Chapter 8

General discussion
In this final chapter, the main findings of this thesis are discussed in light of relevant literature and methodological considerations. Also, clinical implications and recommendations for future research are discussed.

**Questionnaire for Psychotic Experiences (QPE)**

The findings of Chapters 2 and 3, show that the QPE is easily applicable as it is a structured interview in which all questions can be read aloud. The QPE has a relatively short administration time. The QPE interviews were brief in most cases, taking approximately 30 minutes (Chapter 3). The interviews took longer when participants experienced multiple symptoms or when patients were not feeling well, therefore needing more time to response.

As hallucinations can be a relatively unknown symptom to clinicians working in medical disciplines other than psychiatry, the structured fashion in which the QPE is designed enables clinicians and researchers of all disciplines to screen and assess hallucinations (Chapter 3; Chapter 4; Sommer et al., 2018). This, for example, has led to a structured assessment of phenomenological characteristics of post-operative hallucinations at the Intensive Care Unit (ICU) (Ottens et al., 2019). Furthermore, the QPE was found to be applicable in clinical and non-clinical participants (Chapter 3; Linszen et al., in press), resulting in a detailed phenomenological assessment of hallucinations in the general population, which have rarely been reported.

Moreover, the QPE provides an opportunity to assess hallucinations in multiple sensory modalities, whereas disorder-specific questionnaires solely focus on one sensory modality (e.g., PSYRATS focusses on auditory verbal hallucinations). Traditionally, hallucination research focused on auditory verbal hallucinations in schizophrenia, and visual hallucinations in Parkinson’s disease. However, recent studies indicate that visual hallucinations are also regularly experienced by schizophrenia patients (Waters et al., 2014a; Fernyhough, 2019), and auditory hallucinations also occur in Parkinson’s disease (Fenelon & Alves, 2010). The experience of hallucinations in multiple modalities also applies to the general population (Linszen et al., in press). Consequently, the QPE provides a broad overview of symptomatology and its phenomenological characteristics, and focusses on symptoms that would otherwise have been overlooked.

**Phenomenology**

The results of Chapter 4 show that hallucinations occur in a wide variety of disorders, with large differences in hallucination-modality and phenomenological features. A large heterogeneity in phenomenological characteristics is reported within and across diagnoses, which has led to the proposition that subtypes of hallucinations exist (McCarthy-Jones et al., 2014a). These subtypes do not necessarily adhere to diagnostic boundaries as considerable overlap in phenomenological characteristics is observed across diagnoses (Aarsland et al., 2001; Daalman et al., 2011a; Larøi et al., 2012; Slotema et al., 2012; Llorca et al., 2016; Waters & Fernyhough, 2017). Each subtype might
have a unique neural underpinning which require a specific tailored intervention (Stephane et al., 2001; McCarthy-Jones et al., 2014a; McCarthy-Jones et al., 2014b; Hugdahl & Sommer, 2018). As such, phenomenological characteristics can inform on specific neural correlates, such as whether auditory hallucinations are verbal or non-verbal (Sommer et al., 2009; de Weijer et al., 2013), sung or spoken (Angenstein et al., 2012; Jungblut et al., 2012), familiar or unfamiliar (Nakamura et al., 2001). However, to establish psychometrically sound hallucination subtypes, a reliable clinical assessment of the phenomenological features is required (McCarthy-Jones, 2014a). The findings of Chapters 2, 3 and 4 show that the QPE can contribute to this line of research, as the QPE provides a broad assessment of phenomenological characteristics and can facilitate the search for subtypes regardless of diagnosis.

Neural mechanisms

Subtypes

In Chapters 5 and 6, the neural mechanisms that underlie hallucinations were investigated across the psychosis continuum. Previous studies have indicated that the phenomenological characteristics of hallucinations in non-clinical individuals, patients with schizophrenia and patients with bipolar disorder show large similarities (Daalman et al., 2011a; Toh et al., 2015; Waters & Fernyhough, 2017; Toh et al., 2020a; Toh et al., 2020b). Therefore, it was hypothesized that their neural mechanisms may show large similarities as well, based on the expectation that similar subtypes of hallucinations show similar underlying neural mechanisms (McCarthy-Jones et al., 2014a).

The findings of Chapters 5 and 6 show that the neural mechanisms of hallucinations in non-clinical individuals and patients with schizophrenia are highly similar but that hallucinations in bipolar disorder have a different underlying mechanism. Contrary to our initial hypotheses, the findings of Chapters 5 and 6 did not show a similar pattern of functional connectivity alterations across the psychosis continuum, despite overlapping phenomenological features between the groups. As such, contrary to what is previously thought, similarities in phenomenology do not necessarily have corresponding neural mechanisms. Therefore, it seems more likely that multiple underlying mechanisms could lead to the same subtype of hallucinations (McCarthy-Jones et al., 2014a). This highlights the importance of studying both phenomenological characteristics and neural mechanisms.

Bottom-up top-down explanatory theory

In Chapters 5 and 6, we interpreted our findings with regard to the bottom-up top-down explanatory theory. In light of this theory, hallucinations may arise from an imbalance between sensory input (bottom-up) and higher-order cognitive processing (top-down) (Friston, 2005; Fletcher & Frith, 2009; Hugdahl, 2015; Powers et al., 2015; Jardri et al., 2017; O’Callaghan et al., 2017). Top-down processing helps to interpret incoming sensory input based on cognitive expectations, referring to processes such as sustained attention or cognitive control (Sarter et al., 2001; Hugdahl, 2015). It is assumed that top-down processing strongly increases the speed and accuracy of perception
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(Stocker & Simoncelli, 2006; O’Callaghan et al., 2017). Disruption of the top-down and bottom-up balance could lead to disturbed interpretation of sensory information, which could in turn result in false perceptions (i.e., hallucinations).

The largest body of evidence for the top-down bottom-up framework for perception comes from neuroimaging studies. Several brain areas have been implicated in the top-down bottom-up framework. The default mode network and salience networks have been related to predictive encoding (Carhart-Harris & Friston, 2010), and are associated with hallucinations in schizophrenia (Alonso-Solís et al., 2015; Hare et al., 2018; Mallikarjun et al., 2018). Similarly, in Chapter 6, we also found alterations in within- and between-module connectivity for the default mode and salience networks. The anterior insula has recently been implicated in the precision of control and has also consistently been implicated in symptom-capture studies (Jardri et al., 2011; Kompus et al., 2011). We replicated this finding in Chapter 5, by showing alterations in connectivity between fronto-insular regions in non-clinical individuals and schizophrenia patients with hallucinations. Furthermore, the fronto-parietal areas have been implicated in higher-order cognitive processing. For example, impairments in cognitive control (Zandbelt et al., 2011; Lesh et al., 2013; Eich et al., 2014) have been related to dorso-lateral prefrontal cortex dysfunction. We also observed disturbances of the fronto-parietal network in non-clinical individuals and schizophrenia patients in Chapter 5 of this thesis.

Taking these findings together, Hugdahl (2009) proposes that the bottom-up top-down theoretical model for auditory verbal hallucinations (i.e., voices) is mediated by a cortical network of three key regions; 1) sensory areas in the temporal lobe; 2) the prefrontal cortex for inhibitory control; 3) the parietal cortex for attentional focus. This model emphasized that auditory verbal hallucinations arise from an imbalance in connectivity between different brain areas, and that hallucinations do not stem from isolated brain areas. The findings of Chapters 5 and 6 confirm this proposition, as we reported a range of connectivity alterations in all groups with hallucinations (non-clinical, schizophrenia and bipolar disorder, respectively). Also, connectivity alterations between the three key areas as proposed by the Hugdahl (2009) model were found in Chapter 5 confirming a role for these areas in the generation of hallucinations in non-clinical individuals and schizophrenia patients with hallucinations. In Chapter 6, we extended these findings by reporting altered connectivity between networks related to cognitive and attentional control, such as the central executive, cingulo-opercular, and dorsal attention network in both non-clinical individuals and schizophrenia patients with hallucinations.

Furthermore, Hugdahl (2009) states that the main difference between non-clinical individuals with hallucinations and schizophrenia patients with hallucinations lies in the fact that non-clinical individuals often recognize that the voices come from inside the head, whereas the majority of patients with schizophrenia attribute the voices to an external source. This difference can implicate that non-clinical voice hearers have more top-down inhibitory control. In Chapter 6, we directly
compared non-clinical individuals with schizophrenia patients with hallucinations and we did not find any significant differences between these two groups. Our data do therefore not support this hypothesis. However, previous studies on cognitive functioning show that schizophrenia patients have difficulties to suppress irrelevant information (used as a proxy for inhibitory control) (Waters et al., 2003; Soriano et al., 2009; Hugdahl et al., 2013; Badcock et al., 2015). Similar deficits in inhibitory control were reported in non-clinical individuals with hallucinations as compared to schizophrenia, albeit to a lesser extent (Paulik et al., 2007; Daalman et al., 2011b; Mollon et al., 2016). This does suggest that there are differences in top-down processing between non-clinical individuals and schizophrenia patients that are not reflected by the results of Chapters 5 and 6. More research is warranted to elucidate these findings.

A different neural mechanism for hallucinations in bipolar disorder

In both Chapters 5 and 6, we reported a shared neural mechanism in non-clinical individuals and schizophrenia patients with hallucinations, but we found different connectivity alterations in connectivity in bipolar disorder patients with hallucinations. Increased connectivity was found between sensory and higher-order cognitive areas in non-clinical individuals and patients with schizophrenia with hallucinations, whereas decreased connectivity between these areas was found in bipolar disorder patients with hallucinations (Chapter 5). A similar contradictory pattern for hallucinations in bipolar disorder was found in structural imaging. Mørch-Johnsen and colleagues (2018) reported increased cortical thickness in both the left Heschl’s gyrus and superior parietal lobule in bipolar patients with hallucinations, as opposed to a reduced cortical thickness of these areas in schizophrenia patients with hallucinations (Mørch-Johnsen et al., 2017). The increase in cortical thickness was not found in bipolar patients without hallucinations, and is thus specifically related to the experience of hallucinations. Mørch-Johnsen and colleagues (2017) suggest this could point to disturbances in sensory processing in bipolar disorder, and that the opposing direction of cortical thickness alterations could indicate a different neural mechanism for hallucinations in bipolar disorder as compared to schizophrenia. Their conclusion is corroborated by the results of Chapters 5 and 6. Decreased connectivity between fronto-temporal and fronto-frontal areas in bipolar disorder patients with hallucinations suggest alterations in sensory processing and top-down control, but different alterations compared to non-clinical individuals and schizophrenia patients (Chapter 5). Moreover, the results of Chapter 6 indicate that disturbances in top-down/bottom-up processing may exist across the psychosis continuum, but that differential top-down networks are involved in non-clinical individuals and schizophrenia, versus bipolar disorder. Nonetheless, our results regarding a different neural mechanism for bipolar disorder patients should be interpreted with caution, as state and mediation differences between patients with bipolar disorder and schizophrenia could have influenced these findings (please see the limitations section for a further discussion). Studies investigating neural mechanisms of hallucinations in bipolar disorder are scarce. Hence, more studies are needed to address possible confounding of state and medication differences, and a possible differential mechanism for hallucinations.
Hallucinations and global modularity

As discussed above, hallucinations may arise from altered interactions between sensory and higher-order networks. However, hallucinations have also been proposed to arise due to alterations in the global modular organization of the brain. Therefore, in Chapter 6, the global modular organization was investigated. Both a more, and a less, modular network have been hypothesized to relate to hallucinations. A more modular brain network could lead to a more fragmented brain network that gives rise to autonomous modules. Hallucinations can arise when these autonomous modules keep reverberating the same output into the brain’s information flow (Hoffman & Dobschka, 1989; Hoffman & McGlashan et al. 1993; Hoffman et al., 1997). When the brain is less modular, this could result in hallucinations by, for example, causing an overflow of information between the auditory and language modules (David, 1994). However, the findings of Chapter 6 do not support either of these hypotheses.

Transdiagnostic research

Across all chapters of this thesis, hallucinations were studied using a transdiagnostic approach. The transdiagnostic approach was originally put forward as an alternative to the ICD/DSM categorical diagnoses, to improve classification and treatment of mental disorders (Insel., 2010; Cuthbert, 2014). Hallucinations are increasingly seen as a transdiagnostic phenomenon (Ford et al., 2014; Waters et al., 2014b; Waters & Fernyhough, 2017; Pienkos et al., 2019). Chapters 2 and 3 indeed show that hallucinations occur across a variety of medical conditions, and should thus be considered as a transdiagnostic symptom. The results of Chapter 4 confirm that hallucinations are indeed experienced in several disorders, showing both similar and distinctive phenomenological features. The findings of Chapters 5 and 6, emphasize the importance of studying the neural mechanisms that underlie hallucinations across various clinical and non-clinical individuals, as this can inform the development of new treatment options or improve existing treatment protocols.

Transdiagnostic research is still in its infancy, both in the field of hallucinations, as for mental disorders in general. Based on the results of the current thesis, it can be concluded that transdiagnostic research is much needed. Not only will it improve our understanding of hallucinations as a phenomenon, but it can help reduce stigma and facilitate psycho-education. A transdiagnostic comparison of hallucinations is of great importance to enhance collaboration on new treatment options across medical disciplines. Furthermore, to elucidate the mechanisms underlying hallucinations, a broader transdiagnostic approach that acknowledges the complexity and many variations of hallucinations across disorders is required.

In this thesis, we have taken a transdiagnostic “symptom-based” approach. Others have suggested that a sole focus on the symptom hallucinations is too narrow, and that transdiagnostic research should be focused on a broader concept as psychosis manifests in a variety of ways (Pienkos et al., 2019). Hallucinations are rarely experienced as an isolated phenomenon, but occur in multiple
modalities and might be continuous with other psychotic experiences (e.g., thought insertion, out-of-body experiences, dissociation, alterations in perception) (Pienkos et al., 2019).

The transdiagnostic approach was originally put forward as a promising new alternative to the existing classification system. As of yet, transdiagnostic research has not resulted in a shift away from ICD/DSM categorical diagnoses (Fusar-Poli et al., 2019). The transdiagnostic rationale for mental disorders in general is based on around several points, for example 1) symptoms of mental disorders cross diagnostic borders; 2) the high degree of comorbidity (Fusar-Poli et al., 2019); 3) genetic research has indicated that there is no unique genetic predisposition for psychiatric disorders in contrast to neurological disorders (Sommer & Schoevers, 2019); 4) the high number of disorder-specific treatment protocols for the same symptom (Fusar-Poli et al., 2019). In their systematic review, Fusar-Poli and colleagues (2019) conclude that transdiagnostic research has not yet brought on new discoveries, and that transdiagnostic research is not always conducted properly.

The term “transdiagnostic” is still interpreted in many different ways leading to heterogeneous incoherent studies that are focused on a limited subset of psychiatric disorders (Fusar-Poli et al., 2019). Concluding, a more standardized approach to transdiagnostic research is needed to further develop transdiagnostic research.

**Methodological considerations**

Several methodological issues need to be taken into account when interpreting the findings of this thesis. Most of these issues relate to the use of a new questionnaire, characteristics of participant samples, and the acquisition of imaging data.

*Questionnaire for Psychotic Experiences (QPE)*

In Chapters 2 and 3, the QPE was developed and validated. Although the QPE has shown to have good psychometric properties, the QPE needs to be validated in other population groups as well. As of yet, it cannot be concluded that the QPE is valid and applicable across all disciplines and disorders. The QPE needs to be tested for its applicability in other populations, for example as recently was done in a population-based sample (Linszen et al., in press).

Similarly, in Chapters 2 and 3 the QPE was developed and validated in the Dutch and English language. Through collaboration with researchers of the International Consortium of Hallucination Research (ICHR), the QPE is translated and validated in several other languages (Norwegian, German, French, Korean, Chinese, Arabic). The QPE still needs to be validated in these languages as well.

A third limitation stems from the fact that clinical studies can be confounded by co-morbid disorders. In Chapters 2,3 and 4, comorbid disorders could have confounded the results. Previous studies show high comorbidity among patients with borderline personality, with about one third of the patients that has an additional diagnosis of a psychotic disorder (Slotema et al., 2018), and comorbidity with
post-traumatic stress disorder is reported as well (Friás & Palma, 2015). For Lewy body disease, clear overlap in symptomatology is found with Parkinson’s disease, Parkinson’s disease dementia and Alzheimer’s disease making it difficult to establish a precise clinical diagnosis, especially at an early stage of the disease (Foguem & Manchoundia, 2018). Furthermore, the prevalence of hearing and visual impairment increases in elderly, making comorbidity with neurodegenerative disorders not unlikely. At the same time, the high comorbidity in individuals with hallucinations further emphasizes the need to consider hallucinations to be a transdiagnostic phenomenon.

Clinical characteristics
Limitations due to clinical characteristics should be kept in mind when reading Chapters 5 and 6. In these chapters, we were able to investigate hallucinations in a large sample, by combining scans of various studies, all conducted at the University Medical Center Utrecht. The disadvantage of merging these samples was that the participant groups differed in experiencing current or lifetime hallucinations, hence leading to differences in “state” versus “trait” related effects. For example, part of the non-clinical and schizophrenia groups reported hallucinations in the last week or month (i.e., current hallucinations). None of the bipolar disorder patients reported hallucinations in the last week or month, but they all experienced hallucinations at least once in their life (i.e., lifetime hallucinations). This difference in state effects between participant groups could have influenced our findings, especially as functional imaging is known to be more sensitive to state related effects than structural imaging. Nonetheless, we did not find a significant correlation between symptom-scores and connectivity measures (Chapters 5 and 6), suggesting we did not measure state-related effects. Also, in the current sample the non-clinical individuals experienced hallucinations less frequently than the patients with schizophrenia (Sommer et al., 2010; Daalman et al., 2011a), whereas the connectivity alterations were highly similar in both disorders. Taken together, we consider it unlikely that differences in hallucination state could have confounded our results, but future studies should further address confounding factors such as state versus trait related effects. For example, by comparing the neural mechanism of hallucinations between patients with bipolar disorder and schizophrenia using structural imaging, as structural imaging is found to be less sensitive to state related effects.

Another limitation stems from the fact that the participant groups differed in terms of reported hallucination-modality. The majority of the non-clinical individuals and schizophrenia patients reported auditory hallucinations, with some also reporting visual hallucinations. This was the other way around in bipolar disorder patients with hallucinations, as they reported more visual than auditory hallucinations. Previous studies have found modality-specific alterations in patients with schizophrenia, with alterations in the visual cortex related to visual hallucinations, and alterations of the speech and language related areas for auditory hallucinations (located frontal-temporally) (Fernyhough, 2019; Ford & Hamilton, 2019). With regard to resting state networks, altered resting state connectivity in the auditory, language, cognitive control, memory and salience regions have
been linked to auditory hallucinations (Alderson-Day et al., 2016; Ćurčić-Blake et al., 2017). However, similar networks have been found for visual hallucinations, suggesting a domain-general mechanism for hallucinations alongside modality-specific alterations (Rolland et al., 2015; Amad et al., 2014; Ford et al., 2015; Hare et al., 2015; Alderson-Day et al., 2016). In Chapter 5, a machine learning algorithm was used to disentangle modality-specific alterations for each participant group. However, due to the large proportion of the participants that experienced both auditory and visual hallucinations, we were unable to clearly disentangle effects of hallucination modality using a machine learning algorithm in the current dataset. Lastly, the results of Chapters 5 and 6 could be confounded by the experience of other psychotic experiences than solely hallucinations. A large proportion of the schizophrenia and bipolar disorder patients with hallucinations also experienced delusions during their life. The non-clinical individuals experienced hallucinations without delusions. However, these individuals are reported to experience additional subclinical psychotic features such as increased levels of suspicion, a proneness for magical ideation, and formal though disorder (Sommer et al., 2010; Daalman et al., 2011a). To address this confounding factor, a comparison within diagnoses can be made (i.e., schizophrenia patients with hallucinations versus schizophrenia patients without hallucinations). However, this analysis was hindered by the fact that almost all patients with schizophrenia experienced lifetime hallucinations. We were therefore unable to include sufficiently large group of schizophrenia patients without lifetime hallucinations. In the Supplementary Information of Chapter 6, we conducted an exploratory analysis of current versus lifetime hallucinations within each diagnosis (i.e., schizophrenia or bipolar disorder), but did not find any significant results. Future studies should further address this issue in a dataset that is better suitable to explore these effects.

**Neuroimaging**

Neuroimaging studies have various limitations on their own. Caveats of functional connectivity in patient-control research concern movement in the scanner, which is known to differentially affect the network of patients and controls. Specifically, patients tend to move more, causing the network to have more short-range connections and less long-range connections versus healthy controls who move less (van Dijk et al., 2012, Power et al., 2012). This can confound connectivity analysis, as was done in Chapter 5, but also the modular organization as was done in Chapter 6. We therefore carefully applied the most recent motion correction strategies available in the literature (Ciric et al., 2017; Parkes et al., 2018), and have shown minimal effects of motion on connectivity in both chapters. Some controversy exists with regard to the use of structural atlases for functional connectivity analyses. In Chapter 5, the analyses using the structural AAL atlas (Automated Anatomical Labeling; Tzourio-Mazoyer et al., 2002) were therefore replicated using the functional Power atlas (Power et al., 2011). The results between both atlases were comparable, yielding similar alterations in functional
connectivity across all groups. The results of both atlases were included to benefit discussion in the field with regard to the “best” atlas of choice in functional imaging analyses.

Another limitation concerns the fact that we did not include the cerebellum in our functional connectivity analyses of Chapter 5. One of the reasons that the cerebellum is often excluded in functional connectivity studies is because the parcellation of the cerebellum is less well developed and less fine-grained than the cerebral cortex. For example, the parcellation of the cerebellum by use of the AAL atlas (26 regions) is coarser than the cerebral parcellation, which consequently results in different types of network nodes (also see Guell & Schmahmann, 2020; Guell et al., 2018). At the same time, if the cerebellum would be parcellated at the same spatial resolution as the cerebral nodes, this would result in much smaller cerebellar nodes, which provides its own methodological issues (Zalesky et al., 2010). In Chapter 6, the cerebellum was included in the modularity analyses using the Power atlas (Power et al., 2011). However, the Power-atlas is known to undersample the cerebellum and subcortical regions (Power et al., 2011), thus limiting the ability to draw conclusions on the involvement of these areas in the experience of hallucinations. As previous studies have implicated the cerebellum in the experience of hallucinations (Shin et al., 2005; Cierpka et al., 2017; Lawn & ffytche, 2021), future studies should further elucidate the role it may play in discriminating between perceptual experiences from inside the self to perceptual experiences coming from external sources (Ramnani, 2006; Koziol et al., 2014; Ford & Hamilton, 2019).

Clinical implications

Following the results of this thesis, several clinical implications should be discussed. Firstly, the QPE is not only a valuable tool in research settings, but can also be applied in clinical settings. For example, the QPE can be used to measure treatment response for both hallucinations and delusions. The QPE has additional benefits compared to other questionnaires, as it assesses the phenomenological features in multiple modalities (i.e., auditory, visual, olfactory, tactile), not just the auditory modality.

Secondly, the QPE can be easily applied by clinicians who are less familiar with psychotic experiences (e.g., ENT or ICU doctors and nurses). This can facilitate the detection of psychotic experiences in patient populations that are otherwise easily overlooked. Consequently, the QPE can help reduce stigma surrounding the experience of psychotic experiences in diagnoses other than a primary psychotic disorder, and can facilitate psycho-education in these groups.

Thirdly, the QPE can help overcome the ever-growing number of questionnaires. The QPE can be applied regardless of diagnosis and thus overcomes the need of multiple questionnaires, each for a specific diagnosis. When the same questionnaire is used across disciplines, combining data across sites and departments is facilitated. This can in turn contribute to combining datasets of various sites and various diagnostic groups to enhance the search for subtypes of hallucinations and their corresponding neural mechanisms (McCarthy-Jones et al., 2014a; Sommer et al., 2018).
Furthermore, the QPE may help elucidate controversy regarding the existence of hallucinations versus pseudo-hallucinations. Controversy even exists within the field of psychiatry, as hallucinations in borderline personality disorder are traditionally deemed pseudo-hallucinations, because insight into the hallucinations is often intact (Hepworth et al., 2013; Wearne & Genetti, 2015). Similar suggestions have been made for post-traumatic stress disorder (Brewin & Patel, 2010; McCarthy & Longden, 2015). However, more recent studies suggest auditory hallucinations to be phenomenologically similar between both borderline personality disorder, post-traumatic stress disorder and schizophrenia (Kingdon et al., 2010; Slotema et al., 2012; McCarthy & Longden, 2015, Chapter 4 of this thesis). A transdiagnostic comparison of hallucinations and delusions in these disorders could help elucidate this controversy.

The QPE can assist research into subtypes of hallucinations. Research into the existence of subtypes is urgently needed as not all patients respond to treatment. For example, about 25% of the patients with schizophrenia do not respond to anti-psychotic medication (Shergill et al., 1998), which could suggest that these patients experience another hallucination subtype than the majority of patients with schizophrenia. Due to the large heterogeneity in phenomenological characteristics, clustering patients into subtypes can likely increase the chances of finding a suitable treatment option.

Lastly, applying neuroimaging in clinical settings is less straightforward, as the analyses of neuroimaging scans can be cumbersome (Soares et al., 2016). Furthermore, the possibility to draw conclusions based on individual patients’ resting state or task-based fMRI scans is limited (Lee et al., 2013). Nonetheless, functional neuroimaging studies can contribute to psycho-education and reducing stigma by showing patients that there is indeed a biological imbalance in their brain leading to hallucinations. Also, functional imaging can be used to help guide therapy for treatment resistant hallucinations, such as fMRI-guided neurofeedback, TMS or tDCS treatment options (Jardri et al., 2008; Diederen et al., 2013; de Pierre feu et al., 2018; Bauer et al., 2020).

**Future perspectives**

Following the paragraphs above, several factors should be kept in mind in future studies such as that: hallucinations are a transdiagnostic phenomenon; hallucinations occur in multiple-modalities; there are large inter-individual differences in phenomenology characteristics; cognitive, neuroimaging and phenomenological data should be combined to gain a better understanding of hallucinations as a phenomenon; state versus trait differences should be kept in mind when analyzing imaging data; the role of the cerebellum in hallucinations is currently understudied.

Furthermore, besides the bottom-up top-down processing, there are several other theories that seek to explain the occurrence of hallucinations. The most important hypotheses concern concepts such as unstable memories, disturbed source monitoring, and an imbalance in top-down and bottom-up processing, although several limitations and inconsistencies remain (for a review see Ćurčić-Blake et
However, no single explanatory theory is likely to explain the wide variety of hallucinatory experiences, therefore hallucinations should be studied at various levels of explanation, such as cultural, clinical, cognitive, brain imaging, cellular and molecular levels (Hugdahl & Sommer, 2018). Integration of multiple levels of explanation is necessary for a full understanding of the concept hallucinations.

Lastly, as phenomenological characteristics of hallucinations can show both similarities between diagnostic groups, as well as differences within diagnostic groups (Chapter 4, Aarsland et al., 2001; Daalman et al., 2011a; Larøi et al., 2012; Slotema et al., 2012; Llorca et al., 2016; Waters & Fernyhough, 2017). Therefore, the large heterogeneity of hallucinatory experiences in, for example schizophrenia, can hamper the search for a common underlying pathway within this group. Consequently, future studies can increase their chances of finding a common underlying neural mechanism by grouping together individuals with similar subtypes of hallucinations (i.e., with homogeneous phenomenological features) regardless of clinical diagnoses and compare neural mechanisms within and between these subtypes (i.e., deep phenotyping) (Sommer et al., 2018). This would entail that future studies should incorporate both phenomenological assessments (e.g., the QPE) and neuroimaging measures (e.g., functional connectivity). Additional measures of cognition (e.g., inhibitory control) can shed more light on alterations of top-down processing in each of these hallucination subtypes.

Concluding remarks

Hallucinations are a transdiagnostic phenomenon. The QPE is proven to be a valuable assessment tool in transdiagnostic hallucinations research, as the QPE can be applied in clinical and research settings regardless of diagnosis. Our findings suggest the existence of subtypes of hallucinations based on phenomenological characteristics. Hallucinations with similar phenomenological features across the psychosis continuum do not necessarily imply a shared neural correlate. More research is needed to establish what subtypes of hallucinations exists, and what neural correlates underlie these types of hallucinations. A better understanding of hallucinations as a transdiagnostic phenomenon will help progress development of treatment options.
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