

# A comprehensive study on the cognitive mechanisms and neural substrates of hallucination proneness

Citation for published version (APA):

Johnson, J. F. (2022). *A comprehensive study on the cognitive mechanisms and neural substrates of hallucination proneness*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20221101jj>

## Document status and date:

Published: 01/01/2022

## DOI:

[10.26481/dis.20221101jj](https://doi.org/10.26481/dis.20221101jj)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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# Impact Paragraph

Numerous findings reported in this dissertation could offer impactful theoretical or practical contributions to future empirical research, possibly extending to interventions and cross-diagnostics pertaining to a psychosis continuum. Moreover, the included examinations incorporating a spectrum of hallucination proneness may provide a broader value to society itself, in terms of how an advanced knowledge of a psychosis continuum may improve the lives of those affected.

**Potential scientific impact.** The outcomes suggest both short- and long-term impacts to neuroimaging and translational cognitive neuroscience. Already, three methodological findings may be utilized. In **chapter 3**, findings from a widely-used voice perception task indicate a general variability of brain activations across the general population (Pernet et al., 2015). In healthy participants, a hypersensitivity was indicated in the brain region associated with early stages of voice processing, related to an increasing proneness for abnormal perceptual experience. It would therefore be of interest to studies investigating this region to consider how a general variability in response strength may be distributed in their sample, and how this may affect downstream processing of voice. In **chapter 4**, a behavioural task was the first to show that participants are able to correctly identify their own voice when hearing brief half-second vowel sounds. In theory, this implies that such short, simple, stimuli contain sufficient information for recognizing self-voice identity. In the same study, the first functional magnetic resonance imaging (MRI) evidence for a specific pattern of brain activity associated with self-generated, self-attributed, voice was demonstrated when participants played a sound by pressing a button. Therefore, investigators interested in brain responses to varying expectancy of voice features during action, and not speech itself, can adopt a button-press paradigm avoiding vocal production and reduce the associated head movement which lead to difficulties in MRI processing and analysis (Havsteen et al., 2017; Makowski et al., 2019; Zaitsev et al., 2015). Although these methodological reports are innovative, the lack of comparable findings in the literature implies that replication is necessary before accepting the generalizability of these interpretations.

The current dissertation offers longer-term implications to the scientific field. The meta-analysis in **chapter 2** may provide a farther-reaching, lasting, impact. The brain areas indicated as responsive to unexpected errors in sensory feedback suggest a network of motor and sensory regions with different roles in adaptation motor control. This was intended to isolate brain regions relevant to the mechanisms serving hallucinations. However, due the fundamental nature of this investigation, it was presented as a poster at an established conference (Society for Neuroscience, 2018) within the motor control section. Likewise, it was shared among broader circles, and has resulted in numerous citations, which foreseeably will continue to inform any future research into the brain correlates of sensory feedback and adaptive processes.

Two studies will predictably lead to debate, or possibly a shift in understanding, regarding predominant theories of hallucinations. The abovementioned **chapter 3** finding – of a hypersensitivity to voice sounds – views hallucinations as misperceived externally-produced sensations. This appears to conflict with theories positing hallucinations as misattributed, externalized, internally-produced signals (Ford & Mathalon, 2005; Heinks-Maldonado et al., 2007; van Lutterveld et al., 2011; Whitford et al., 2012). However, as suggested in the **chapter 6** discussion, these positions may not be mutually exclusive, reflecting a general abnormality in salience processing. It is anticipated that future research will determine the contribution of both internally- and externally-generated signals to overactive brain regions serving perception and the emergence of false perceptions. Although schizophrenia research has provided plausible neurochemical aetiology for this salience deficit (Corlett et al., 2011; Heinz et al., 2019; Jardri et al., 2016; Karoutzou et al., 2007; Sterzer et al., 2018), the underlying source of these abnormalities related to false perceptions across the general population remains to be determined. Deeper understanding of the function or imbalance of these inputs may help describe neurochemically how these experiences manifest in the healthy brain and establish an etiological or development distinction specific to schizophrenia.

In **chapter 5**, analyses on the structural pathways connecting brain regions showed a pattern opposite to many reported in schizophrenia compared to healthy participants (e.g., Fitzsimmons et al., 2013; Kubicki et al., 2005; Tamnes & Agartz, 2016). As

hallucinations are a main symptom of schizophrenia, this finding pertaining to hallucination proneness also appears to conflict with contemporary disconnection theories (Coyle et al., 2016; Friston & Frith, 1995; Pettersson-Yeo et al., 2011; Rubinov & Bullmore, 2022; Silverstein et al., 2016). However, there has been a lack of consensus across clinical samples, and the report of effects in both directions when assessing symptom severity, for example, in hallucinated voices (e.g., Bopp et al., 2017; Ćurčić-Blake et al., 2013; Mulert et al., 2012; Psomiades et al., 2016; Rotarska-Jagiela et al., 2009; Seok et al., 2007; Szeszko et al., 2008). It has been suggested that research using non-clinical groups may be of particular help in assessing the underlying cognitive functions and related brain areas associated with symptoms of psychosis. For example, investigations into white matter structure related to hallucinations may be difficult in schizophrenia samples, as changes to these pathways are also susceptible to effects of antipsychotic medication (e.g., Leroux et al., 2017; Seok et al., 2007). Additionally, white matter research may help inform the aforementioned neurochemical associations to false perceptions, and differences between the schizophrenic and healthy brain prone to hallucinations, as these pathways are structurally affected by imbalances in the neurotransmitters implicated in psychotic symptoms (Davis et al., 2003; Goff & Coyle, 2001; Mighdoll et al., 2015; Plitman et al., 2014; Suárez-Posos et al., 2020; Takahashi et al., 2011; Walterfang et al., 2006, 2011).

**Potential social impact.** A continuum theory of psychosis provides more than theoretical discussion among researchers, as it offers a vital perspective for how variability in these experiences can be perceived within society. All over the world, a proneness for abnormal perceptual experience such as hallucinations has been reported across large population-based samples (e.g., Moseley et al., 2021; Siddi et al., 2019). Likewise, at a higher level of that spectrum, experiences similar to symptoms of psychosis occur at various frequencies in the general population (e.g., Bitta et al., 2022; Bourgin et al., 2020; McGrath et al., 2015; Subramaniam et al., 2016). Finally, some subgroups of the general population experience chronic psychosis-like experience without the need for care or clinical diagnoses (e.g., healthy hallucinators) (Baumeister et al., 2017; Johns, 2014; van Os et al., 2009). Although different cultures provide varying explanations for the source of these experiences (e.g., religious or spiritual) (Larøi et al., 2014; van Elk & Aleman, 2017), it is evident that they are present in the

lives of many different people at many different levels, existing on a continuum with normal human experience. The findings in **chapter 3 and 5** indicate a correlation of brain function and structure with hallucination proneness in healthy people, supporting this theory. However, a dichotomous, categorical, perspective has led to much stigma, further impairing the mental health and help-seeking behaviour of those affected (Corrigan et al., 2017; Lien et al., 2015; Peter et al., 2021). Therefore, this dissertation may contribute to a general shift in perspective to a continuum, allowing for an understanding that abnormal perceptual experiences are nothing to hide or scorn, and allow those who have them to feel more comfortable in sharing with others, including clinicians, when requiring care.