Deafferentation as a cause of hallucinations

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Purpose of review
The association between hallucinations and sensory loss, especially vision- and hearing-impairment, has been firmly established over the past years. The deafferentation theory, a decrease of the threshold for activation in the brain and the consequential imbalance between excitatory and inhibitory brain networks, is hypothesized to underly this relationship. Here we review the studies investigating this theory with a focus on the most recent literature to better understand the contribution of sensory loss to hallucinations.

Recent findings
A large cross-sectional study has recently confirmed the relationship between auditory impairment and deafferentation. However, the underlying mechanisms of deafferentation are still under debate, with hyperexcitability and deviations in bottom-up and top-down processes being the most likely explanations. Social isolation following sensory impairment increases the risk for hallucinations. Better knowledge and awareness about the contribution of deafferentation and loneliness would benefit diagnosis and treatment of hallucinations.

Summary
Studies imply activity in higher order areas, corresponding to the functional mapping of sensory system, and a general state of higher excitability as neurobiological explanation. Auditory deafferentation, tinnitus and other auditory hallucinations, likely lie on a continuum. Social isolation mediates psychotic symptoms in sensory-impaired individuals. Currently, there is no standard treatment for deafferentation hallucinations.

Keywords
auditory hallucinations, Charles Bonnet syndrome, deafferentation, social deafferentation, visual hallucinations

INTRODUCTION
Hallucinations, conscious perceptions in the absence of an appropriate external stimulus, can be frightening and disturbing for an individual. They can lead to anxiety, social isolation, and decreased quality of life [1–3]. Furthermore, hallucinations may complicate the task of caregivers, increasing the need for professional care. Hallucinations can occur as symptom of psychiatric or neurological disease, sometimes together with formal thought disorder and/or delusion. However, certain forms of hallucinations, namely deafferentation hallucinations, arise from partial or complete sensory loss [4], typically in absence of thought disorder or delusions. Their existence is long known, with the first descriptions of the visual variant, better known as Charles Bonnet syndrome (CBS), dating back to 1760 [5], but relatively little research has focused on understanding this type of hallucinations. With the expected increase of visual and auditory impairment in the upcoming years because of population aging [6,7], this type of hallucination will be encountered even more frequently in clinical settings. To increase understanding and awareness of deafferentation hallucinations, we will explain the mechanism of deafferentation, that is the loss of afferent input to sensory cortices, and review the recent literature in the field focusing on the visual and auditory domains.

SENSORY IMPAIRMENT AND HALLUCINATIONS
The first experimental investigations of links between sensory deprivation and hallucinations...
auditory deafferentation hallucinations are mainly of musical content [14–16]. This novel insight that auditory deafferentation hallucinations are in fact most often verbal indicates the need to check hearing loss in people newly diagnosed with auditory verbal hallucinations.

Shoham et al. [17**] tested the effect of self-reported severity of hearing or visual impairment on occurrence of psychotic symptoms, including hallucinations. Of their 7107 subjects, 1207 reported hearing impairment, 934 reported visual impairment, and 241 reported both. They found a general association between sensory impairment and psychotic symptoms. Based on self-report measures they further categorized the level of sensory impairment as ‘mild’, ‘moderate’, and ‘severe’. For moderate visual impairment and severe hearing impairment, the association with psychotic symptoms remained; for mild visual impairment and mild auditory impairment, a weak association was found with psychotic symptoms, showing a magnitude-dependent mechanism in these groups, similar to the linear relationship between the severity of hearing impairment and prevalence of hallucinations found by Linszen et al. [13**]. Surprisingly, the association vanished for the strong visual impairment and the moderate auditory impairment group in the study by Shoham et al. [17**], contradicting the findings of Linszen et al. [13**]. This difference might be because of Shoham et al. [17**], relying on self-report measures of severity instead of using audiometric testing.

**DEAFFERENTATION AND HYPEREXCITABILITY**

Although a link between sensory impairment and hallucinations has been established, the underlying mechanisms are still under debate. Similar to other hallucinations [18–22] Bayesian models, based on changes in the interplay between bottom-up and top-down processes [18,19], are hypothesized to be at the root of deafferentation hallucinations [20,21,23]. The brain is assumed to react to the decreased input from sensory organs and the resulting deafferentation in a maladaptive way, by lowering the threshold for activation to restore homeostasis [4,24–26]. However, this compensation mechanism might make the neural networks unstable, leading to changes in cortical excitability and causing either abnormal excitatory activity or interference with inhibitory networks of the sensory system. Because of this instability, networks connecting the primary sensory cortices to other cortical areas exhibit hyperexcitability [24,27,28]. In fact, experimentally induced abnormal activity in the visual cortex has led to hallucination-like
perceptions [29] with a phenomenology corresponding to the functional mapping.

Similar mechanisms of imbalances of top-down and bottom-up processing are described in auditory verbal hallucinations in schizophrenia. Within that framework it has been suggested that hallucinations might arise from an increased dependence on top-down expectations and decreased top-down inhibitory control [20,21]. This overreliance on higher-order processes combined with bottom-up misinterpretations or hyperexcitability is supposed to lead to hallucinations [21,30]. These processes are assumed to be shaped by deviations in the thalamocortical circuit, which is involved in the inhibition of spontaneous activity [23]. Because diminished sensory input following sensory impairment should lead to higher reliance on top-down processes, an increased activity in higher order brain areas could be expected. Direct empirical support for the deafferentation theory, however, is sparse, in both the visual and auditory domains.

**Visual deafferentation**

Although a number of studies investigated the underlying neurobiological changes and mechanisms of deafferentation in patients with visual impairment, they are mostly limited to cases or small-scale studies in CBS [31–36,37,39].

Based on several single-photon emission computed tomography (SPECT) studies, visual deafferentation hallucinations have been shown to be associated with hypoperfusion, i.e. a decrease in blood flow, in the occipital areas, including the primary and secondary visual cortices [31,32], and more medial parts of the occipital lobe [31]. Hypoperfusion was reported in the striatum and thalamus [33]. Regarding the higher order visual areas located in the lateral parts of the occipital lobe, findings are contradictory, with some suggesting an increase [33] and others a decrease [31] in blood flow. Further investigations of metabolic processes using positron emission tomography (PET) imaging revealed similar patterns. Here hypermetabolism was reported in the inferior temporal areas and thalamus [34], while lower activity was found in frontal areas, including Broca’s area, both the anterior and posterior cingulate, and again the primary visual cortex [35].

Functional neuroimaging studies suggest increased brain activity in visual areas corresponding to the functional mapping based to the hallucinations’ content [32,36,37]. When recording brain activity during the hallucinatory perception of faces, ffytche et al. [36] reported increased activity in the fusiform face area, an area known to be active during face perception. Likewise, Kazui et al. [32] found hyperactivity in higher order visual areas when their patient experienced complex visual hallucinations of flowers and fish.

Martial et al. [37] investigated deviations in cortical thickness and functional connectivity in a patient with CBS, taking the effect of visual impairment into account, by comparing them to late blind without hallucinations and normally sighted subjects. Similar to other case studies, cortical thinning was observed in associative and multimodal cortices of the patient with CBS, but not of the other subjects. Interestingly, compared to the other subjects the patient with CBS showed an increase in functional connectivity not only in the visual areas, but also in the salience network. Since this network is involved in the processing of salient internal and external stimuli, it is not surprising that it might be involved in deafferentation hallucinations [38].

The effect of hyperexcitability was recently empirically assessed in patients with age-related macular degeneration [39]. Here, brain activity of patients with visual impairment because of macular degeneration with and without visual hallucinations, and healthy controls was recorded during peripheral visual field stimulation. At the same time, they controlled for modulatory effects of attention. Interestingly, even without the actual experience of hallucinations during the task, patients with macular degeneration with hallucinations showed increased activity in their visual cortex compared to healthy controls and to macular degeneration patients who never experienced hallucinations. This study extended the idea that deafferentation hallucinations are the result of hyperexcitability and showed that hyperexcitability is not just related to the actual occurrence of hallucinations but is generally present in patients with sensory impairment. These suggest that not hyperexcitability itself underlies the occurrence of hallucinations, but rather facilitates their onset.

**Auditory deafferentation**

Like deafferentation hallucinations in the visual domain, auditory deafferentation has predominantly been studied in either case or small-scale studies [19,40–44]. Suggested areas associated with auditory deafferentation include, but are not limited to auditory pathways [40,41], basal ganglia [40,43,44] and frontal areas [19,40,42,43]. In an empirical study contrasting the brain activity of hearing-impaired patients with complex auditory hallucinations, tinnitus patients, and healthy controls, Vanneste et al. [45] suggested that tinnitus and auditory hallucinations in hearing-impaired
patients share similar activity patterns. Differences between the two groups seemed to be related to brain activity in areas of higher order functions, such as music and language processing, indicating a relationship between the content of the hallucination and brain activity.

**Deafferentation hallucinations as part of a continuum**

Recently, Coebergh et al. [46*] discussed the relationship between musical hallucinations, including auditory deafferentation hallucinations and epilepsy. Although they support the idea of a disequilibrium between bottom-up and top-down processes, they also raise another interesting point, namely that auditory deafferentation hallucinations lie on a continuum with other auditory hallucinations. Support for this was found in the changes in phenomenology of the hallucinations described by the patients. Patients reported that their hallucinations shifted from a perception of music to either more complex or less complex auditory hallucinations (auditory verbal hallucinations or tinnitus, respectively). Especially, tinnitus could be considered a simpler form of deafferentation and might help early detection of physical impairments, which can lead to complex deafferentation hallucinations, such as tumors affecting the auditory nerve and other impairment of the auditory pathways [47]. Behrendt et al. even argued the majority of hallucinations not only lie on a continuum with deafferentation [23], but are also independent of external sensory information, that is fully represent internal processes.

**SENSORY IMPAIRMENT AND SOCIAL DEAFFERENTATION**

The social deafferentation hypothesis, first described by Hoffman [48], states that social withdrawal can induce complex hallucinations resembling people to make up for the lack of social interaction. Because sensory impairment highly influences the abilities and possibilities to continue a certain level of social interaction, this is an important aspect to point out. Increased isolation following sensory impairment can result in feelings of loneliness, depression, and anxiety [49–51]. Especially in the elderly, decreased social participation can be seen following sensory deterioration [50,51]. Social isolation has been associated with hallucinations and other psychotic symptoms [25]. Interestingly, Shoham et al. [17**] found a mediating effect of social functioning on psychotic symptoms, including hallucinations, in sensory impairment.

With roughly half of the relationship being attributed to decreased social functioning (50% in visual impairment and 42% in hearing impairment), their results show that social functioning can play a substantial role in psychotic symptoms in sensory impairment. This is in line with an epidemiological study [52] investigating the effect of urbanization, an environment frequently associated with decreased social networks [53], on psychotic symptoms in hearing-impaired individuals. They found that self-reported psychotic symptoms, showed not only an association with objective hearing-impairment, but that this relationship was amplified in individuals that lived in a densely populated area [52].

**IMPLICATIONS FOR DIAGNOSIS AND TREATMENT**

Many patients and even some healthcare workers are not aware of the link between sensory impairment and hallucinations [54**,55]. This can be a barrier for patients to seek appropriate help, as they may be afraid of being diagnosed with mental illness or dementia [56]. Lack of awareness among physicians can result in inappropriate treatments and misdiagnoses. Indeed, often patients suffering from deafferentation hallucinations do not receive clear and appropriate information about their condition, a factor that has been linked to a more negative quality of life [57].

A study on awareness of CBS among family physicians in Canada has shown that more than 50% did not know about CBS and roughly 20% were only slightly aware of it, for example a colleague has previously mentioned it to them [54**]. This low level of awareness is concerning given the fact that the majority of respondents consults at least one patient with visual hallucinations a year and does not consider deafferentation as possible diagnosis.

Even if deafferentation hallucinations are correctly diagnosed, there is still no agreement on the best treatment. Treatment for deafferentation hallucinations differs from treatment for hallucinations of a primary psychotic syndrome such as schizophrenia or delirium. Antipsychotic treatments, targeting increased dopamine synthesis, are not expected to be very effective, as dopamine has never been shown to be involved in deafferentation hallucinations [58–60]. Generally, the improvement of the patient’s sensory abilities, for example good lights in the room or the use of hearing aids, has been successful in resolving deafferentation hallucinations [26,58,59]. However, this is not always possible. Commonly physicians offer
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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


Counselling and education, or refer the patient to a specialist, that is psychiatrist, otologist, or neurologist [54]. Frequently, learning about their condition or simple behavioral interventions, such as listening to music, helps patients to manage their hallucinations [58]. Psychotherapy, especially in the form of support groups, can also be beneficial [59]. Although most pharmacological interventions show modest to no effects, acetylcholinesterase inhibitors seem promising for auditory deafferentation hallucinations [58]. Since acetylcholine plays an important role in the thalamocortical circuit, this supports the involvement of this circuit in deafferentation hallucinations [23]. Other pharmacological treatments that were less effective than acetylcholinesterase inhibitors, but still showed results were antiepileptics and antidepressants [23]. As reflected by this wide array of options there is no standard treatment for deafferentation hallucinations and success rates of the individual treatments differ per patient.

CONCLUSION

In two recent large studies, the link between sensory impairment and hallucinations has been firmly established, showing deafferentation to be a relatively common cause of hallucinations in nonpsychotic patients, especially in elderly. Overall, there seems to be a neurobiological relationship between the phenomenology of the hallucinatory experience and the brain areas active. Based on phenomenological auditory deafferentation and other auditory hallucinations are likely part of a continuum.

Raising awareness of the existence of deafferentation hallucinations is essential for effective patient care and treatment, as patients suffering from deafferentation tend to be reluctant to disclose their hallucinations and seek help. It is important to provide them with appropriate information about their condition to further avert the negative impact on their quality of life. Regarding treatment, there are many options, but no gold standard as of yet. However, often simple measures to increase a patient’s social environment and sensory abilities could already be of help.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.
Saliency, switching, attention and control: a network involvement of both visual and salience networks.


A Neuroimaging study investigating functional connectivity in patients with Charles Bonnet syndrome, while controlling for sensory impairment. The results show involvement of both visual and salience networks.


This article shows that hyperexcitability is generally found patients suffering from Charles Bonnet syndrome, not just immediately preceding the hallucinations.

