A transdiagnostic comparison of hallucinations

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Chapter 1

General introduction
Chapter 1

Hallucinations and related phenomena

Hallucinations are perceptions experienced in the absence of external stimuli. Hallucinations can occur in every perceptual modality, e.g., auditory, visual, tactile, and olfactory modalities (see Box 1 for examples).

**BOX 1. Examples of hallucinations in various modalities**

<table>
<thead>
<tr>
<th>Hallucination modality</th>
<th>Examples given by individuals who participated in our studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory</td>
<td>The doorbell, Christmas song “Jingle Bells”, or insulting voices “You're fat”.</td>
</tr>
<tr>
<td>Visual</td>
<td>Camels in the room, deceased grandparents, a black shadow.</td>
</tr>
<tr>
<td>Tactile</td>
<td>A hand on the person’s arm or cheek, itching little creatures.</td>
</tr>
<tr>
<td>Olfactory</td>
<td>A sudden smell of bananas, the smell of fire.</td>
</tr>
</tbody>
</table>

A milder form of hallucinations is termed “minor hallucinations” which includes misperceptions, illusions, passage hallucinations, and sensed presence. The definitions of these phenomena are explained in Box 2.

Delusions are beliefs that are clearly false and indicate an abnormality in the affected individual’s content of thought. This false belief is not in line with the individual’s cultural or religious background or his or her level of intelligence. A key feature of delusions is the high level of conviction that this belief is true. There are various types of delusions. An example is a paranoid delusion in which the individual is highly convinced that he or she is being observed by the secret service all day. Delusions can co-occur with hallucinations. In combination, hallucinations and delusions can be frightening, are sometimes associated with aggression and self-harm, and are invariably related with poor psycho-social functioning (Kaplan & Harrow, 1999; Evensen et al., 2011; Penagaluri et al., 2010). Assessing the presence of both hallucinations and delusions could help establish later risk of psychosis in individuals with a diagnosis other than a primary psychotic disorder (Waters et al., 2017).

Both hallucinations and delusions are psychotic experiences. The term psychotic experiences generally refers to subthreshold forms of hallucinations and delusions, whereas psychotic symptoms refer to full threshold positive phenomena (Yung & Lin, 2016). In this thesis, we use the term psychotic experiences as an umbrella term for both subthreshold and full threshold phenomena.
BOX 2. Definition of hallucinations and related phenomena

<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hallucinations</strong></td>
<td>Hallucinations are perceptions in the absence of external stimuli, e.g., hearing a voice whereas no one else can hear this.</td>
</tr>
<tr>
<td><strong>Illusions</strong></td>
<td>Illusions are misperceptions of an external stimuli, or perceiving something different than it is in reality, e.g., seeing a person when there is actually a coat on a hanger.</td>
</tr>
<tr>
<td><strong>Passage hallucinations</strong></td>
<td>Passage hallucinations concerns a sensation that something is passing sideways, e.g., seeing an animal pass in the corner of your eye that is not there when you turn your head.</td>
</tr>
<tr>
<td><strong>Sensed presence</strong></td>
<td>Sensed presence refers to the sensation that someone is nearby, without seeing that person or anyone actually being present, e.g., a guardian angel.</td>
</tr>
<tr>
<td><strong>Misperceptions</strong></td>
<td>The term misperception is often used as an umbrella term for both hallucinations and illusions (Blom, 2010).</td>
</tr>
<tr>
<td><strong>Delusions</strong></td>
<td>Delusions are false beliefs that are very persistent, unreal and are not shared by others with the same educational and cultural background. These beliefs should include a strong degree of conviction.</td>
</tr>
</tbody>
</table>

**Transdiagnostic approach**

The usefulness of the current psychiatric classification, which is based on the ICD/DSM categorical diagnoses (APA, 2013), remains a debatable issue (Kendell & Jablenksky, 2003; First et al., 2018). As a promising alternative, the “transdiagnostic” approach has been put forward. This approach cuts across existing categorical diagnoses and could thereby improve the way we classify and treat mental disorders (Cuthbert et al., 2014).

Until recently, a diagnosis-based approach dominated the way hallucinations were conceptualized and researched. Hallucinations are traditionally studied within context of schizophrenia. This diagnosis-based approach has determined how treatment options have been developed and evaluated. Whilst this approach has proven effective in the past, previous studies have indicated that hallucinations are not necessarily a hallmark symptom of psychosis (Waters et al., 2018), but also occur in a wide range of other diagnoses (Sommer et al., 2012). Consequently, there is growing consensus among international experts that a transdiagnostic approach, symptom-based approach, is needed to further enhance the hallucination research field (Ford et al., 2014; Waters et al., 2014b; Waters & Fernyhough, 2017; Pienkos et al., 2019). A transdiagnostic approach is compatible with the Research Domain Criteria (RDoC) established by the US National Institute for Mental Health, as an alternative for DSM criteria (Insel et al., 2010).

**Phenomenology**

Hallucinations can present in various forms across individuals characterized by similarities and/or differences in phenomenological features. Phenomenology refers to the clinical characteristics of hallucinations, such as frequency, duration, amount of distress, content, and insight into the realness
of hallucinations. A large heterogeneity in phenomenological characteristics is reported within and across diagnoses (McCarthy-Jones et al., 2014).

Questionnaires and interviews can be used to assess phenomenological characteristics of hallucinations. There is a wide variety of questionnaires, each used to assess a set of psychotic experiences in one specific diagnosis. For example, the Psychotic Symptom Rating Scales (PSYRATS; Haddock et al., 1999) is used in schizophrenia. the Scales for Outcomes in PArkinson’s disease-Psychiatric Complications (SCOPA-PC; Visser et al., 2007) in Parkinson’s disease, the Neuropsychiatric Inventory (NPI; Cummings et al., 1994) in dementia, and North-East Visual Hallucinations Interview (NEVHI; Mosimann et al., 2008) in the elderly.

**Hallucinations across diagnoses**

Hallucinations are considered a core symptom of schizophrenia. However, hallucinations also occur in a range of other psychiatric, neurological and general medical disorders, and even in a minority of the healthy individuals (Sommer et al., 2012). Hence, psychotic experiences cut across diagnoses and are not uniquely diagnostic of schizophrenia (Waters et al., 2017; Waters & Fernyhough, 2017). Box 3 illustrates this by some case examples of individuals who experience hallucinations.

**BOX 2. Examples of hallucinatory experiences in different diagnoses**

<table>
<thead>
<tr>
<th>Hallucination</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peter hears voices for over 20 years. He hears both gods and devils that yell at him and tell him to hurt himself. He tries to ignore the voices, but that does not always work.</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Susan has vision loss, yet she sees angry faces alongside the street who keep staring at her.</td>
<td>Visual impairment</td>
</tr>
<tr>
<td>Elizabeth sees visitors that no one else sees and she has tea with them. Sometimes she wishes they would not visit her as she prefers to be alone with her husband.</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Dennis remembers frightening ‘unreal’ experiences during his stay at the ICU, but he is ashamed to admit it because he thinks that people might assume he is mentally unstable.</td>
<td>Delirium</td>
</tr>
<tr>
<td>Sally hears a voice of the men that threatened her during a robbery a few months ago. She hears him shout and use his gun when she relives this horrific moment.</td>
<td>Post-traumatic stress disorder</td>
</tr>
</tbody>
</table>

**Hallucinations in psychiatric disorders**

**Schizophrenia**

Patients with schizophrenia often report hearing voices (i.e., auditory verbal hallucinations), but hallucinations in other modalities are experienced as well (Waters et al., 2014a). Around 60-80% of the patients with schizophrenia experience voices (Andreasen & Flaum, 1991), of which 25% is
treatment resistant (Shergill et al., 1998). Patients often experience voices on a daily basis often last for more than an hour per episode (Nayani & David, 1996). The voices often have a negative content such as comments on their behavior, criticism, or instructions to harm themselves or others (Nayani & David, 1996; Close & Garety, 1998; Davies et al., 2001; Delespaul et al., 2002; Johns et al., 2002). These voices can be so destructive, that they can lead to hospitalization and increase risk of suicide (Hor et al., 2010). Most patients have no insight in the realness of their hallucinations, making the experiences even more frightful (Amador & David, 2004). Delusions often co-occur with hallucinations in schizophrenia and are often persecutory or paranoid in nature. Hallucinations and delusions can be strongly intertwined, confirming each other in their realness (Rosen et al., 2016).

**Bipolar disorder**

Up to 57% of the patients with bipolar disorder have reported to experience hallucinations during either a depressive or manic episode (Taylor and Abrams, 1975; Hammersley et al., 2003; Baethge et al., 2005). Hallucinations are mostly auditory, although hallucinations also occur in other modalities (Toh et al., 2015). Whereas the phenomenology of hallucinations in schizophrenia is extensively investigated, few studies exclusively focused on the phenomenological features of hallucinations in affective psychosis (Toh et al., 2020a). There is considerable phenomenological overlap with hallucinations in schizophrenia (Okulate & Jones, 2003; Toh et al., 2015). The voices are heard almost continuously, are negative or self-referential in content, and predominantly include command hallucinations (Okulate & Jones, 2003; Kumari et al., 2013). Delusions are also experienced in both manic and depressive episodes. During manic episodes, delusions of grandeur are typical, although delusions of persecution are common as well (Bebbington & Freeman, 2017).

**Borderline personality disorder**

Hallucinations are experienced in as many as 50% of the patients with borderline personality disorder (Kingdon et al., 2010; Niemantsverdriet et al., 2017). Auditory verbal hallucinations are the most common form, although visual and olfactory hallucinations also occur. There is a large phenomenological overlap with schizophrenia patients (Kingdon et al., 2010; Slotema et al., 2012), including distressing voices that frequently occur over long periods of time with an equally or even more severe negative content (Yee et al., 2004). Paranoid delusions often co-occur with hallucinations in borderline personality disorder and are common in 20-33% of the patients (Kingdon et al., 2010; Pearse et al., 2014). There is a strong association between childhood trauma, hallucinations, and delusions in borderline personality disorder (Niemantsverdriet et al., 2017; Bebbington & Freeman, 2017).

**Post-traumatic stress disorder**

Prevalence rates of auditory hallucinations can be as high as 50% in patients with post-traumatic stress disorder (Anketell et al., 2010). Psychotic experiences in post-traumatic stress disorder include auditory, visual, olfactory and tactile hallucinations, and delusions that are often paranoid in nature (Butler et al., 1996; Hamner et al., 2000; Morrison et al., 2003; Campbell & Morrison, 2007).
Hallucinations in post-traumatic stress disorder are comparable to hallucinations in schizophrenia with regard to severity and phenomenological features, although command and derogatory hallucinations are more common in post-traumatic stress disorder (Hamner et al., 2000; Jessop et al., 2008). Delusions in patients with post-traumatic stress disorder are commonly less severe than in schizophrenia patients (Hamner et al., 2000). Patients with post-traumatic stress disorder often report persistent voices that can be related or unrelated to their past traumatic experiences (e.g., hearing voices that cry for help in combat veterans) (Wilcox et al., 1991; Hamner et al., 2000; Jessop et al., 2008; Anketell et al., 2010). Hallucinations in post-traumatic stress disorder are associated with high levels of distress and a history of suicidal ideation and behavior (Scott et al., 2007; Jessop et al., 2008; Anketell et al., 2010).

**Hallucinations in the general population**

**Non-clinical individuals**

Whereas hallucinations are typically seen as a hallmark symptom of schizophrenia, hallucinations also occur in around 5-15% of the healthy population (Tien, 1991; Kråkvik et al., 2015). These individuals do not meet the criteria for a mental health disorder and are not in contact with a mental health service (Sommer et al., 2010; Powers et al., 2017). Therefore, these individuals are often referred to as “non-clinical”. Auditory verbal hallucinations, i.e., hearing voices, are most commonly reported in these individuals. These voices are often heard a couple of times per week, lasting for a few minutes, with a high degree of perceived control. The voices often relate to religious or supernatural aspects (Sommer et al., 2010; Daalman et al., 2011; Powers et al., 2017). The proportion of non-clinical individuals that experience negative hallucinations ranges from a minority to slightly over half, with minimal disturbance to daily functioning (Honig et al., 1998; Sommer et al., 2010; Daalman et al., 2011). Hallucinations in other modalities (i.e., visual, tactile and olfactory) are relatively frequent as well (Toh et al., 2020b). These individuals report no delusions, but present with increased levels of paranoid tendencies, magical thinking and subclinical levels of disorganization (Sommer et al., 2012).

**Hallucinations in general medical disorders**

**Delirium**

Post-operative psychotic experiences are not uncommon, but often remain unnoticed and are under-researched (Webster & Holroyd, 2000; Eriksson et al., 2002; Ottens et al., 2020). Hallucinations and delusions are symptoms of delirium (Webster & Holroyd, 2000), but post-operative psychotic experiences can also occur non-delirious patients (Eriksson et al., 2002; Ottens et al., 2020). Of those with delirium, up to 67% of patients have psychotic experiences, including hallucinations in all modalities and delusions (Webster & Holroyd, 2000; Eriksson et al., 2002; Ottens et al., 2020). Visual hallucinations are most commonly experienced (Webster & Holroyd, 2000; Ottens et al., 2020). These post-operative hallucinations can be relatively mild, as few patients experienced significant
discomfort or anxiety (Ottens et al., 2020), whereas vivid hallucinations in delirium can be traumatic for the patient (O’Keeffe, 1999). Delusions are reported in 25% of delirium patients, with paranoia being the most common type (Webster & Holroyd, 2000).

**Hallucinations in neurodegenerative disorders**

**Alzheimer’s disease**
Hallucinations occur in about 6-40% of patients with Alzheimer’s disease (Ballard et al., 1995; Farber et al., 2000; Street et al., 2000; Wilson et al., 2000; Zhao et al., 2016; Linszen et al., 2018), with visual hallucinations experienced most often (Lin et al., 2006; Holroyd et al., 2000). The prevalence of delusions is between 9-59% and is mostly paranoid in nature, or concern delusions of misidentification (Zhao et al., 2016; Bebbington & Freeman, 2017). For instance, patients believe that their partner or someone close to them is stealing from them, or burglars trying to steal their property. The presence of psychotic experiences in patients with Alzheimer’s disease is associated with reduced well-being, increased caregiver distress, and worse prognosis (e.g., earlier placement in a nursing facility) (Lyketsos et al., 2002; Steffens et al., 2005).

**Dementia with Lewy bodies**
Hallucinations are considered a core symptom in dementia with Lewy bodies, and occur in about 80% of these patients (McKeith et al., 2017). Hallucinations present in all modalities (McKeith et al., 1992), but most often include visual hallucinations that are vivid, realistic events, featuring people, children or animals (McKeith et al., 2017). The patient’s response to their hallucinations varies in both emotional reaction and insight (McKeith et al., 2017). Some patients also experience minor hallucinations, such as passage hallucinations, sensed presence, and visual illusions. Up to 57% of the patients experience delusions, such as paranoid delusions or delusions of misidentification (Aarsland et al., 2001; Nagahama et al., 2007). Delusions of misidentification concern ideas that one’s home is not their home, or a relative is being replaced by an imposter (Bebbington & Freeman, 2017). In some patients, psychotic experiences may lead to symptoms of anxiety and agitation (McKeith et al., 2017).

**Parkinson’s disease**
Hallucinations and delusions can be part of the symptomatology of Parkinson’s disease. Visual hallucinations are among the most experienced (Fénelon et al., 2000; ffytche et al., 2017). Minor hallucinations (e.g., illusions, passage hallucinations, and sensed presence hallucinations) often present in the early stages of the disease with a prevalence of 17-72% in newly diagnosed patients with Parkinson’s disease (Pagonabarra et al., 2016; Fénelon & Alves, 2010). These minor hallucinations are often benign and do not necessarily distress the patient. The prevalence of visual hallucinations ranges from 22-38% (Fénelon & Alves, 2010) and typically concern complex images such as animals or people. Visual hallucinations occur more frequently in the evening or at night, and often occur several times a day, lasting from seconds to several minutes (Ravina et al., 2007; Fénelon et al., 2000;
Auditory hallucinations occur less often (22-28%) and are often described as simple noises, voices or music (Inzelberg et al., 1998; Fénelon et al., 2000; Chou et al., 2005; Fenelon & Alves, 2010). The presence of cognitive deficits, sleep-wake disturbances, and duration of the disease have been associated with an increased risk of psychotic symptoms (Fénelon et al., 2000). Delusions are less common than hallucinations and tend to be paranoid in nature, concerning stealing, infidelity, or misidentification (Aarsland et al., 2001; Chou et al., 2005).

**Hallucinations in sensory impairment**

**Visual impairment**

In people with visual impairment, about 11% report the presence of complex visual hallucinations (Teunisse et al., 1995; Teunisse et al., 1996; Menon et al., 2003). Visual impairment can be caused by a wide variety of ocular pathologies anywhere along the visual pathway, from the eye itself to the occipital cortex (Menon et al., 2003). Some of these patients experience recurrent complex visual hallucinations, have full or partial insight into the unreal character of their hallucinations, and do not report hallucinations in other modalities, or delusions (Teunisse et al., 1996). These individuals meet the diagnostic criteria of Charles Bonnet Syndrome (Teunisse et al., 1996), although other definitions have been proposed as well (Menon et al., 2003; ffytche, 2007). The hallucinations are often neutral or even positive in emotional content but have also been reported to be irritating and distressing (Teunisse et al., 1996; Santhouse et al., 2000; Menon et al., 2003). The hallucinations concern images of people, disembodied faces, animals, or scenes. Simple hallucinations, such as flashes, repetitive patterns occur more often than complex hallucinations in individuals with visual impairment, and prevalence rates are likely to be underestimated (ffytche, 2005). Visual hallucinations in these individuals are thought to be caused by reduced sensory input from the eyes (a phenomenon often referred to as deafferentation) resulting in increased spontaneous activity in the visual cortex (ffytche, 2009), although others have suggested that deafferentation alone fails to explain why only a minority of visual impairment patients experience hallucinations (ffytche, 2007).

**Hearing impairment**

Auditory hallucinations are common in patients with hearing impairment. In these individuals, musical hallucinations have been reported (Teunisse et al., 2012), but other forms of auditory hallucinations, such as voices and doorbells, have also been described (Cole et al., 2002; Linszen et al., 2018). The prevalence of complex auditory hallucinations in adults with hearing impairment is 16% (Linszen et al., 2018), which increases with severity of the impairment. According to some, tinnitus can be regarded as a simple form of hallucinations resulting from spontaneous activity in the auditory cortex. Tinnitus often co-occurs with auditory hallucinations in patients with hearing impairment (Linszen et al., 2018). Hallucinations mostly restrict to the auditory modality and delusions are absent (Waters et al., 2017).
Psychosis continuum

The notion that psychotic experiences also occur in milder forms in the general population suggests the existence of a psychosis continuum. This psychosis continuum comprehends the range of subclinical psychotic experiences in healthy individuals on one end, to individuals with a psychotic disorder on the other (Van Os et al., 2000). It is generally assumed that when hallucinations share phenomenological properties, such as auditory verbal hallucinations in healthy individuals and patients with schizophrenia (Daalman et al., 2011), they also share a neural mechanism. As of yet, it is unclear whether hallucinations across the psychosis continuum indeed share neural mechanisms.

The brain as a complex network

The brain can be considered a complex network. The network organization is important for effective communication between different brain areas (Bullmore & Sporns, 2009; Stam, 2014). Schizophrenia is proposed to be a “disconnection syndrome” (Friston & Frith, 1995; Friston, 1998, Stephan et al., 2009) as early neuroimaging studies provide evidence for aberrant functional connectivity (Volkow et al., 1988; Weinberger et al., 1992). Disconnectivity of the brain network can lead to a range of symptoms, including positive, negative and cognitive symptoms, thereby explaining the heterogeneity of the disease.

The brain network can be studied using structural (sMRI) and functional Magnetic Resonance Imaging (fMRI). Whereas the structural brain network can be seen as the roads that connect different brain areas, functional brain networks can be seen as the “cars” that drive on the road so that information can be exchanged between different brain areas. The functional brain network can be studied using resting state fMRI. Hence, the brain is considered a functional network in which continuous information transfer takes place between functionally linked regions of the brain. A functional link, or connection, is defined as the temporal coherence in neuronal activation of anatomically disturbed brain regions during task or at rest (i.e., resting state) (Friston et al., 1993; van den Heuvel and Hulshoff Pol, 2010). The coherence in neural activation between any two regions in the brain is considered a proxy for the extent to which these regions cooperate. Using network theory, the brain regions are termed nodes, and the connections between them are called edges (Rubinov & Sporns, 2010). The term functional connectome refers to the brain’s functional connectivity network defined by a matrix representing all possible pairwise edges between each node (Sporns, 2014).

Network theory has arisen as a valuable tool to investigate complex neural phenomena (Fornito et al., 2012). When comparing patient populations with healthy controls, abnormalities in network connectivity can be detected that may provide insight into the underlying neurobiological mechanism of disorders or symptoms, such as hallucinations (Bassett & Bullmore, 2009; Hugdahl & Sommer, 2018). Furthermore, by investigating the hallucinating brain as a complex network, we consider the possibility that areas involved in the occurrence of hallucinations do not function in isolation, but rather result from aberrant interactions between brain areas or networks.
There are several ways in which properties of the brain network can be investigated. In this dissertation, we focus on; 1) altered connectivity between individual nodes of the functional connectome to obtain information on local network alterations; 2) the modular organization of the functional connectome to investigate possible alterations in the global modular organization, and alterations in within- and between-module connectivity between subnetworks of the brain. Both concepts will be explained in the following paragraphs.

Network-based statistics (NBS) is a method to carry out statistical analyses on large networks to detect differences between groups (Zalesky et al., 2010). Using NBS, every connection in the network can be tested while controlling for multiple comparisons to investigate disconnectivity related to hallucinations (Zalesky et al., 2010). In this dissertation, this method is specifically used to investigate connectivity between higher-order cognitive and sensory regions following the top-down and bottom-up theoretical model.

Modular organization refers to the concept of functional large-scale networks that form identifiable “modules” at rest (Power et al., 2011). These modules, and their inter- and intra- connectedness, are suggested to support specific (cognitive) functions (Power et al., 2011). Nodes within each module are typically strongly interconnected (within-module connectivity), and are sparsely connected to nodes outside of their module (between-module connectivity) (Newman & Girvan, 2004; Gu et al., 2016). The strong connectivity of nodes within a module suggest that these nodes share a common function (i.e., integration), whereas weak connectivity between nodes of different modules suggests they are likely to have different functions (i.e., segregation). For example, nodes in the auditory, visual, sensory and motor areas of the brain are densely connected in modules and are therefore specialized for sensory and motor functions. Higher-order cognitive functions, such as working memory, attention and planning have not been localized to a particular cortical area. Hence, these functions are more likely to depend on network integration rather than a segregated modular function (Baars, 1989; Dehaene & Naccache, 2001).

**Aim of this thesis**

The aim of this thesis is to gain more insight in transdiagnostic hallucinations by studying the possible similarities and differences in phenomenological features and neural mechanisms. In line with the RDoC criteria, we advocate for a symptom-based approach to hallucinations, instead of the commonly applied diagnosis-based approach. To this end, the thesis is divided in two parts.

Part I describes the phenomenology of hallucinations across disorders. In **Chapter 2**, a new transdiagnostic measure, the Questionnaire for Psychotic Experiences (QPE), is developed and validated. The QPE facilitates investigation of hallucinations and delusions across diagnoses. In this chapter, the introduction and psychometric validation of the Dutch version of the QPE is described. In **Chapter**
In Chapter 3, the validation of the English version of the QPE is described in a population of patients with schizophrenia and mood disorders. In Chapter 4, detailed phenomenological comparison of hallucinations and delusions across a wide range of disorders is described.

In part II, functional Magnetic Resonance Imaging (fMRI) is used to investigate overlap in neural correlates between schizophrenia patients with hallucinations, bipolar disorder with and without hallucinations, non-clinical individuals with hallucinations and healthy controls without hallucinations. More specifically, in Chapter 5, we investigate alterations in individual connections of the functional connectome using NBS to examine if similar disturbances are related to hallucinations in individuals with hallucinations across the psychosis continuum. In Chapter 6, we investigate the modular organization of the functional connectome to examine whether alterations in the global modular organization, or alterations in segregation and integration between networks relate to the occurrence of hallucinations across the psychosis continuum. Lastly, in Chapter 7, the findings of this thesis are summarized and a general discussion is provided in Chapter 8.
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Chapter 1


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Chapter 1


General introduction