Chapter 7

Summary
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Hallucinations are perceptions in the absence of an external stimulus which present in the context of a wide range of clinical disorders, including psychiatric, neurological and other medical disorders. A minority of individuals in the general population also experience hallucinations. These individuals have no identifiable clinical disorder and do not require treatment, and are therefore referred to as non-clinical individuals with hallucinations.

Hallucination research traditionally uses a diagnosis-based approach, mainly focusing on auditory verbal hallucinations in patients with schizophrenia, or visual hallucinations in Parkinson's disease. However, since hallucinations are not unique to psychiatric or neurological disorders, there has been growing consensus that hallucinations should be investigated using a broader transdiagnostic, symptom-based approach instead of the currently used diagnosis-based approach. The aim of this dissertation is to investigate hallucinations using a transdiagnostic symptom-based approach, which could further enhance our understanding of this phenomenon.

Part I – Do hallucinations across disorders show similar phenomenological characteristics?

In part I of this thesis, a new measurement tool that enables transdiagnostic hallucination research was developed and validated. As of yet, transdiagnostic research is hindered due to the lack of a suitable measurement tool that can be applied across multiple disorders. Currently existing questionnaires are specifically tailored to psychotic experiences in one diagnosis, but not applicable to other diagnoses. To this end, the Questionnaire for Psychotic experiences (QPE) was developed, which enables assessment of severity, frequency and phenomenology of psychotic experiences across disorders. In Chapter 2, the development and validation of the QPE in the Dutch language is described. The QPE was assessed in participants with a wide range of clinical disorders, including participants with schizophrenia spectrum disorders, Parkinson’s disease, Lewy Body Dementia, Alzheimer’s disease, hearing impairment, visual impairment, post-traumatic stress disorder, borderline personality disorder, and recent major surgery. In Chapter 3, the validation of the QPE in the English language is described. The QPE was assessed in participants with schizophrenia, schizoaffective disorder, bipolar affective disorder, major depressive disorder, and in non-clinical individuals with hallucinations. In both languages, the QPE was found to have good psychometric properties, including structure validity, internal validity and convergent validity. Participants with various disorders endorsed a wide range of psychotic experiences, further emphasizing the need for a transdiagnostic tool. The QPE has a relatively quick administration time and can be a valuable tool in both clinical and research settings. Furthermore, the QPE facilitates assessment of psychotic experiences in disorders that are otherwise easily overlooked. In Chapter 4, the QPE was applied to assess transdiagnostic phenomenological characteristics of psychotic experiences. Phenomenological characteristics such as frequency, severity, duration, content, insight and amount
of interaction with hallucinations were assessed in participants with schizophrenia spectrum disorders, Parkinson’s disease, Lewy Body Dementia, Alzheimer’s disease, hearing impairment, visual impairment, post-traumatic stress disorder, borderline personality disorder, and recent major surgery. The results of this comparison suggests that hallucinations within the psychiatry and neurodegenerative categories were more alike than previously thought, whereas hallucinations across these categories were phenomenologically different. Psychotic experiences, such as hallucinations, are not specific for a particular diagnosis (i.e., schizophrenia) but should be seen as transdiagnostic experiences. The results of this phenomenological comparison confirm previous findings that similar phenomenological features can exist across disorders, therefore suggesting the existence of various subtypes across diagnoses.

Part II – Do hallucinations across disorders share a neural mechanism?
In part II of this thesis, functional Magnetic Resonance Imaging (fMRI) was used to investigate the neural mechanism across the psychosis continuum. The psychosis continuum comprises hallucinatory experiences that range from non-pathological experiences in the general population on the one end, to hallucinations in severe psychotic disorders on the other. Due to similarities in the phenomenological characteristics of hallucinations across the psychosis continuum, it has been hypothesized that these individuals also share a neural mechanism.

Prior studies have indicated that hallucinations arise from an imbalance between sensory and higher order cognitive brain regions, which is reflected by alteration in functional connectivity. In Chapter 5, individual connections of the functional connectome were investigated using network-based statistics. Non-clinical individuals with hallucinations, schizophrenia patients with hallucinations, and bipolar disorder patients with and without hallucinations were compared to healthy controls. Non-clinical individuals and schizophrenia patients with hallucinations exhibited increased connectivity among sensory and higher-order cognitive regions, mainly among fronto-temporal and fronto-insula/cingulate areas as compared to healthy controls. Differential effects were observed for bipolar disorder patients with hallucinations versus healthy controls, mainly characterized by decreased connectivity between fronto-temporal and fronto-striatal areas. Bipolar disorder patients without hallucinations showed no connectivity alterations compared with healthy controls.

In Chapter 6, the modular organization of the functional connectome was investigated across non-clinical individuals with hallucinations, schizophrenia patients with hallucinations and bipolar disorder patients with and without hallucinations, and healthy controls. An altered modular organization was hypothesized to underlie hallucinations across the psychosis continuum, characterized by 1) alterations in the global modular brain network organization; and 2) alterations in connectivity within and between modules, such as sensory and higher-order cognitive modules. The results indicated that the global modular organization was not altered in any of the hallucination groups as compared to healthy controls. Hallucinations in non-clinical individuals and patients with
schizophrenia were related to altered within- and between-module connectivity of the auditory, visual, somatosensory, cognitive control, salience, subcortical and memory modules. In bipolar disorder patients with hallucinations, alterations between the visual, default-mode and memory network were found, whereas connectivity patterns between the visual, salience and cognitive control modules were unaltered. These findings provide evidence for alteration of the modular organization of the functional connectome in individuals prone to hallucinations. Non-clinical individuals and patients with schizophrenia show similar alterations in the modular organization of the sensory and higher-order cognitive modules, whereas other higher-order cognitive modules were found to relate to hallucinations in bipolar disorder. In parallel to Chapter 5, this study also indicates a different mechanism exists for hallucinations across the psychosis continuum.

Concluding remarks
When integrating the findings of this thesis, the QPE proves to be a valuable instrument for both clinical and research settings. The QPE enables transdiagnostic comparison of hallucinations. The results from this thesis further encourage assessment of hallucinations in diagnoses other than primary psychotic or neurological disorders. Contrary to what is previously thought, hallucinations in schizophrenia can be highly similar in phenomenology as compared to other psychiatric disorders, such as post-traumatic stress disorder and borderline personality disorder. The phenomenological characteristics of hallucinations between various neurodegenerative disorders also largely overlap.

Our findings of the neuroimaging studies do not support the existence of similar neural mechanisms across disorders, meaning that hallucinations with similarities in phenomenology do not necessarily indicate a shared neural mechanism. More research on phenomenological characteristics and their corresponding neural mechanisms could help to establish whether subtypes of hallucinations exist, and whether phenomenology can be a predictor of pathogenesis. Concluding, the results of the current thesis further enhance our understanding of hallucinations as a transdiagnostic phenomenon.