal directions) of the various links between ICs. As Dynamic Causal Modelling and Granger Causality [24, 25] are highly controversial for use in fMRI [20, 26], we opted for Bayesian network-modeling techniques. Most problems regarding the inference of causal directions in fMRI data can be overcome using these techniques [27], which have been tested on simulated fMRI data [20, 28, 29] showing $\geq 95\%$ accuracy [19]. Essential to this approach is to i) start by applying a model-selection algorithm to reduce the number of links, then ii) create an undirected sparse graph, and, during the next stage, iii) use non-gaussian information in the skeleton graph to estimate causal directions.

First, to establish links between the various ICs, single-subject time courses were reconstructed by regressing group-spatial maps into each subject's 4D dataset [30]. Next, the time courses of the 98 individual ICs were concatenated (98 ICs with 85 x 794 time points) to calculate group-level covariance matrices. This yielded a fully saturated network with 98 x 98 links, even though some correlations were weak. Secondly, we used EBIC-glasso (Extended Bayesian Information Criterion, graphical least absolute shrinkage and selection operator) [31, 32], as implemented in the R-package *qgraph* (psychosystems.org) [33], to perform initial model selection. EBIC-glasso is a data-driven method that employs a measure of information conservation (the EBIC) [34] to optimally converge onto a network solution that possesses a high sparsity, but still succeeds in properly explaining the data. Glasso [35] is a regularization technique for fast estimations of optimal models in large networks. The basis for these estimations is a saturated partial correlation matrix where spurious connections are controlled for by means of a tuning parameter λ (lambda) for the penalization of the maximum likelihood estimation. It thus creates 100 network solutions, ranging from fully saturated to fully disconnected. From this range of networks, the graph with an optimal solution of sparsity while still representing the data (i.e., the EBIC score) was selected. Covariance-based methods using regularization techniques are accurate in estimating the presence of network connections across a range of fMRI conditions [20]. EBIC scores have been used successfully in fMRI studies that aimed to obtain sparse network models [36, 37] while investigating limited sets of nodes (e.g., regions of interest, ROIs). The hyperparameter γ (gamma) was set to a default of 0.5, which produces optimal solutions in most simulated datasets [31]. Third, the Linear Non-Gaussian Orientation, Fixed Structure (LOFS) algorithm was used to estimate the direction of links with the aid of the R3 rule [19]. LOFS uses rules that (like the LiNGAM algorithm) infer orientation in a linear, non-Gaussian system, while orienting links in a pairwise manner, without reference to the additional context in the graph. Effective connectivity is established by estimating the model with the highest non-gaussianity of the error term. We estimated the degree of non-gaussianity by using Anderson-Darling scores [38]. The R3 rule was chosen for its conservative character in appointing causal links in combination with high accuracy [19]. Links between functional networks are expected to be reciprocal and, as such, we did not want to force direction, and only attain dominant directions of influence. Links with ambiguous directions were conceptually taken as bidirectional. Graph analyses were conducted using TETRAD-V (v.5.3.0; http://www.phil.cmu.edu/projects/tetrad).

2.7 Modularity

We detected a modular structure in the sparse network by using the Louvain algorithm developed by Blondel et al. [39], a search algorithm that optimizes modularity, which is capable of using weighted links and detecting nested clusters (i.e., smaller clusters

within larger clusters). A methodological study by Rubinov and Sporns [40] concluded that modularity primarily depends on the relative difference between weight magnitudes. Therefore, in the analysis we decided to include absolutes of negative links (7 %), as these can provide valuable extra information regarding the organization of networks by indicating instances of *deactivation* of functionally related ICs. In conformity with the calculations of links in the IC network, we also detected interactions at the level of IC modules, and thus created an IC-network graph.

2.8   General linear model with balloon presses

The function of the various ICs and IC modules within the multimodular IC network was inferred by i) examining their spatial patterns, and comparing them with previous reports on the function of such networks, and ii) linking hallucinations to individual IC-time series with the aid of within-scanner hallucination timings. The time courses of consciously experienced VAH (as indicated by individual patients within the scanner with the aid of balloon presses) were linked to the time courses of subject-level ICs by performing a post-hoc general linear model (GLM) analysis with subject-level IC time series as an independent (to be explained) variable and the subject-level model of the BOLD response to the VAH as a dependent (explanatory) variable. The BOLD responses coinciding with VAH were modeled by a boxcar based on the within-scanner balloon presses, which was subsequently convolved with a single gamma function without post-stimulus undershoot to model the hemodynamic response. Excluded from this part of the analysis were patients who exhibited continuous VAH ($n = 2$), recorded no VAH during scanning ($n = 1$), reported difficulties with the balloon presses ($n = 3$), or showed > 50 % ambiguous ($n = 10$) or missing ($n = 5$) VAH responses. Consequently, 64 patients qualified for this part of the analysis. Each participant's VAH model was tested with the 98 ICs remaining after discarding noise ICs, resulting in 64 participants x 98 beta values. Calculated beta values were fed into a bootstrapping procedure ($n = 10,000$ repetitions) to create an across-ICs confidence interval. We used an FWE threshold at $p < 0.05$ to identify VAH-related ICs, and also took the numerical beta value into account to keep an open perspective and value relative activation and deactivation of ICs during VAH. These post-hoc analyses provided information on the 'distance' of ICs to hallucinations and, thus, yielded information on the positioning of hallucination-related ICs in the IC network as a whole.

2.9   Network metrics

Individual ICs were examined for the singular influence that they were likely to have in directing the flow of information through the network of IC correlations. Interconnecting hubs were calculated using the betweenness-centrality measure adapted for weighted networks, with high values indicating that ICs participated in a large number

of relatively short paths between the ICs of the network [41]. As interconnecting hubs comprise a large part of the information flow through networks (often bridging different modules), they are considered crucial for efficient communication and control of networks [42]. Furthermore, we calculated the weighted degree for a measure of local influence in the network. To investigate sources of brain activity that are *indirectly* linked to VAH (see Introduction), we calculated the weighted degree using only links with the VAH-related ICs identified in the GLM analysis. The accordingly identified ICs were called 'tributaries' to indicate their hypothesized contributory function in the VAH circuits; a Z-score > 2.56 was used to identify these tributaries and their interconnecting hubs.

3. RESULTS

3.1 Identification of ICs

The multi-modular network of the 98 group-level ICs that we constructed allowed a global view of the 'network context' or 'embedding' of all ICs. Within the IC network, we identified seven modules, together covering 97 of the 98 ICs (for summary slides of all ICs, see supplementary materials of the digital version, Fig. 1). To establish the role of ICs in the flow of information throughout the network, hubs were identified and a network graph was constructed (Fig. 1). In the network graph, nodes were automatically assigned coordinates based on a force-directed layout algorithm that treats nodes as positive charges that repulse each other, while being constrained by their links (Gephi 0.9.1, gephi.org). Permutation tests revealed that, of the 98 ICs, 18 had significant associations with VAH-related balloon presses as recorded within the scanner, of which 11 had positive betas. These 11 ICs, which synchronized with balloon presses, functioned as the anchor points for the interpretation of our data. The ICs that activated or deactivated in relation to VAH clustered together within specific modules. The betweenness-centrality measure indicated ICs with a disproportional influence on information transfer throughout the whole network. Thus, ICs 3, 5, 7, 46, 54, 58, 76, 93, and 97 were identified as *interconnecting hubs*, whereas ICs 9, 11, 13, 14, 39, 50 were identified as tributaries in the VAH-related circuit. Table 1 lists the 98 ICs with their anatomical descriptions, grouped per network module, with beta values for associations with the balloon presses and network metrics. The seven IC modules can be described as follows.

Module I, the sensorimotor module
Module I contained nine ICs, comprising a number of brain regions that we characterize as the *sensorimotor module* (SM module). This module comprises the pre- and
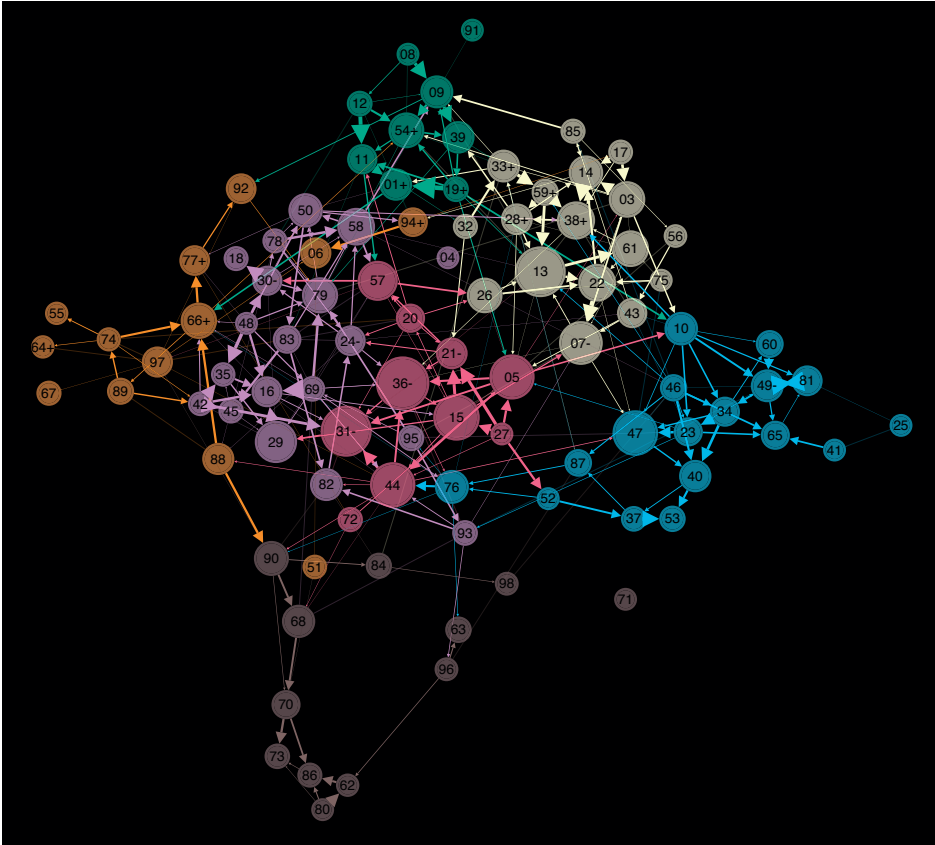
Figure 1 – IC network graph
Network graph visualization of the IC network using the ForceAtlas-algorithm (gephi.org), with edge thickness for partial correlations (r > 0.02-0.29) grey color for positive correlations, red color for negative correlations. Node color for modularity (see table 1). Node size for betweenness centrality. Nodes were automatically assigned coordinates based on a force-directed layout algorithm which treats nodes as positive charges that repulse each other, while being constrained by their links.

postcentral gyri (IC1, IC8, IC54), the supramarginal gyrus (IC19, IC54), frontoparietal opercular cortices (IC 19, IC 39, IC91), the posterior insula (IC 39), and the superior temporal gyrus (STG), which includes Heschl's gyrus and the planum temporale (IC9, IC91). Based on previous reports on the functions of these ICs and brain areas, it is likely that the module as a whole has a central function in auditory and motor processing. Primary and secondary auditory cortices in the posterior STG (IC9) showed no significant activation during VAH.

Module II, the cognition, evaluation/salience, and response formation (C-E-R) module
Module II contained 17 disparate ICs, representing brain activity in prefrontal regions and brain areas centered around the temporo-parietal junction. Among them, three 'ex-

Table 1 – Independent components (ICs) per module

Module	IC	Brain areas	GLM Beta	Betweenness	Tributaries
I Sensorimotor	1	L Precentral, postcentral gyrus (superior), cerebellum	**0.171**	41.6	-
	8	L+R Precentral, postcentral gyrus (inferior)	-0.004	0.0	0.03
	9	L+R STG (anterior to posterior)	0.049	167.7	**0.31**
	11	L+R SPL	0.009	52.7	**0.39**
	12	R Precentral, postcentral gyrus	-0.017	27.1	0.19
	19	L>>R SMG, postcentral gyrus, central opercular cortex	**0.116**	164.7	-
	39	R Insula (posterior), central opercular cortex	0.052	63.7	**0.40**
	54	R SMG, postcentral gyrus	**0.066**	199.1	-
	91	L Parietal operculum cortex, STG	0.009	0.7	0.01
II Cognition, evaluation/salience and response formation (C-E-R)	3	L>R Fronto-parietal network	-0.033	**178.3**	0.14
	7	R>L Fronto-parietal network	**-0.064**	**258.9**	0.02
	13	L+R Fronto-parietal-occipital network	0.051	77.7	**0.28**
	14	L IFG (Broca)	0.032	14.4	**0.41**
	17	L MFG	0.009	65.8	0.16
	22	L>>R MFG + IFG + MTG	0.032	54.0	0.00
	26	R SPL + SMG	0.004	22.3	0.07
	28	R>>L Insula (anterior), IFG (Broca)	**0.097**	109.2	0.00
	32	L Postcentral gyrus + precentral gyrus (medial)	0.012	3.2	0.15
	33	L+R SFG (posterior medial, SMA)	**0.094**	120.6	-
	38	L+R SFG (superior medial) + frontal pole + L IFG (Broca) + L+R MTG + R caudate	**0.080**	81.0	-
	43	R MTG (anterior)	-0.011	40.6	0.03
	56	L SMG, angular gyrus, STG (posterior) + MTG	0.009	51.0	0.00
	59	L+R dorsal ACG, paracingulate	**0.067**	34.1	-
	61	R Frontal pole	-0.011	32.7	0.11
	75	R MFG (posterior)	-0.014	7.6	0.00
	85	R Temporal pole, STG anterior	0.047	43.5	0.01
III Cerebellar	6	R Cerebellum (crus)	0.040	50.1	0.16
	51	R Cerebellum (anterior inferior)	0.013	39.3	0.00
	55	L Cerebellum crus	0.020	12.6	0.00
	64	L Cerebellum (medial)	**0.058**	4.1	-
	66	Cerebellum vermis (superior)	**0.092**	165.0	-
	67	L Cerebellum (inferior medial)	-0.010	0.0	0.00
	74	L+R Cerebellum (crus)	-0.002	66.1	0.21
	77	R Cerebellum (medial)	**0.062**	9.8	-

Table 1 – Independent components (ICs) per module (continued)

Module	IC	Brain areas	GLM Beta	Betweenness	Tributaries
III Cerebellar	88	L+R Cerebellum (medial superior)	0.027	56.6	0.17
	89	Cerebellum vermis (inferior)	-0.038	11.2	0.07
	92	R Cerebellum (inferior medial)	0.014	44.9	0.16
	94	R Cerebellum (inferior)	**0.068**	46.6	-
	97	L Cerebellum (inferior medial)	-0.013	**227.6**	0.03
IV Visual imagery / episodic memory (VI-EM)	4	R ITG (posterior)	-0.008	0.0	0.00
	16	L+R Primary visual cortex	-0.024	54.9	0.04
	18	L+R Lateral occipital cortex	-0.018	4.5	0.01
	24	L>R Lateral occipital	**-0.093**	61.6	0.00
	29	L+R Occipital pole, cuneus	-0.037	35.8	0.00
	30	R Lateral occipital (superior), SPL	**-0.07**	107.2	0.01
	35	R+L Occipital pole	0.008	16.2	0.00
	42	R Lingual gyrus	-0.011	56.5	0.09
	45	L>R Lateraal occipital gyrus	-0.021	11.0	0.00
	48	R Occipital fusiform gyrus, lingual gyrus	0.024	16.9	0.10
	50	R>L Cerebellum crus	0.056	135.9	**0.28**
	58	R MTG (temporooccipital), lateral occipital gyrus	-0.019	**235.5**	0.06
	69	R Lingual gyrus	-0.023	103.7	0.05
	78	L>R Temporooccipital fusiform cortex	-0.035	147.6	0.00
	79	L>R Temporal occiptal fusiform cortex	0.008	132.6	0.03
	82	L Lingual gyrus, hippocampus	-0.051	37.8	0.00
	83	L Temporal occipital fusiform cortex	-0.001	114.9	0.02
	93	L+R Hippocampus, parahippocampus	-0.015	**260.5**	0.00
	95	R Hippocampus	-0.026	37.1	0.00
V anterior DMN	10	L+R SFG (anterior medial)	-0.050	120.0	0.25
	23	R Frontal pole, paracingulate	-0.055	102.7	0.03
	25	L Frontal orbital cortex	-0.008	53.3	0.00
	34	L>R ACG, L+R frontal orbital cortex and frontal pole	0.014	33.0	0.01
	37	R Thalamus, caudate	-0.006	18.4	0.00
	40	R Caudate	0.012	80.8	0.02
	41	R Frontal orbital cortex	-0.001	0.0	0.00
	46	L +R Putamen	0.029	**232.0**	0.10
	47	Paracingulate R	-0.020	35.7	0.01
	49	L rostral ACG, MFG	**-0.061**	44.3	0.00
	52	R PCG, thalamus	0.009	2.1	0.00

Table 1 – Independent components (ICs) per module (continued)

Module	IC	Brain areas	GLM Beta	Betweenness	Tributaries
V anterior DMN	53	R Thalamus (anterior)	-0.014	3.1	0.00
	60	L Caudate	-0.011	4.2	0.00
	65	R Frontal pole, frontal orbital cortex	-0.006	67.2	0.00
	76	R Thalamus	-0.003	**223.6**	0.08
	81	L Frontal pole	-0.048	32.1	0.00
	87	R>L putamen, pallidum	0.004	136.3	0.06
VI Subcortical	62	R Temporal fusiform cortex, temporale pole	-0.010	1.1	0.00
	63	Brainstem	-0.004	15.8	0.00
	68	R>L Cerebellum (superior anterior)	-0.043	88.3	0.00
	70	Brainstem	0.040	52.1	0.00
	71	L Putamen	0.015	0.0	0.00
	73	Brainstem	0.013	64.7	0.00
	80	L Parahippocampus, hippocampus	0.032	47.8	0.00
	84	L Thalamus	0.038	34.4	0.05
	86	Brainstem	0.000	17.8	0.00
	90	Brainstem + L+R STG	-0.015	152.1	0.00
	96	R Temporal fusiform cortex, parahippocampus	-0.023	93.6	0.00
	98	L Pallidum, amygdala	0.031	99.7	0.00
VII posterior DMN	5	L+R Posterior cingulate, precuneus + L+R lat. occipital	-0.057	**195.3**	0.16
	15	L+R Precuneus	-0.025	82.5	0.00
	20	R Lateral occipital (superior), SPL	-0.050	47.4	0.00
	21	L+R Precuneus	**-0.064**	64.9	0.00
	27	L+R Posterior cingulate (midcingulate)	-0.027	114.2	0.00
	31	R Precuneus, posterior cingulate	**-0.064**	30.1	0.00
	36	R>L Precuneus	**-0.082**	111.8	0.09
	44	L+R Posterior cingulate, precuneus	-0.041	167.9	0.00
	57	L Lateral occipital cortex superior, R precuneus	-0.035	94.5	0.00
	72	L+R Cerebellum (IX)	-0.034	33.8	0.04
none	2	L ITG, MTG	0.007	0.0	0.00

Brain areas derived from local maxima in Harvard-Oxford brain atlas as implemented in FSL, plus (+) for separated clusters, commas (,) for contiguous activation. Betweenness centrality and tributaries bold for Z > 2.56. GLM beta's with bold for p<0.05 (corrected). SMG supramarginal gyrus, STG superior temporal gyrus, MTG middle temporal gyrus, ITG inferior temporal gyrus, SPL superior parietal lobule, SFG superior frontal gyrus, MFG middle frontal gyrus, IFG inferior frontal gyrus, ACG anterior cingulate gyrus

ecutive' fronto-parietal ICs were discernible, of which two were more lateralized (IC7, IC3), and one more balanced (IC13), which we assume to represent subdivided components of the CEN. The right-sided CEN (IC7) and the left-sided CEN (IC3) appeared to be interconnecting hubs. Additionally, we found several 'cognitive' ICs involving language production (IC28, IC38), working memory, self-referential processing, task coordination (IC38), and motor planning (IC33); of note, these may also be involved in other cognitive functions. This module also contained two ICs (IC28, IC59) that together form the salience network (SN). The SN is involved in risk prediction (i.e., the chance of reward), based on information streams of the highest level of integration (i.e., combined emotional and cognitive information). It continuously weighs the risks that are inherent to any operation (whether involving the self, others or the 'common ground'), potentially resulting in a full change of sensory predictive models, executive functions, and subsequent motor (verbal) actions via the CEN [43]. We therefore termed this module the *cognition, evaluation/salience, and response formation* module (C-E-R module). The ICs associated with the balloon presses included the right anterior insula and Broca's homologue (IC28), the bilateral supplementary motor area (SMA, IC33), the bilateral frontal pole, the superior frontal gyrus, Broca's area (IC38), and bilateral dorsal anterior cingulate cortex (ACC, IC59). Thus, hallucinatory activity in module II mostly involved cognitive (speech production, self-representation), and evaluative (SN) components, but not the executive parts (CEN) of the C-E-R module. The left-sided CEN mainly bridged the pDMN and the visual-imagery/episodic-memory module (i.e., module IV).

Module III, the cerebellar module
Module III, the *cerebellar module*, comprised 13 ICs almost exclusively located in different cerebellar regions. Remarkably, our methodological approach revealed an elaborate cerebellar network of more or less separate functional compartments, which is in line with the notion of repeated cerebellar micro-complexes with a different input and output [44], and with limited intracerebellar communication. Four ICs (IC64, IC66, IC77, IC94) showed a positive relation with the balloon presses, and probably had a function in the motor control necessary for this activity; however, these ICs might also reflect the exertion of higher-order cognitive control, i.e., prediction, error monitoring, and online modulation of language and/or speech production [45-47].

Module IV, the visual-imagery/episodic-memory module (VI/EM module)
The 18 ICs of Module IV comprised mainly occipital brain regions, along with several medial temporal and temporo-occipital regions; therefore, this was called the *visual-imagery/episodic-memory module* (VI/EM module). Three of these ICs (IC21, IC31, IC36) were negatively correlated with the balloon presses. The medial temporal regions,

including the hippocampus (IC82, IC93, IC95), showed no significant association with the balloon presses. IC 93, which represents the bilateral hippocampus, appeared as an interconnecting hub joining a network of ICs that deactivated during the VAH (IC7, IC36, IC49) or showed a trend towards deactivation.

Module V, the anterior default-mode network (DMN) and social-reference module

Module V contained 17 ICs limited to prefrontal regions, the thalamus, and the striatum. We termed it the *anterior DMN and social-reference module* because the medial prefrontal regions of the anterior DMN [48, 49] and the orbitofrontal regions are associated with the integration of limbic areas, the valuation of social cues, and emotion regulation [50, 51]. IC49, which represents the ACC and the medial frontal gyrus, showed a negative association with the balloon presses. Two extrapyramidal regions behaved as interconnecting hubs. The putamen (IC46) mainly bridged the aDMN and C-E-S module, whereas the thalamus (IC76), as expected, was found to function as an interconnecting hub with links throughout all modules.

Module VI, the subcortical module

Module VI contained 13 ICs representing the brainstem (IC63, IC70, IC73, IC86, IC90), the thalamus, the basal ganglia (IC71, IC84, IC98), the temporal fusiform gyrus, and the parahippocampus (IC62, IC80, IC98). We called this the *subcortical module*. It showed no significant associations with the balloon presses.

Module VII, the posterior DMN module

Module VII's ICs represented anatomically closely connected regions located in the posterior cingulate and precuneus, with some extensions to lateral visual cortex (IC20, IC57). Its network showed a recognizable similarity to the posterior subdivision of the DMN, and was therefore termed the *posterior DMN module*. Three ICs (IC21, IC31, IC36) deactivated during the VAH, with most of the other ICs showing a trend towards deactivation. The module takes up a central position in the IC network, suggesting that it has considerable influence on information processing throughout the network. The posterior cingulate (IC5) behaved as the module's only interconnecting hub, with a substantial proportion of inverse correlations with extramodular ICs. Interestingly, this module hub positively correlated with the lateralized CEN hubs of the C-E-S module (IC3, IC7), as well as with the module VI hub, the hippocampus (IC 93).

3.2 Effective connectivity

The EBIC-glasso algorithm produced a sparse graph with 456 links (i.e., 9.3 % of the original) with a -0.13 to 0.29 range for partial correlations. We were able to estimate the effective connectivity for 114 links (i.e., 25.0 % of the total number of links in the
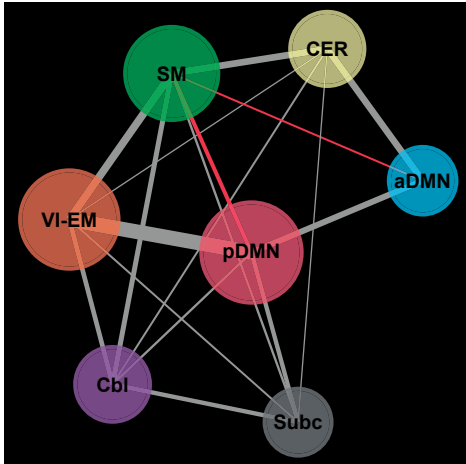
Figure 2 – IC-modules network graph with partial correlations
Edge weight for edge thickness, max partial correlation 0.44, grey color for positive correlations, red color for inverse correlations. Node size for weighted degree. Abbreviations; SM- sensorimotor module, C-E-S – Cognition, evaluation/salience and response formation module, Cb – Cerebellar module, VI-EM– Visual Imagery and Episodic memory module,, aDMN- anterior Default Mode Network, pDMN – posterior Default Mode Network, Subc – Subcortical module
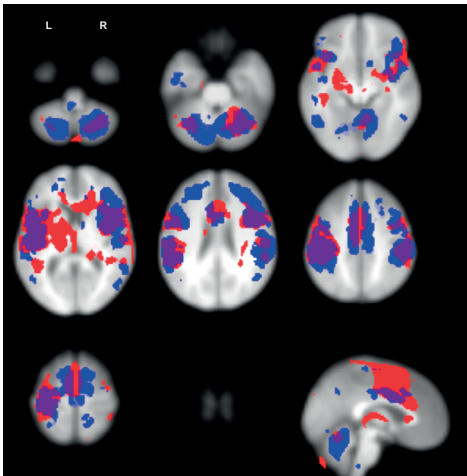
Figure 3 – Model-based vs model-free activation maps of VAH-related associated brain areas
Red color for the study by Looijestijn et al. [15] using a symptom capture approach, blue color for the stacked ICs with significant positive beta's in the current study.

sparse graph) using LOFS R3. The selected links and their directions were incorporated in the IC-network graph in Fig. 1 (for details on the functional circuits, see the Discussion).

3.3   IC modules: interaction

Figure 2 shows the seven modules that were found, including their partial correlations. Of note, the posterior and anterior DMN were inversely correlated with the sensorimotor network, which is line with their original description as 'task-negative' networks [52]. As regards its function, the visual-imagery/episodic-memory (VI/EM) module was strongly connected with the posterior DMN, thus seeming to combine efforts to integrate and uphold representations from brain-wide memory networks.
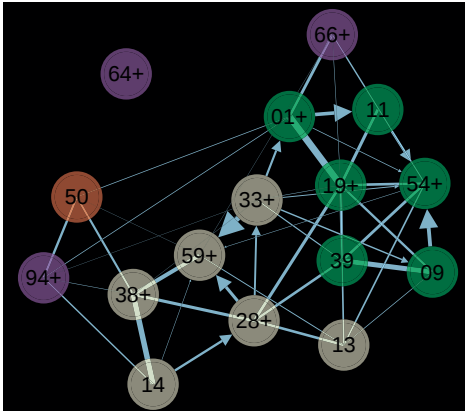
Figure 4 – Hallucination circuit
Detail of IC network graph. ICs selected for significant positive beta's and identified tributaries. Partial correlations filtered at >0.02. No direct links for IC64.

The C-E-S module was most strongly connected with the anterior DMN and the sensorimotor network, showing very few connections with the other modules. For an anatomical overview of the modules found, a 3D rotating animation is available in the Supplementary Materials of the digital version (Fig. 2-8).

4.   DISCUSSION

This study explored the relationship between verbal auditory hallucinations (VAH) and the brain circuits involved in their mediation, using a model-free, network-based approach to analyze fMRI data obtained from 85 patients diagnosed with a schizophrenia spectrum disorder. The analysis yielded 98 ICs of the brain, of which 18 correlated with the conscious experience of VAH. In addition, the 98 ICs clustered into seven modules with distinct and recognizable functions based on network metrics, a study of the literature, and a post-hoc association study. On the basis of these results, we created a network graph to provide a comprehensive overview of the brain's functions at the level of neural networks and to illustrate the networks' direct and indirect relationships with the mediation of VAH.

4.1   General architecture of the IC network

Using our model-free network approach, large-scale functional networks (such as the CEN, DMN, and SN), but also the cerebellum and other structures traditionally conceptualized as constituting single functional components, now appeared to fragment into smaller functional units. An explanation for the high level of detail of our ICA decomposition might be the high sampling rate of the PRESTO scan, which offers a fine delineation of functional (a)synchrony. Thus, the high level of detail yielded by

our ICA decomposition allowed comprehensive mapping of the brain's subfunctions involved in the mediation of VAH, whilst still acknowledging the brain as an extensively connected and intrinsically complex functional network [20]. We made a systematic effort not to impose theoretical or pre-specified models onto our data. Therefore, it was noteworthy that the force-directed layout algorithm produced a relative positioning of ICs and IC modules that closely resemble the actual neuroanatomical positions of these areas in the adult human brain (Supplementary Materials, Fig. 9). Overall, the high level of correspondence between the IC network and the anatomical network structure of the human brain, provided a first indication of the validity of our approach.

Major hubs were the left-sided and right-sided fronto-parietal networks (IC7, IC3), the precuneus and posterior cingulate (IC5), the thalamus and putamen (IC76, IC46), the hippocampus (IC93), the supramarginal gyrus (IC54), and a network surrounding the right temporo-occipital junction (IC58). This configuration is in strong accordance with the so-called 'rich club' of the human brain, a network of densely connected hubs thought to account for a large proportion (e.g., 80 %) of information transfer within the brain [53], thus providing a second validation of our approach.

4.2   Relationship between IC modules and verbal auditory hallucinations

The strongest links to VAH were found for ICs located within the sensorimotor (SM) module, the cognition, evaluation/salience, and response formation (C-E-S) module, and the cerebellar module (see below for further details per IC). Together they represent all the 11 ICs that significantly *activate* during VAH. In this study, DMN activity was found to be at a distance from hallucination-related regions, with the posterior DMN subdivisions mostly *deactivating* during VAH. Although functional hyperconnectivity and hyperactivity of DMN subdivisions are suggested to be essential processes for the occurrence of VAH [49], our exploratory approach does not support that view. Bearing in mind the replicated findings concerning DMN hyperactivity in patients diagnosed with schizophrenia and their first-degree relatives [54, 55], this might be indicative of other types of psychopathology (i.e, not hallucinations). In their study, Jardri et al. [5] found a comparable disengagement of the DMN during VAH and also found evidence for a role of spatial and temporal DMN instability in the emergence of VAH; therefore, their study is indicative of the complex constituents of VAH on multiple scale levels. In our study, apart from the anterior and posterior DMN regions, the brainstem and subcortical regions were mainly positioned at a distance from hallucination-related ICs and, therefore, appeared to have no significant role in the mediation of VAH. Also, the visual-imagery/episodic-memory module showed little or no relationship with VAH. This contradicts hypotheses suggesting that VAH have a source in unstable (episodic) memory (e.g., (para)hippocampal areas or putamen) [56, 57].

4.3 Relationship between individual ICs and verbal auditory hallucinations

The 11 ICs showing significantly positive relationships with hallucination timings comprise the cerebellum (both hemispheres and the vermis), the right anterior insula, Broca's homologue (right), the left pre- and postcentral gyri, the bilateral supramarginal gyrus, the medial frontal areas (including the anterior cingulate), the bilateral supplementary motor areas, and the bilateral frontal poles. These structures are often found in model-based studies of VAH [15, 58-61], although several model-based studies also reported involvement of subcortical structures [10, 57, 58]. Figure 3 shows the spatial maps of the *activated* ICs within a single brain, and contrasts these with the activation map from a previous study by our group based on model-based analyses of signal changes in VAH [15]. As shown in Fig. 3, these model-based and model-free activation maps largely overlap, with the model-based study yielding additional activity surrounding the thalamus and motor cortex in the activation map, and more extensive medial cerebellar, medial prefrontal, and fronto-polar activity in the stacked ICs from the present model-free study. The increased activation found by our previous model-based study in thalamus and motor cortex might be due to a number of factors. One explanation is the possibly superior power of the event-related approach to detect brain activity (due to the balloon presses) in these regions. In our model-free approach, the extensive activation of the medial cerebellum is of special interest in view of earlier studies that proposed a causal role for the cerebellum in psychosis and hallucinations [46, 62, 63]. Powers et al. [63] found that the decreased activation of cerebellum corresponded with diminished belief-updating and rigidity of psychotic patients, and hypothesized that the cerebellum dysfunctions in updating top-down predictions; furthermore, they identified the superior temporal sulcus and the insula as discriminant regions that activate during the hallucinatory state.

4.4 Functional circuits

The method we selected to estimate effective connectivity is among the most reliable available for detecting causal directions in fMRI data. Nevertheless, we could establish causal directions (arrows) for only 25 % of our links. This posed limits to a more precise understanding of the functional circuits at hand. For instance, it prevented us from detecting a clear causal hierarchy between the various ICs, and from finding or excluding possible 'Garden-of-Eden states' (first movers) of hallucinations. Despite that limitation, Fig. 4 provides an overview of the ICs that emerged from our analysis. The circuit is built-up of VAH-activated ICs, and ICs that show a strong direct link with these ICs.

Of all ICs, left-sided motor cortex (IC1) showed the highest beta value, which most likely indicates the motor action coinciding with the balloon presses made by our study patients. The motor cortex was also found to have the strongest connection with so-

matosensory association cortices, including the auditory regions (IC19), which might represent the processing of language and/or the reciprocal feedback taking place during motor action [61]. The bilateral superior parietal lobule (SPL, IC11) is strongly informed by IC1, probably receiving input from the hand during balloon presses.

The SMA (IC33) - which provides input to motor cortex (IC1) - and the ACC (IC59) also showed strong activation during VAH. The SMA has been endowed with a number of functions, including motor preparation, the initiation of internally driven movement, and the processing of sequences of input within multiple domains [64, 65]. The pre-SMA has been implicated in complex sequencing, ambiguity resolution, and task switching in relation to language [66]. A study on the functional connectivity of the SMA shows pre-SMA output going to the posterior IFG, angular gyrus, and ACC [67], which matches with the effective connectivity found by us, albeit with a reversion of the reciprocal influence of pre-SMA and IFG. In a study directly hinting at a function of the SMA in mediating hallucinations, Clos et al. [68], observed increased connectivity between the left IFG, the SMA, and the insula in psychotic patients experiencing VAH, which they explained in terms of increased inner-speech generation.

The ACC has partially overlapping functions, such as cognitive control, salience, various top-down processes, and self-monitoring [69, 70]. All these functions may play a role in the mediation of VAH. In our analysis, we found that the ACC (IC59) receives input from the right-sided anterior insula and Broca's homologue (IC28), which matches with the study by Sridharan et al. [71], who found that a right-sided fronto-insular network strongly co-activated with the ACC (which is part of the SN). Together, these areas have an important causal role in modulating DMN and CEN activity which, as we saw, plays an important role in hybrid models of VAH mediation. The anterior insula has been proposed to function as the most crucial part of the SN, attributing 'salience' to intrinsic and extrinsic stimuli, and propelling this information forwards to the ACC for preferential attention in higher-order cognitive (prefrontal) areas interacting with the CEN or DMN [72]. Salience attribution seems to involve a process of risk assessment: the insula takes highly integrated (i.e., combined multimodal emotional and cognitive) information as its input and 'calculates' expected reward or punishment as a result of this input [43]. Predictions with maximum expected results are then prioritized within the ACC, and appropriate measures are prepared, e.g., whether to relax and enter into a resting/DMN state, or to become vigilant and enter an active/CEN state.

The right anterior insula and Broca's homologue (IC28) were also strongly connected with a prefrontal and SFG-focused component (IC38), although we were unable to establish any causal ties. Moreover, the SFG network includes the bilateral frontal pole, the temporal pole, the middle temporal gyrus, the cerebellum, and Broca's area. We hypothesize that this reflects working memory and associative functions following the conscious experience of VAH. The SFG network strongly connects with the

anterior medial SFG (IC10) and Broca's area (IC14). In our analysis, Broca's area was the strongest tributary, contributing to the activity levels of IC28, Broca's homologue, and the insula. Interestingly, Sommer et al. [59] reported on the relative inactivity of Broca's area, as compared to its homologue. Our findings are similar, but indicate that Broca's area does have a function in the mediation of VAH, albeit indirectly, e.g. by producing language that further 'upstream' is wrongly valued by the SN, and retained in working memory.

We found the right-sided posterior insula (IC39) to be connected with a range of VAH-related ICs, including the anterior insula. The posterior insula is thought to be functionally dissociated from the anterior insula, and to have a specific function in sensorimotor and somatosensory processing [72, 73]. Correspondingly, we found the posterior insula to be strongly connected with auditory cortices (IC9). Therefore, we hypothesize that the links between the inferior parietal lobule (IC54) and the posterior insula (IC39) represent the back-projection of perceived hallucinations in the salience network, and the subsequent somatosensory registration of the ensuing percept.

In our analysis, the left-sided CEN (IC3) emerged as a hub that was inversely correlated with another hub, i.e., the right-sided IPL (IC54). Together with the inverse correlation with the SMA (IC33) of the left CEN (IC3), this suggests a relative *deactivation* of the lateralized CEN during VAH, although this was not found to be significant. The right-sided CEN (IC7) did deactivate significantly during VAH, acting as an interconnecting hub bridging the pDMN-module. The left-sided CEN (consistently found in resting-state studies) has been implicated in cognition and language processing, whereas the right-sided CEN is more often associated with somesthesis and action inhibition [74]. This suggests that the abdication of lateralized cognitive control has a relation with the conscious experience of VAH. Rotarska-Jagiela et al. [75] found that the right-oriented CEN shows a disrupted intrinsic organization and a decreased rightward lateralization in patients experiencing VAH. Further away, we found that the pDMN hub (IC5) is inversely correlated with hallucination-activated ICs (IC19, IC28), but positively correlated with the lateralized CEN hubs. This partially conflicts with earlier studies that found inverse correlations between CEN and DMN, and the subsequent models that emphasize the competition between the CEN and DMN in their preponderance [6, 76, 77.] The deactivation of the DMN is proportional to the height of the cognitive demands of within-scanner tasks for subjects [76]. Therefore, in the present study, the correlation between the DMN and the lateralized CENs could indicate the relatively limited cognitive demands of the hallucination reporting. The bilateral CEN (IC13) correlated negatively with the pDMN hub (IC5), and was strongly connected with the hallucination-activated ICs (IC19, IC28, IC54, IC59). All this suggests that the CEN is functionally segregated into three subunits, with different relations to

the aDMN, pDMN, SN, and hallucinatory activity. Therefore, further studies should take into account the functional separation of different CEN networks.

Lastly, a strong relation was found between the cerebellum and the patients' within-scanner balloon presses. Focusing on the cerebellar ICs that strongly link with other VAH-related ICs, the right cerebellum (IC94) was found to have a stronger connection with the ICs in the cognition, evaluation/salience and response formation (C-E-S) module, whereas the cerebellar vermis (IC66) had a stronger connection with the ICs of the sensorimotor module. Additionally, IC50 (also located in the cerebellum vermis) was identified as a strong tributary. The cerebellum is known to operate in a feed-forward system, e.g., in the computational processing of cerebral input, looping it back to the cerebrum with limited internal transmission. This function could be summarized as analyzing neural input for the prediction of a future sensory state, and the detection of discrepancies with actual signal patterns (i.e., sensory error prediction) [47], thereby supporting timing and learning in mental processes. Hypothetically, when timing of cortical processes becomes desynchronized, this could amount to self-monitoring deficits of language networks and thus to VAH. However, it remains unclear whether the cerebellum is solely involved in the motor coordination of speech and the emotional modulation of speaking, or whether it also has a function in language [78].

4.5 Integration

Integrating the results of our analysis, we propose that the mediation and subsequent perception of VAH in the context of schizophrenia spectrum disorders relies on the involvement of medial prefrontal regions, the insula, the cerebellum, and the homologue of Broca's area. In this patient group, these components of the hallucination network appear to be essential in the mediation of VAH. The right-sided insula and Broca's homologue (IC28) are positioned centrally within the hallucination network, and appear to be responsible for the production of preconscious linguistic constructs to which salience is assigned by the SN (IC28, IC59). The insula propagates the stimulus further downstream in the direction of middle frontal regions, where the SMA and ACC appear to respond to the false prediction, activating the planum temporale (which projects the voices into external space) [15], and enforcing the conscious perception of VAH. Sustained attention to the ensuing percept is probably provided by the working memory ICs (IC38 and CENs). The bilateral CEN showed the strongest connection with these VAH-related ICs. The cerebellum, in turn, might be involved in the disrupted updating and learning from the false sensory predictions in psychosis or in a more physiological process, such as emotional modulation [62, 63].

The mediation of VAH as outlined above aligns most strongly with established (model-based) hypotheses of VAH involving the disrupted self-monitoring of inner speech. Indeed, the central role of the anterior insula in falsely predicting threat or risk

from harmless, internally generated narratives, fits the evolutionary model of psychosis as a partially adaptive strategy to increase the 'true positive' (successful) detection of threats (such as gossip or intrigue) at the cost of 'false positives' (hallucinations). Such a strategy may be rewarding in threatening situations that require high levels of vigilance or even a healthy amount of paranoia. In effect, the hypothesis presented here is a hybrid model that characterizes the mediation of VAH as a failure of source monitoring due to SN dysfunction, with subsequent processing of the internally mediated percepts as if they were mediated externally.

4.6   Limitations and suggestions for future research

The present study has several limitations. Firstly, the results of our model-free analysis depended on post-hoc statistical analyses and literature searches in order to attribute meaning to the reported ICs. Studies such as these need to consider the problem of 'reverse inference', i.e., (incorrectly) deducing the function of ICs on the basis of brain activation maps reported in previous studies [79]. The criticism being that the attribution of a phenotypical function attributed to brain regions A in study X, on the basis of earlier research Y is invalid, as the brain regions A in study Y operate in a network of other brain regions and will probably have a role in multiple functions, in the sense that they are not specific to certain phenotypes. However, if the goal is to identify an optimal causal model for a phenotype within a broad context of neural mechanisms, this criticism is less relevant [80]. Attributing psychological functions to specific brain regions is arbitrary and, instead, the focus should be on assessing the global mechanistic model of the symptom, disease or cognitive process under study. Secondly, a substantial number of ICs was found to originate primarily from noise, and had to be removed using denoising algorithms based on supervised learning. The substantial amount of noise in the data might have been due to the liberal method of temporal filtering used or, alternatively, to the possibly lower signal-to-noise ratio of the PRESTO scanning technique [81]. Nevertheless, the higher sampling rate of PRESTO (in comparison with Echo Planar Imaging) was a clear advantage of our study with regard to power and the ability to discern potentially meaningful signals from physiological noise [82].

In the third place, the absence of a control group prevented us from making any firm inferences regarding the specific pathological deficits or pathogenetic mechanisms involved in the mediation of hallucinations. However, it should be emphasized that the primary goal of this study was not to investigate such pathogenetic mechanisms, but to identify the mechanistic model for the occurrence of VAH within the context of the afflicted brain: more specifically, to facilitate local intervention with the aid of repetitive transcranial magnetic stimulation or transcranial direct current stimulation. Pathological changes in psychosis may significantly alter normal functional neuroanatomy (both in terms of structure and function) [3, 83]. Therefore, for the purpose of clinical interven-

tion, it is necessary to know the neural mechanisms underlying psychotic experiences within the context of the disease, rather than the healthy situation. Additionally, our study shows that many functionally significant ICs are not significantly associated with VAH experience, providing a within-subject control condition. Future studies that aim to examine pathogenic mechanisms might benefit from including a control group consisting of healthy controls, siblings of psychotic patients, non-hallucinating patients with previous episodes of psychosis, or patients with infrequent hallucinations. Such imaging studies can be performed during the resting state or during an auditory stimulus-detection task that is matched to the psychotic experiences of the patients. In the fourth place, as noted above, the LOFS R3 algorithm used allowed to determine causal directions for only 25 % of the links. As LOFS R3 does not make any forced choices, this may indicate the existence of reciprocal connections in the remaining links, as can be expected in neural networks [12]. On the other hand, it may also indicate that this algorithm prefers accuracy of directionality over directionality. One way to improve this estimation would be to i) choose components of interest based (COIs) on the present study, ii) use the time series of COIs in relation to the modelled BOLD response according to the hallucination timings to estimate the order of activation of COIs, and iii) pre-inform the causal search algorithm with directions of links based on this order of activation. Although this would only be feasible in individual subject-level analyses of effective connectivity, the benefit would be substantial as a detailed depiction of functional circuits involved in the mediation of VAH would allow accurate predictions of locations to be targeted with therapeutic techniques within individuals, i.e., by selecting the most influential nodes in the functional networks at hand [84]. Moreover, enforcing further sparsity in the network might also help to estimate causal links, as this will reduce cyclical (feedback) connections and benefit the display of the dominant direction of information in the brain circuits under study.

4.7   Conclusions

We systematically decomposed the fMRI data from the hallucinating brains of patients diagnosed with a schizophrenia spectrum disorder into functional subnetworks, and reconstructed these into a whole-brain directed network. This method, which we compared to the draining of a pond to lay bare its entire ecosystem, revealed 98 independent components (ICs) which were active in patients who had consciously experienced VAH during the time of scanning. These ICs clustered into seven modules with distinct physiological functions, involving resting state, central-executive, salience, cerebellar, subcortical, and stimulus-response processing. Functional subnetworks comprising the hallucination network are Broca's right homologue, the right insula, the bilateral anterior cingulate, premotor cortex, and the supramarginal gyrus, whereas the CENs, Broca's area, and cerebellar regions constitute probable and more distant tributaries

to the mediation of VAH. On the basis of the present findings, we conclude that VAH in this patient group appear to be largely mediated by the SN making false predictions about the risk and (hence) origin of linguistic percepts derived from Broca's homologue, followed by subsequent processing errors in the anterior cingulate gyrus, and other cognitive areas. Our findings mostly comply with model-based studies reporting faulty error monitoring as a major factor for the mediation of VAH. Future local intervention studies should consider focusing interventions on Broca's homologue or on SN subparts, anterior insula, and anterior cingulate cortex, instead of the traditional left temporoparietal cortex (T3P3 in EEG electrode placement system) [85].

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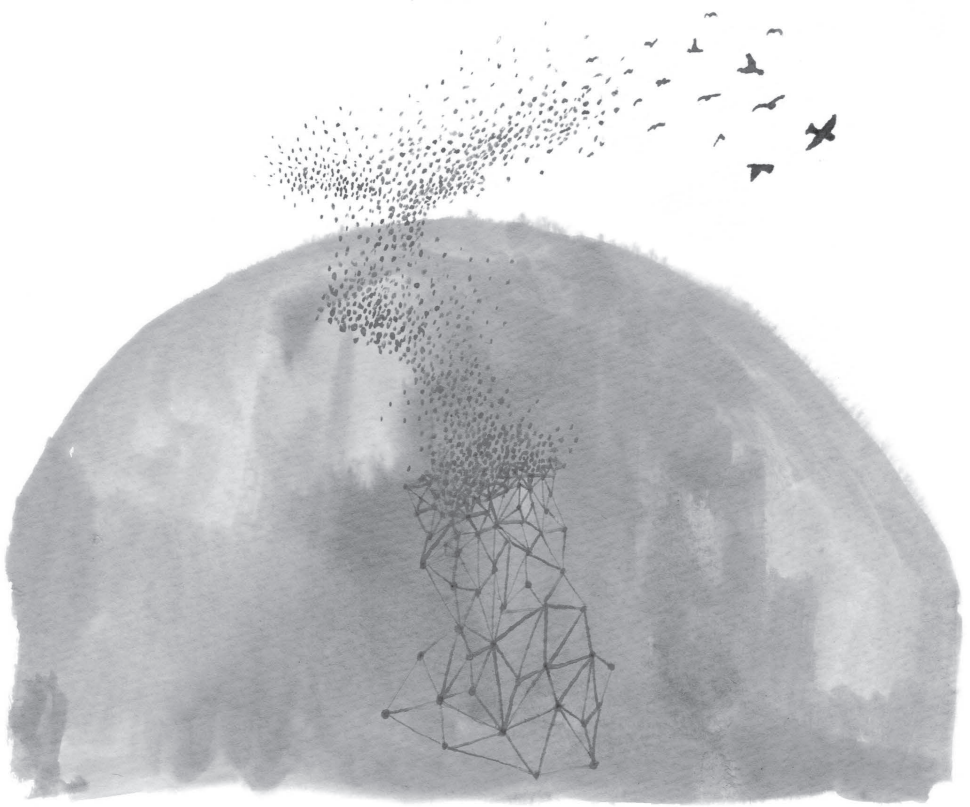
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Chapter 6

General Discussion

The aim of this thesis was to gain further insight into brain functions that represent the occurrence of verbal auditory hallucinations (VAH). In this chapter, the main findings are summarized and methodological issues related to the study of VAH using functional MRI are addressed. Then, after a general discussion on VAH studies, some recommendations are made for future research.

1.   MAIN FINDINGS

Chapter 2 describes the presentation of VAH in a single patient, highlighting the diagnostic and co-morbidity issues involved. Functional MRI (fMRI) revealed activation of the primary auditory cortex, speech areas (Broca, Broca's homologue and Wernicke), basal ganglia, anterior cingulate gyrus and dorsolateral prefrontal cortex; these results are in line with earlier studies (for a meta-analysis see Jardri et al. [1]). In this particular patient, VAH were in full remission after treatment with repetitive transcranial magnetic stimulation directed at Wernicke's area, together with remission of a range of metamorphopsia and depressive symptoms. Although current knowledge on the pathophysiology of VAH on a neural level is still at an early stage, the studies presented here show the potential of fMRI to guide novel treatment. These studies also indicate that the brain is an integrated network within which local influence can spread across different brain functions.

The study in **Chapter 3** investigated whether neurophysiological differences exist between internal VAH and external VAH. This is highly relevant, because the clinical tradition generally considers internal VAH to be less pathological and atypical for psychotic disorders. According to this tradition, internal VAH are often referred to as 'pseudohallucinations' [2]. Our hypothesis is that the difference between internally perceived versus externally perceived VAH is limited to additional activation in the auditory 'where' pathway, i.e. a network of brain regions dedicated to locating sounds in our environment [3]. Results from fMRI show increased activation of the right-sided medial frontal gyrus and the left-sided planum temporale in persons experiencing external VAH. This indicates that the 'where' pathway could indeed play a substantial role in the projection of hallucinated voices into external space. Correspondingly, internal VAH are neurophysiologically distinguished from external VAH by their lack of activity within the 'where' pathway. Considering that a small amount of auxiliary activation can explain the difference between internal and external VAH, we suggest that caution is required when applying the term 'pseudohallucinations'. This recommendation is in line with clinical studies reporting that there is no evidence for a differential impact or effect in patients experiencing either internal or external VAH [4].

Chapter 4 steps back from the phenomenological level of studying VAH. The increasing amount of research on schizophrenia and psychotic symptoms has identified a range of factors suggested to be causal to the psychotic state. Although these explorative studies are highly valuable (providing data on, amongst others, genetics, neurodevelopmental trauma, altered brain connectivity, and/or social factors) they should be viewed within a larger context. In our work, an integrative model is proposed for psychosis based on network theory. This model states that the human brain is a 'scale-free' structure in which the multilevel and (complex structural/functional) organization contributes to the formation of hallucinations. Within the scale-free biological network, functional brain dysconnectivity is viewed as an intermediary scale level, under reciprocal influence from microlevel and macrolevel states. This 'integrated network model of psychotic symptoms' (INMOPS) is described, together with various possibilities for its application in clinical practice.

Based on our INMOPS theory (Chapter 4), an exploratory study was conducted in **Chapter 5** to investigate the occurrence of VAH from the perspective of the multilevel and complex (functional) organization of the human brain. The aim was to develop a mechanistic account of the way in which the interaction of multiple functional networks leads to VAH in schizophrenia spectrum disorder. Our used 'model-free' method was compared to the draining of a pond to lay bare its entire ecosystem, instead of fishing with a matched spinner for one fish. An Independent Component Analysis (ICA) of fMRI data was performed for a large group of persons experiencing frequent VAH, decomposing the overall general function of the brain of these patients into a set of constituent functional subnetworks. The interaction between these functional networks was further studied using network analysis to estimate the flow of activity in the brain circuits that subserve VAH. Firstly, it was found that our rigorous procedure for denoising the data in combination with ICA, decomposed the data into a fine-grained system of 98 functional networks in which 7 higher-level modules could be identified mathematically. These modules constituted plausible functional networks which, in an unsupervised layout produced by a force-directed orientation algorithm, neatly positioned themselves according to global brain anatomy. These so-called large-scale networks of the brain, i.e. default mode network (DMN), central executive network (CEN), and salience network (SN), decomposed into several subunits, each with their own interaction profiles and degrees of correspondence with hallucinatory activity as reported by the patients. These findings show that the commonly reported large-scale networks should not only be studied in their entirety, but also that their constituent parts serve important subfunctions that contribute differentially to the global psychotic phenotype. These results also fit our INMOPS theory, by showing that multiple levels of (functional) organization indeed contribute to the formation of hallucinations. Interestingly, several subparts of the global cerebellar network contributed differentially

to the experience of VAH, indicating a more complex pathogenesis of VAH than previously thought. The functional networks showing the most direct involvement with VAH experience were the bilateral anterior cingulate cortex, the right anterior insula, the cerebellum, and the homologue of Broca's area. Based on the causal structure of their mutual connections, we hypothesize that the right-sided insula and Broca's homologue are responsible for the production of preconscious linguistic constructs ('error') to which superfluous importance is assigned by the salience network, producing a conscious experience that matches this disproportionately high level of salience.

2. METHODOLOGICAL CONSIDERATIONS

In each of the individual studies, the specific methodological strengths and limitations are addressed. Here, we discuss the process of studying hallucinations using fMRI in general, as well as aspects found to be methodologically challenging during the performance of these studies. Starting from its development in the early 1990s, fMRI has provided the main body of neuroscience data. The first decades of fMRI revealed the unique potential of fMRI to unravel the processes involved in the workings of the brain and mental disorders. Gradually, improvements in scanning technology, image acquisition and statistical methods enhanced the level of detail and signal-to-noise ratio, and further increased the capabilities of fMRI. Thus, fMRI contributes to revealing the neuronal mechanisms of cognitive processes by means of a coarse mapping of the different functional modules and their interactions, which allows to formulate additional hypotheses. VAH studies based on fMRI can support one another as well as reveal inconsistencies and discrepancies [5]. Although this may be inevitable for a relatively young field of research, it also implies that proper analysis is required of the methods used.

The following methodological items are discussed: 1) fMRI as a measure for brain activity, 2) noise in fMRI data, 3) the appropriate scale level of study, 4) top-down and bottom-up study design, 5) 'state' and 'trait' studies, 6) inference of brain function, and 7) group-wise analysis of VAH.

1. BOLD fMRI provides an indirect measure of neuronal activity dependent on blood flow in microvasculature. Although methodological studies have confirmed the strong correlation between neural activity and fMRI responses, they also show that the signal is dependent on the type of neuronal activation and that the BOLD fMRI signal can be lagged with different time frames in different parts of the cortex [6-8]. This warrants the use of other neurofunctional techniques, such as EEG, MEG and electrode recordings, to test for fMRI-derived hypotheses. It is also important to acknowledge that the spatial unit of volume used in fMRI, the voxel, represents

neuronal mass action. Most fMRI experiments have a voxel size of no less than 1 mm^3 and, together, about 1,200,000 voxels make up the complete volume of the brain. The most accurate count of neurons in the human brain reports 8.6x10^10 neurons [9]. Thus, each voxel represents an estimated 72,000 neurons and relative activation or deactivation of the voxel represents a summary account. If there is a need to acquire a higher resolution to match the studied scale level of information processing, some technological advancement (e.g. magnetic field strength) can be beneficial, but will increase the computational efforts and noise.

2. The signal in the fMRI data derived from neuronal activation is accompanied by a considerable body of noise. In all fMRI studies, an attempt is made to statistically control for this interference, or to filter out noise. This type of noise originates from bodily functions such as cardiac/respiratory actions, head movements, and scanning artefacts. Random noise will reduce statistical power. However, when signal displacements are correlated with a stimulus such as balloon presses (i.e. contracting a muscle in the neck area and subsequent head displacement due to squeezing of the hand) they can result in both false-positive and false-negative re-sults. Because no standardized approach to clean up fMRI time series is available [10] this has a negative impact on the interchangeability and comparability of results from similar studies. Chapter 5 describes the use of supervised learning algorithms to extract noise. By performing a preliminary ICA, noise components can be identi-fied and subtracted from the data per individual. In our study, ICA performed on the cleaned-up fMRI time series led to a vast increase in the number of identified functional components of the brain, emphasizing that increasing the signal-to-noise ratio provides a more detailed view of brain function.

3. When studying a phenomenon such as VAH, it is important to be aware of the scale level of the instruments used. The hierarchical modular structure of the brain has been well established [11-13]. Large-scale functional networks spread across the brain and consist of increasingly smaller functional units localized in brain regions, neural columns and collections of neurons. At highest capacity, fMRI can capture the dynamics at the level of millimeters and several seconds, e.g. relatively slow processes in collections of neural columns or brain areas. fMRI attempts to find the correct functional decomposition on this scale level, and then model its organiza-tion. The organization of the biological network at smaller or larger scale levels requires additional equipment e.g. microscopes, electrode recordings, EEG, and interviews and/or behavioral observations. Additionally, it is emphasized that the functions of the brain cannot be attributed to specific brain regions irrespective of their interaction with other brain regions and functional networks, as functional networks can only perform within a 'unified mind'. Chapter 4 reviews how an inte-grated model of the brain across scale levels can be built-up using the mathematical

framework for network science, and shows that this also allows to integrate the social factors that also play a role in the occurrence of VAH.

4. Similar to the top-down and bottom-up processes in the brain, the investigation of research data is done using top-down and bottom-up approaches [14]. In a top-down study design on hallucinations, researchers decide on the neuropsychological dysfunctions that they will look for before they start the analysis, thereby giving robust statistic power. However, this carries the risk of simply validating or discarding the hypothesis, while potentially missing valuable information present in the data and failing to gain a more comprehensive overview of hallucinations. In a bottom-up study design the aim is to apply a minimum of *a priori* assumptions and structurally explore the data. While being inclusive, this design carries the risk of being overtly inductive in associating the measured biology with hallucinations and has less discriminative power. In practice, each study will have a top-down or bottom-up starting point, but will generally apply both approaches to some extent. For our study in Chapter 5, a mainly bottom-up approach was applied. It is possible that a better balance between the diverging and converging forces might have improved the accuracy of the results. In studies by Maniolu et al. and Leroy et al. a more or less similar study approach has been used, however they clearly differ in an earlier selection of the components-of-interest active in the brain (the functional networks) [15, 16]. Thus, by reducing the state space of possible outcomes, these studies have the potential to provide more accurate findings.

5. During VAH, the performance of the brain is examined globally by either 'state' or 'trait' studies. State studies investigate the processes of the brain directly before and during the state of experiencing hallucinations. Trait studies investigate subject-related properties or 'traits' of being vulnerable to or having the necessary preconditions for experiencing VAH. Conversely, trait differences could signify cognitive adaptations to the frequent state of experiencing VAH. This thesis deals with the *state* of hallucinating, i.e. the experience of having VAH and its symptoms (Chapter 1 and 2), and the 'acute' or state-level pathophysiological processes directly before and after the occurrence of VAH (Chapter 5). It is important that modeling the pathophysiology of VAH deals with both the more static and more dynamic influences and (ultimately) each with their own possible approaches for intervening in the occurrence of VAH. The trait deficit of hallucinating can often be investigated by contrasting the activation patterns of psychotic individuals with frequent VAH, with those of psychotic persons reporting little or no VAH. This can be done during the resting state, or while presenting control persons with auditory stimuli that somehow match the psychotic experiences of patients. Additional traits that predispose to VAH can be examined by contrasting hallucinating persons and non-(frequent) hallucinating individuals while performing hypothesis-based cogni-

tive tasks, such as speech monitoring. For example, Kuhn and Gallinat [17] performed a meta-analysis on state and trait fMRI studies and concluded that, in state studies, the inferior frontal gyrus, postcentral regions and parietal operculum were the most strongly associated with VAH. In contrast, trait studies of VAH revealed more associations with increased activation of middle temporal gyrus, anterior cingulate cortex, premotor cortex and superior temporal gyrus.

6. Drawing inferences about brain functions from BOLD fMRI time series requires considerable caution, similar to when studying the experience of VAH. Activation or deactivation of a brain region could relate to a neural function mediating the symptom, or a process modulating the apprehension of a percept, or perhaps a secondary emotional or behavioral response. Narrowly designing a control condition for persons to experience VAH can minimize the risk of subjective inference, but requires making specific assumptions about the nature of VAH (see point 4). In Chapter 5 we attempted to partially overcome this issue by assessing functional networks active in the whole brain and studying their dynamic interactions. A comprehensive view on the neurofunctional circuits that make up VAH, including the direction of influence, can help elucidate the function of their subparts [4]. Furthermore, if primarily interested in designing an optimal intervention to circumvent the occurrence of VAH, the use of a control group to describe the pathological process that distinguish illness from a healthy state is less relevant. Acquiring a mechanistic account of VAH (as proposed in Chapter 5) is sufficient to guide where to effectively intervene in the circuits underlying VAH.

7. Lastly, it should be taken into account that not all VAH are the same in all individuals under study. Phenotypically, they may differ in characteristics such as loudness, attributions, and emotional valence. However, more importantly, it remains debatable as to what extent the range of VAH experienced by studied persons has a shared pathophysiology. In fact a final common pathway [18], a commonly shared and crucial pathophysiological factor in the occurrence of VAH, might not be present. Although studies on group level can generate some hypotheses, when designing an individual therapy the psychiatrist aims to direct its approach to the personal pathophysiological factors that seem both feasible and effective to reduce VAH.

3.   DISCUSSION

What can we learn from this thesis? The use of fMRI allows a step-by-step description of the interacting brain functions that constitute the experience of VAH, with the localization of such functions being a precondition for localized intervention. Chapter 2 shows how local brain interventions using *repetitive transcranial magnetic stimulation*

(rTMS) can be applied to treat VAH. Local intervention techniques, such as rTMS, provide a direct form of guided intervention in the live brain and are, therefore, potent treatment options. However, a clearer understanding of the underlying principles of brain organization is necessary to more effectively modulate the hallucinating brain [19, 20]. Targeting the largest activation blob using fMRI-guided rTMS will probably not be sufficient because, since the introduction of fMRI-guided rTMS [21], no major studies have supported the efficacy of such an approach.

Then, Chapter 3 shows that the phenomenology of VAH is reflected by specific patterns of neural activity at the scale of neural systems. Although the experience of VAH is in itself a specific category, VAH have a wide range of phenomenological characteristics that have different counterparts in the brain (Chapter 3). This is important since only a 'mild altering' of the experience of VAH, rather than a total shutdown of such phenomena, could be a welcoming approach for patients who are treatment resistant to VAH. Reducing the intrusiveness of the VAH experience by altering specific characteristics (e.g. location, origin or emotional context) could improve the levels of distress and the daily functioning of patients that experience VAH [22-24]. Activation of the planum temporale, that we found in patients experiencing external VAH, indicates a secondary role of this anatomical structure in the mediation of VAH in schizophrenia spectrum disorders. As planum temporale activation is not present in the internal VAH group, it is not a prerequisite for a VAH experience and probably reflects the process of externalizing VAH. A similar phenomenological variability might be reflected by the differing degrees of activation of the primary auditory cortex during VAH, as also reported by others [1, 25, 26]. The peripheral role of the auditory cortices is also reflected in the study in Chapter 5, where the auditory cortices were observed to be less central to the functional networks related to the actual hallucination experience. Therefore, the underconstrained activity of the auditory cortex, as the source of VAH, is less likely as a model for the pathogenesis of hallucinations.

The question remains as to what model can accurately explain the occurrence of VAH at the scale level of communicating brain regions. A range of models has been proposed for the development of VAH, each with (some) overlap and associated discrepancies (see Chapters 1 and 4). Studies on functional connectivity related to VAH also differ with respect to several aspects of their findings. This may be due to the phenotypical heterogeneity of even such a narrowly defined symptom as VAH. In general, however, functional connectivity studies have consistently shown aberrant connectivity between the superior temporal gyrus/temporoparietal junction (Wernicke), inferior frontal gyrus (Broca), anterior cingulate, insula, cerebellum and parahippocampus [27-33], whether it be reduced or increased connectivity and/or in the left-sided dominant language regions as their homologues. Therefore, distorted interaction within and between the language networks and cognitive control networks can be considered a general neuro-

functional proxy of hearing voices. Additionally, studies converge on the presence of aberrant connectivity between memory and language networks, particularly directly preceding the occurrence of VAH [4, 31, 34, 35]

Generally, hypothesis-based fMRI studies run the risk of missing important information in the data, i.e. they might be too constrained with regard to the involvement of other functional networks and/or the methodology might be so restricted that only the dominant models are examined. As described by Kuhn [36], this could confine the research field until there is a dead end, or until so many anomalies are discovered that a paradigm shift is necessary. Our studies, borrowing from neighboring fields of research and using data-driven techniques, have provided an alternative or complementary perspective. Chapter 4 shows how the concepts from network science can be used to integrate the different fields of research that examine psychotic symptoms, e.g. the attractor networks on the microscale in biomathematics, the communicating brain areas of neuroimaging on the mesoscale, or the social and cultural aspects in social science on the macroscale. In our INMOPS theory (Chapter 4), the instability of attractor networks on the microscale result in fleeting representations and brisk associations, which work through to a higher level of organization. The phenomenological variability of VAH could also be integrated into a network model, with certain pathological factors connecting to specific phenomenological aspects of VAH. The main message is that integration of the pathophysiological factors allows to build a mechanistic model that psychiatry can work with. Chapter 5 presents an attempt to maximally uphold data-driven research, while borrowing tools from network science to assist in analyzing the complex flow of information through the brain. In this way, we obtained a more comprehensive view, compared with previous approaches, of neural events at a systems level that contributes to the experience of VAH in humans. Thus, we were also able to explore a range of hypotheses that were generated in the past decades related to the experience of VAH in human patients.

Neuroimaging analyses such as ours estimate the directions of links between functional entities, allowing for the delineation of functional *circuits* responsible for hallucinations and other symptoms. Derived from Northoff and Qin, our INMOPS states that large-scale networks (such as DMN and CEN) show an increased susceptibility to noise intrusion, with noise 'spilling over' from the DMN to the CEN to be mistakenly taken for external percepts [37]. However, this hypothesis did not hold in our data-driven study in Chapter 5. Both anterior and posterior DMNs were situated at a greater distance from that hallucinatory experience in the network. Similarly, Jardri et al. [38] found that the occurrence of VAH was concomitant with *withdrawal* of the DMN, although the temporal and spatial instability of the DMN generally did correlate with the severity of VAH. Memory-related brain regions were also found at a distance from the hallucination-circuit, suggesting that memory-networks are unlikely as being

involved in the direct experience of VAH. With this data, however, it is still possible that the DMN or language-networks provides the content that is wrongly attributed further downstream, as hypothesized by several authors [34, 35, 38].

Manoliu et al. [15] studied the intrinsic connectivity (as well as interactions) between subparts of the CEN, DMN and SN and correlated these with schizophrenia symptoms. Specifically for hallucinations, the intrinsic connectivity of right anterior insula inversely correlated with hallucination severity, as measured with the Positive and Negative Syndrome Scale (PANSS). Increased functional connectivity between the anterior DMN and right CEN was positively correlated with hallucination severity. Additionally, they also found that time-lagged functional connectivity (1-3 seconds) from SN to the DMN and CEN was reduced in patients with schizophrenia. These findings are suggestive of an important role for the salience network and its constituents. In Chapter 5 we found that a circuit consisting of supramarginal gyrus, Broca's homologue, the right anterior insula, bilateral anterior cingulate and the premotor cortex, was the most central in the occurrence of VAH. The latter three regions are considered to be constituents of the salience network and, in our study, inference of directionality indicated that the right anterior insula gives input to the premotor cortex and anterior cingulate. The critical positioning of Broca's homologue and the right anterior insula, and their functional coupling into one functional network, led to our hypothesis that, in our patient group, VAH appear to be largely mediated by the salience network making false predictions about the risk and (hence) origin of linguistic percepts derived from Broca's homologue, followed by subsequent processing errors by other cognitive areas. The right anterior insula and Broca's homologue, together with the anterior cingulated gyrus, should be considered potential foci for interventions to improve local intervention techniques, such as *transcranial magnetic stimulation*. Although our localization of the primary sources of hallucinations is only a few inches away from that of previous hypotheses (e.g. the auditory cortex), such a small distance may produce widely differing results, and represents a major break with the traditional thinking and methods. Nevertheless, additional studies are required to further test this hypothesis.

3.1   Future directions

For the study of brain function in VAH, one fundamental principle need to be consistently acknowledged, i.e. that the brain is a layered network functioning within the context of a larger biological network. It is in the interaction of all the structural elements (from neurotransmitters to neurons and brain regions) that both the functions and dysfunctions emerge and the 'mind' exists. The mind is in constant interaction with the environment and develops under the influence of environmental stimuli, driven by the need to maneuver through the environment and survive. Similarly, men-

tal symptoms (such as hallucinations) are constructed by organic and environmental aspects. This type of 'systems thinking' is essential to advance understanding of the complex causal pathways of psychiatric illness and symptoms, and to guide future intervention [39]. Features of these multilevel networks can be related to genetics, molecular neuroscience, brain circuits, character traits, social networks and/or cultural influence, as well as their interactions. Only a well-operationalized phenotype which includes different levels of symptomatology (symptom - symptom clusters - syndromes) will enable an accurate fit with the different scale levels of the bio-psycho-social network. However, adoption of network science will not eliminate all the 'rivalry' between the levels; a fundamental difference will remain between a neurofunctional explanation versus a psychological explanation. A psychological explanation will 'tell the story' of why a particular person has a specific debilitating hallucination in that particular context. However, in the future, neurofunctional studies will provide a mechanistic or computational account of how some of the patient's genes and life events over time have increased the chance to experience a particular hallucinatory state. Although technically possible, this patient-tailored mechanistic account of VAH is not yet realized and further advancements are required in this field.

An important challenge is to develop a search procedure that will consistently converge on the correct directional information in fMRI studies for all links in the network [40]. Nevertheless, some general provisions can be proposed to provide suitable fMRI acquisition and preprocessing of fMRI data to allow a mechanistic model of VAH. Simulation studies by Smith et al. [41] and Ramsey et al. [40] have shown that accuracy in the estimation of directed links in fMRI data is dependent on factors such as the number of time points and nodes, temporal filters used, the presence of noise components, and the regions of interest (ROIs) selected. The use of functionally 'bad' ROIs (spatial map not matching the functional unit) was found to be detrimental to almost all methods used to estimate effective connectivity [41], and advocates the use of ICA-based network nodes (as in our studies) rather than atlas-based ROIs. The mixing of noise components in a network is a hazard to causal analysis, as these noise sources will provide a common cause for voxel activity (e.g. heartbeat) and create associations between voxels that are not due to direct causal links between the voxels. This called for the use of sophisticated methods to 'clean up' the fMRI time series. One effective method is to use automated classification algorithms (as shown in Chapter 5), although many possibilities to reduce interference from noise can be considered [10]. Our studies also indicate the need to study functional networks acquired with fMRI in higher spatial and temporal detail. A symptom such as VAH and its phenomenology will be reflected in aberrant interactions between subparts of the traditional large-scale networks, such as the DMN, CEN, SN and language networks. A simplification of these complex networks to such large structures carries the risk of inconsistencies in the results and of

drawing overgeneralized conclusions. The spatial scale of fMRI is steadily improving, and high-field MRI of 7+ Tesla has the potential to estimate the interactions between the separate cortical layers of a brain region [42], adding another level to the hierarchical network. After fMRI data acquisition, and preprocessing and decomposition of the functional networks, a model has to be selected to acquire functional circuits. Model selection first requires 'pruning' of the links, and current methods often apply an arbitrary cut-off to be chosen at some point in the analysis. This arbitrary cut-off can jeopardize an optimal balance between sparsity in the network and maintaining information, and can even lead to confirmation bias. Thus, additional work is needed to non-arbitrarily estimate the optimal graphical model for subsequent use in estimating the direction of links, e.g. the Bayesian information criterion [43]. Lastly, the question remains how to deal with unknown (latent) confounders in estimating the dominant direction of influence between two nodes and how best to search for dependencies that are non-linear. For instance, non-linear dynamics at a lower scale level (e.g. between cortical layers in a neural column) might strongly influence the state of a functional network as currently measured using fMRI.

Ultimately, in a robustly estimated directed network, the 'driver nodes' responsible for a hallucinatory state in an individual patient can be identified by calculating the control centrality of nodes [44]. Networks inherently learn and strive towards a limited set of dynamic states, and switch between these states under the influence of endogenous and exogenous stimuli [45]. Driver nodes have maximum ability to control a directed weighted network towards a desired state. Using local intervention techniques or fMRI-based neurofeedback, identified driver nodes can be used to design an efficient strategy to guide the functional networks to a healthier state. As such, the 'in silico' simulation of the patient's brain network is used to minimize the intervention while maximizing the effect. With the multiple challenges that remain, it is clear that the use of mechanistic network models to describe behavior is still in its infancy. Nevertheless, this field has the potential to make the translational advancements in the neuroscientific study of VAH that can help ameliorate the symptoms of the many individuals suffering from hallucinations and other psychotic phenomena.
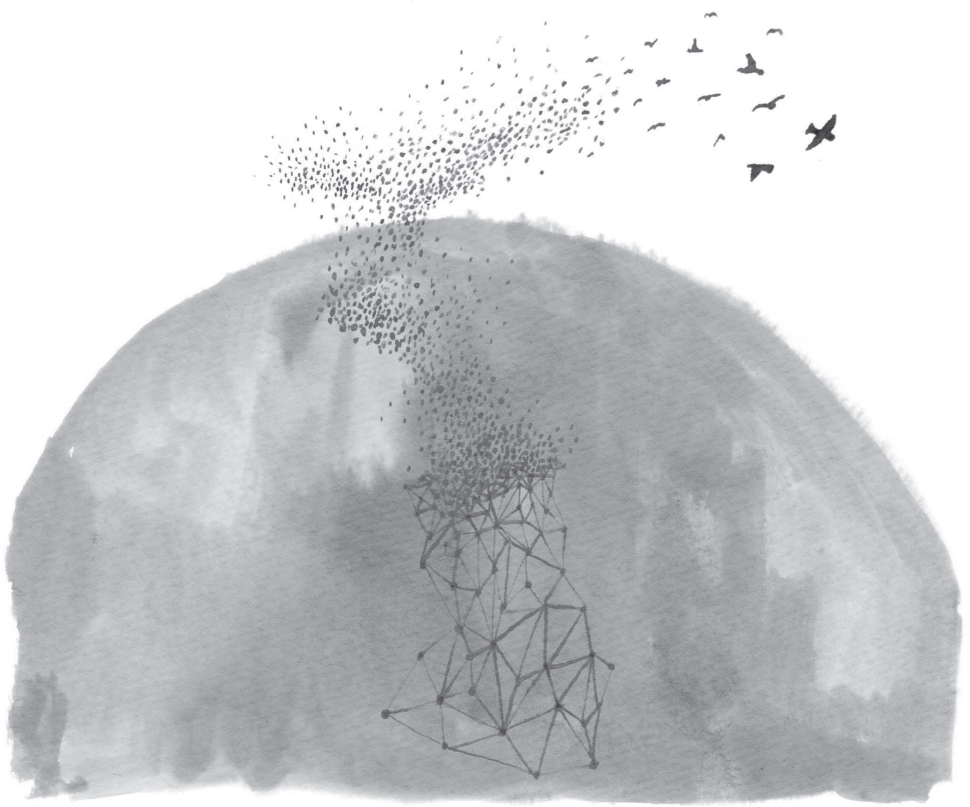
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Addendum

Samenvatting

Dankwoord

Over de auteur

Publications

SAMENVATTING

'Stemmen horen' roept voor velen het beeld op van de verwarde psychiatrische patiënt, in het bijzonder de patiënt met schizofrenie. Verbale akoestische hallucinaties (VAH) komen inderdaad het meest voor bij schizofreniepatiënten (70 %), maar zij komen ook voor bij traumagerelateerde stoornissen, stemmingsstoornissen, de borderline persoonlijkheidsstoornis en bij somatische aandoeningen, waaronder een groot aantal neurologische aandoeningen. De stemmen bij psychiatrische patiënten hebben vaak een negatieve inhoud en kunnen emotioneel ontregelend zijn. Dit in tegenstelling tot de stemmen die worden ervaren door de ca. 10 % 'gezonde' stemmenhoorders in de populatie, die over het algemeen een meer neutrale of steunende boodschap horen. Historische figuren zoals Socrates en Gandhi hoorden stemmen die hen de weg wezen bij moeilijke keuzes. In dat licht is stemmen horen op zichzelf niet indicatief voor een psychiatrische stoornis.

Dit proefschrift is erop gericht om de onderliggende mechanismen in het brein bij VAH op te helderen bij patiënten met schizofrenie, met als uiteindelijk doel om betere behandelmethoden te ontwikkelen. De behandeling van VAH heeft maar een beperkte groei doorgemaakt de afgelopen jaren. Zo bieden nieuwe antipsychotica geen aanvullende mogelijkheden voor therapieresistente patiënten met hallucinaties en zijn de bijwerkingen op korte en lange termijn nog steeds aanzienlijk. Alternatieve benaderingen zoals transcraniële magneetstimulatie hebben bovendien nog maar beperkt resultaat opgeleverd, vermoedelijk omdat niet duidelijk is waar in het netwerk van communicerende hersengebieden effectief ingegrepen kan worden. Methodologische ontwikkelingen op het gebied van functionele MRI en netwerkanalyse bieden de mogelijkheid om het brein meer omvattend en als een interacterend functioneel netwerk te beschouwen en op deze wijze realistischer modellen van hallucinatoire activiteit te ontwikkelen, wat hard nodig is bij onze zoektocht naar gerichte interventies voor VAH.

In de eerste studie (hoofdstuk 2) wordt de casus beschreven van een vrouw met diverse hallucinaties en perceptuele vervormingen, bekend als het Alice-in-Wonderland-syndroom, die werd behandeld met transcraniële magneetstimulatie. Het hoofdstuk biedt inzicht in het scala aan symptomen dat bij psychiatrische stoornissen vaak een rol speelt. Met gebruik van functionele MRI werden bij deze vrouw hersengebieden gevonden die betrokken waren bij het optreden van haar VAH. Overeenkomstig de literatuur waren dat de auditieve schors en taalgebieden, inclusief het gebied van Wernicke, de basale ganglia, het anterieure cingulum en de dorsolaterale prefrontale cortex. De behandeling met transcraniële magneetstimulatie, gericht op het gebied van Wernicke, resulteerde in volledige remissie van de VAH én van de visuele verschijnselen passend bij het Alice in Wonderland-syndroom., Daarnaast verdwenen de stemmingsklachten

en cognitieve klachten waaraan deze patiënte ook nog eens leed. De studie is illustratief voor de potentie van functionele MRI om nieuwe interventiemethoden informatie te bieden voor een meer gerichte toepassing. Daarnaast toont deze aan dat lokale stimulatie van het brein invloed kan hebben op een wijd vertakt netwerk van neurale structuren met zeer uiteenlopende functies.

VAH hebben vele verschijningsvormen. Bij de klinische beoordeling wordt traditioneel onderscheid gemaakt tussen hallucinaties die in het hoofd worden gehoord ('interne VAH') en die van buiten het hoofd lijken te komen ('externe VAH'). Interne VAH, soms ten onrechte 'pseudohallucinaties' genoemd, zouden duiden op minder ernstige pathologie. In de tweede studie (hoofdstuk 3) wordt onderzocht of vanuit neurofysiologisch perspectief redenen bestaan om een dergelijk onderscheid in de klinische praktijk te blijven hanteren. Eerder onderzoek heeft laten zien dat geluiden uit de omgeving worden verwerkt via twee netwerken in het brein, de zogenaamde 'where' en 'what' pathways. Vanuit de hypothese dat externe VAH gekenmerkt zouden worden door additionele activatie van de 'where' pathway voor auditieve stimuli, werd specifiek gekeken naar het planum temporale, de middelste frontale gyrus en de inferieure pariëtale kwab. Daartoe werden de fMRI-data van 52 psychotische patiënten met ofwel interne ofwel externe VAH onderzocht op hersenactiviteit ten tijde van de VAH. Patiënten rapporteerden tijdens het scannen het optreden van hallucinaties door te knijpen in een ballon. De analyse liet zien dat bij patiënten met externe VAH het planum temporale en de middelste frontale gyrus actief zijn, waar dit niet zo is bij patiënten met interne VAH. Onze conclusie is dan ook dat additionele activatie van de 'where' pathway bepalend is voor de ervaring dat VAH van buiten komen en dat dit het enige neurofysiologische verschil is tussen interne en externe VAH. Dit geringe verschil sluit aan bij klinische studies, die geen verschil vonden in de mate van intrusiviteit op het dagelijkse leven waarmee interne en externe VAH gepaard gaan. De bevinding pleit ook tegen het hanteren van de ongelukkige term 'pseudohallucinaties'.

In hoofdstuk 4 zetten we een stap achteruit en introduceren wij een netwerkmodel voor psychotische symptomen. Al meer dan honderd jaar worden pathofysiologische modellen gepresenteerd die het ontstaan van psychotische symptomen moeten verklaren. In de tussentijd is evenwel duidelijk geworden dat alle psychiatrische stoornissen multifactorieel zijn en dat het dus ook bij de psychosen een heilloze weg is deze te bezien vanuit een enkelvoudig perspectief van bijvoorbeeld genen, miscommunicatie in het brein of een ongelukkige sociale omgeving. Netwerken zijn wiskundige modellen die de onderlinge beïnvloeding van knopen in het systeem beschrijven middels links (verbindingen). Knopen kunnen in zo'n netwerk genen, neuronen of hersengebieden vertegenwoordigen, maar ook mensen in hun sociale context of bijvoorbeeld symptomen. Een fundamentele eigenschap van biologische netwerken is dat zij meerdere schaalniveaus hebben, wat inhoudt dat de toestand van elke knoop in het netwerk

mede wordt bepaald door onderliggende en/of bovenliggende netwerken van kleinere of grotere temporele en/of ruimtelijke schaal. Biologisch netwerken bieden de mogelijkheid om informatiestromen te analyseren. In het door ons uitgewerkte 'Integrated Network Model Of Psychotic Symptoms' (INMOPS) in hoofdstuk 4 wordt beschreven hoe psychotische symptomen verklaard kunnen worden op een drietal schaalniveaus (micro, meso en macro). Op het *microniveau* beschrijft het model populaties van neuronen die andere populaties stimuleren of er juist de competitie mee aangaan, daarbij gebruik makend van zogenaamde attractoren, toestanden van lage energie (resting state) of hoge energie (active state). Door stimulatie van een attractornetwerk kan dit sneller gaan vuren, en overgaan in een toestand van hoge energie, waardoor naburige netwerken worden gestimuleerd of juist geïnhibeerd. Bij psychotische patiënten kunnen deze attractornetwerken instabiel worden en snel wisselen tussen toestanden van hoge en lage energie. Het INMOPS-model veronderstelt dat op deze wijze intrusies optreden van vluchtige resting-state toestanden in de hoge active-state toestanden van het netwerk en dat deze ruis-intrusies als robuuste stimuli worden ervaren. Klinisch kan dit zich bijvoorbeeld vertalen als het waarnemen van dingen die er niet zijn (hallucinaties). Op het *mesoniveau* spelen dezelfde principes een rol, maar dan bij drie grootschalige, over het brein gedistribueerde functionele netwerken: het 'default-mode network' (DMN) , het 'central executive network' (CEN) en het 'salience network' (SN). Het INMOPS-model veronderstelt dat het taakgerichte en extern georiënteerde CEN bij psychosen wordt overspoeld door ruis vanuit het instabiele DMN. Het DMN is de tegenhanger van het CEN en wordt vooral actief bij interne processen zoals dagdromen, het ophalen van herinneringen en vrije associatie. Het SN heeft een rol in het toewijzen van cognitieve aandacht en lijkt bij psychosen niet in staat te zijn om tussen het DMN en CEN een heldere scheidsrechter te zijn. Hierdoor kunnen cognities vanuit het DMN zich opdringen aan het CEN en zich vervolgens manifesteren als werkelijke ervaringen. Op *macroniveau* wordt de kans op het optreden van hallucinaties en andere psychotische symptomen verklaard in termen van sociale isolatie. Sociale isolatie en afwijzing voeden factoren als angst en achterdocht en leiden in het brein tot een toestand van alertheid. Zo ontstaat een vicieuze cirkel, waarbij psychotische kwetsbaarheid en sociale isolatie elkaar versterken en het netwerk als geheel een voorkeursstand ontwikkelt voor het genereren van psychotische belevingen. Op deze manier beschrijft het gelaagde INMOPS-model hoe uiteenlopende psychopathologische mechanismen in onderling verband de kans op het optreden van psychotische symptomen beïnvloeden.

Na de voorgaande theoretische onderzoeking worden op basis van fMRI-data functionele netwerken bestudeerd die ten grondslag liggen aan VAH (het mesoniveau van het INMOPS-model). Uitgangspunt voor deze studie was om met zo min mogelijk à priori aannames in het gehele brein te zoeken naar circuits die betrokken zijn bij het optreden van VAH. De fMRI-data van 85 patiënten met psychotische stoornissen en

frequente hallucinaties konden worden opgedeeld in 98 functionele netwerken die de gehele toestand van het brein omvatten. Deze 98 functionele netwerken clusterden in zeven modules, die op hun beurt metafuncties van het brein vertegenwoordigden. Vervolgens werden de functionele netwerken die actief werden bij het optreden van VAH geïdentificeerd. Om de informatiestroom in neurale circuits goed te kunnen duiden, werd met behulp van netwerkanalyses hun dominante richting vastgesteld. Het neurale circuit direct betrokken bij het optreden van hallucinaties bestond uit het anterieure cingulum, de rechter anterieure insula, de rechter homoloog van het gebied van Broca en onderdelen van het cerebellum. Het anterieure cingulum en de anterieure insula vormen gezamenlijk het centrale deel van het SN. Op basis van onze bevindingen is onze hypothese dat VAH bij deze doelgroep ontstaan doordat taalkundige constructen vanuit de rechtszijdige homoloog van het gebied van Broca in het SN een niet passende betekenis wordt toebedeeld. De primaire auditieve schors en de verschillende onderdelen van het DMN, inclusief de (para)hippocampus lijken daarbij een minder belangrijke rol te spelen. Los van de bovenstaande neuropsychologische duiding van breinprocessen, biedt onze studie een mechanisch inzicht in het optreden van hallucinaties en is daarmee in staat richting te geven aan het focus van interventies. Wij verwachten dat het richten van lokale interventietechnieken zoals transcraniële magneetstimulatie op het SN en/of de rechtszijdige homoloog van het gebied van Broca effectiever zal zijn dan interventie op de standaardlocatie (de linkszijdige temporopariëtale overgang).

De uitgevoerde onderzoeken laten zien dat het gebruik van functionele MRI inzicht kan bieden in de ontstaanswijze van hallucinaties en met grote nauwkeurigheid hersengebieden kan identificeren die hierbij een actieve rol spelen. Bovendien laten zij zien dat deze hersengebieden met behulp van netwerkmodellen kunnen worden begrepen in de context van het brein als geheel. Op deze wijze wordt meer recht gedaan aan de complexiteit van het horen van stemmen en aan alle daarbij betrokken factoren. Al met al laat dit proefschrift zien dat het gebruik van netwerkanalyses en fMRI-technieken uitzicht op behandelingen conform de principes van *personalised medicine*, met daarbij de mogelijkheid om op individueel niveau te voorspellen waar in het netwerk het meest effectief ingegrepen kan worden.

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OVER DE AUTEUR

Jasper Looijestijn (Voorburg, 1983) startte zijn studie geneeskunde in 2001 aan de Universiteit Leiden. Tijdens zijn opleiding werkte hij als explanteur voor de donatie van botten bij Eurotransplant/Bio Implant Services, en hij deed voor de start van zijn co-schappen een periode vrijwilligerswerk in een ziekenhuis in Sivakasi, India. In 2008 studeerde hij af als arts. In hetzelfde jaar startte hij met de opleiding tot psychiater bij de Parnassia Groep te Den Haag. Tijdens zijn eerste opleidingsstage werkte hij mee aan een onderzoek aangaande de behandeling van hallucinaties met behulp van transcraniële magneetstimulatie. Deze studie vormde de basis voor het promotietraject van Jasper, een samenwerking tussen de Parnassia Groep, het UMC Utrecht, en het UMC Groningen. In 2013 rondde Jasper zijn opleiding tot psychiater af, en ging als psychiater aan het werk bij PsyQ Rotterdam op de poli persoonlijkheidsstoornissen: een afdeling gespecialiseerd in groepspsychotherapie in een multidisciplinair kader. Als teampsychiater zet hij zich in voor het zoeken van een passende behandeling voor de patiënten die tussen wal en schip dreigen te vallen. Daarnaast geeft hij groepstherapie en is in opleiding tot therapeut volgens de Mentalisatie Bevorderende Therapie (MBT). Sinds januari 2017 is hij plaatsvervangend opleider voor de opleiding psychiatrie van Parnassia Rijnmond, waar hij mee werkt aan het opbouwen van een jonge opleiding en onderwijs geeft aan de psychiaters in opleiding. Jasper en zijn vriendin Anne Kampstra hebben drie kinderen, Morris (2014), Wies (2016) en Juno (2017), en wonen in Voorburg.

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