Exploring function in the hallucinating brain

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Chapter 1

General introduction

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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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