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Review

The missing pieces: an investigation into the parallels between Charles Bonnet, phantom limb and tinnitus syndromes

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***Abstract*:** Charles Bonnet syndrome (CBS) is a condition characterised by visual hallucinations of varying complexity on a background of vision loss. CBS research has gained popularity only in recent decades, despite evidence dating back to 1760. Knowledge of CBS among both the patient and professional populations unfortunately remains poor, and little is known of its underlying pathophysiology. CBS parallels two other better-known conditions that occur as a result of sensory loss: phantom limb syndrome (PLS) (aberrant sensation of the presence of a missing limb) and tinnitus (aberrant sensation of sound). As 'phantom' conditions, CBS, PLS and tinnitus share sensory loss as a precipitating factor, and, as subjective perceptual phenomena, face similar challenges to investigations. Thus far, these conditions have been studied separately from each other. This review aims to bridge the conceptual gap between CBS, PLS and tinnitus and seek common lessons between them. It considers the current knowledge base of CBS and explores the extent to which an understanding of PLS and tinnitus could provide valuable insights into the pathology of CBS (including the roles of cortical reorganisation, emotional and cognitive factors), and towards identifying effective potential management for CBS.

Keywords: auditory, hallucination, sensory deafferentation, visual

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Introduction

If the body is a map, the nervous system is the cartographer, carefully designing, maintaining and refining a sensory map centred around the five core senses – touch, sight, hearing, smell and taste. These senses form the basis of our external perception of the outside world and are also important in internal perception. Stimuli are detected by different types of specialised receptors which are often concentrated into dedicated sensory organs such as the eyes, ears and nose. The subsequent activation of these receptors causes nervous impulses to be transmitted to the brain, where they are interpreted and integrated to facilitate appropriate responses.

Loss of input from receptors hinders complete processing of the five senses. This could be transient, such as anaesthesia during operations, or loss of smell and taste from viral infections, most recently COVID-19.[1] However, it can also be permanent. In such situations with sustained, consistent loss of sensory information, the nervous system often attempts to 'fill in the gaps'. Unfortunately, this process can be unreliable and error-prone, with the potential to result in dysfunctional states.

Perhaps the most widely known example of such a state is phantom limb pain – the sensation of pain in a missing limb, usually following amputation. Tinnitus, known to many as 'ringing in the ears' – usually following a hearing loss – is also commonly recognised.[2,3] In both conditions, there is a significant loss of sensory input in one of the five core senses. Over the past few decades, an unfamiliar but similar condition – Charles Bonnet Syndrome (CBS) – following vision loss,

has been gaining awareness within the scientific community.

CBS remains poorly understood, despite its discovery dating back to 1760.[4,5] CBS refers to vivid visual hallucinations occurring with impaired vision,[6] and was first described by Charles Bonnet, whose grandfather suffered from visual hallucinations after losing his vision to cataracts.[5] Vision loss causing CBS is not restricted to a specific pathological process,[7] as it has also been reported in conditions associated with typically irreversible damage such as cerebral infarction or retinal degeneration.[8,9]

While sources vary, CBS is believed to affect around 10%–50% of people suffering from vision loss,[10,11] though this is likely an underestimation due to the stigma associated with reporting the symptoms.[12,13] CBS hallucinations for most patients are often transient, occurring around once a week and lasting seconds to minutes.[14] Hallucinations can vary significantly in form, complexity and nature, ranging from simple lines or flashes of light to animals and people.[6] They are typically colourful and can be either stationary or in motion.[6] Often, the hallucinations are so vivid that patients understandably express concerns over their sanity before they are provided with reassurance. However, in contrast to psychiatric conditions such as schizophrenia and bipolar disorder, CBS patients are typically aware that what they see is not real.[6] Unfortunately, they have no conscious control over the hallucinations,[5] and can be afflicted by them for several years. Indeed, studies such as Santhouse et al. and Khan et al. provide evidence that CBS hallucinations can persist even 9 years after diagnosis.[15,16] A prolonged disease course poses a significant problem for CBS patients who experience distress from the hallucinations. A London study with 492 patients with CBS showed that 38% had a negative reaction towards the hallucinations at onset.[14] In a smaller questionnaire study, out of 97 AMD patients with symptoms consistent with CBS, around 23 were negatively impacted by the hallucinations they experienced.[15]

Despite its long history, it is only in recent years that CBS has gained traction within the scientific community. This may be a consequence of increased prevalence of visual impairment worldwide brought about by an ageing population.[7,17] Lamentably, awareness of CBS among the patient population remains poor. Around two-thirds of newly diagnosed CBS patients have not previously heard of the syndrome.[14] Even worse, CBS awareness is low among medical practitioners. In a survey of 499 Canadian general practitioners, over half of them reported no prior knowledge of CBS and therefore the majority had never discussed CBS with their visually impaired patients.[18] This reflects not only insufficient awareness of the signs and symptoms of CBS but also potentially an underestimation of its significance. Combined, these factors could foster significant underreporting, which has likely contributed substantially to the shortage of empirical research regarding CBS.

Enough information about CBS exists, however, to draw reasonable parallels to conditions that are much more widely known. Two such conditions are phantom limb syndrome (PLS) and tinnitus, which share sensory loss as a precipitating factor, as well as similar theories surrounding pathogenesis (Figure 1 and Table 1). Indeed, the similarities between the three conditions have been referenced in several previous articles[6,7] and CBS has also been referred to as 'phantom vision'.[19] To date, however, we are aware of no dedicated reviews analysing the similarities across the three conditions.

The review will first summarise the existing knowledge of the pathology and psychology of CBS, and then explore the pathogenesis of PLS and tinnitus. It will then examine how existing and emerging treatments for tinnitus and PLS could refine existing and inspire new management practices for CBS. Given the breadth of the scope of this review, emphasis has been placed on drawing parallels between the three conditions rather than discussing each of them in detail.[6,7,20–23]

CBS: Theories and psychology

The general consensus among the scientific community is that CBS is caused by vision loss.[6] However, the majority of patients with visual impairment have no symptoms of CBS.[5] Of the conditions causing vision loss, macular and retinal diseases, primarily causing visual acuity loss, appear to be overrepresented in the CBS population.[24] Crane et al. showed that over three-quarters of the 284 individuals with CBS involved in their study suffered from either macular or retinal disease, while only 7% had ocular disease of other origins, including corneal, lenticular or vascular

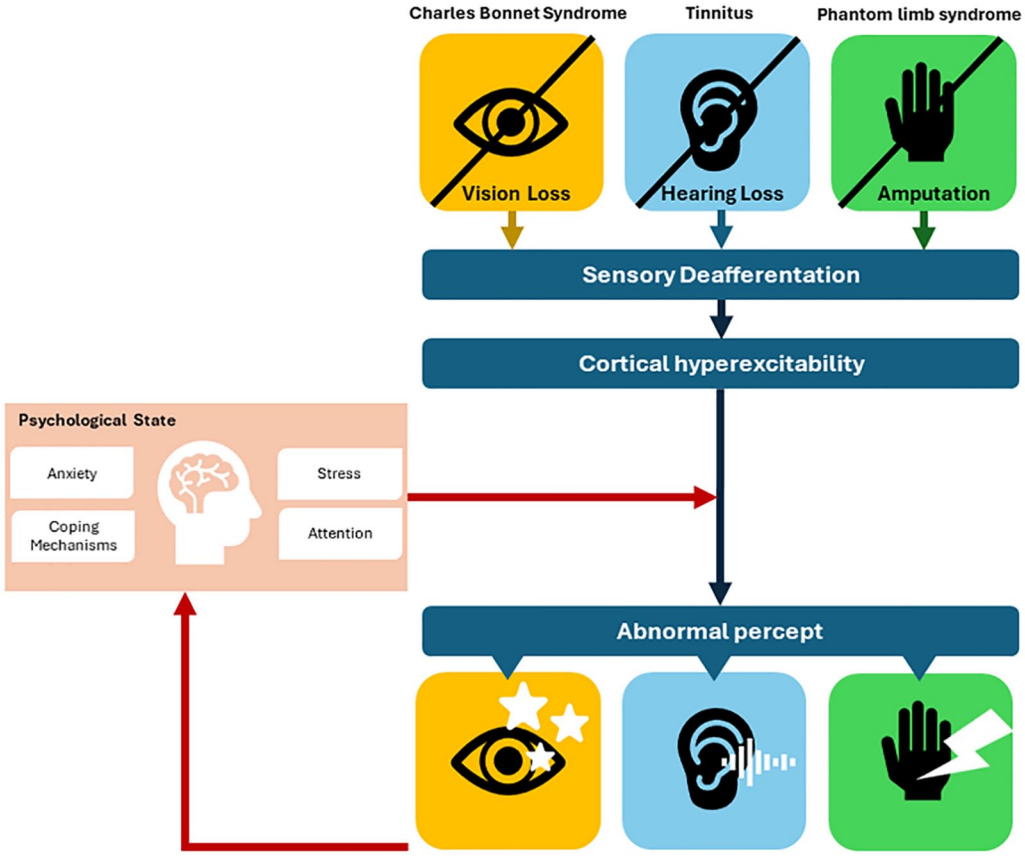

Figure 1. Representation of the factors influencing the development and persistence of Charles Bonnet Syndrome, phantom limb syndrome and tinnitus.

Table 1. Table showing similarities between Charles Bonnet Syndrome, phantom limb syndrome and tinnitus.

Condition	CBS	PLS	Tinnitus
Main feature	Visual hallucinations	Sensation of missing limb	Misperception of sound
Cause	Vision loss	Amputation or spinal injury	Hearing loss
Prevalence	Unclear, depending on source estimated to be between 10% and 50% of people with vision loss (likely underreported)	30%–90% of amputees	30%–80% of adults with hearing loss
Symptoms	Visual hallucinations of varying form and complexity	Sensation and/or pain originating from missing limb/body part	Wide range of sounds, for example, ringing, buzzing, pulsing, music/ indistinct speech
Presence of symptoms	Intermittent	Constant	Constant
Dominant proposed pathophysiology	Deafferentation causing central sensitisation and cortical reorganisation	Deafferentation causing central sensitisation and cortical reorganisation	Deafferentation causing central sensitisation and cortical reorganisation
Other pathophysiological theories	Perpetual release theory Irritative theory	Peripheral theory	Peripheral model

CBS, Charles Bonnet syndrome; PLS, phantom limb syndrome.

insult.[7] However, many of the studies on CBS have focused on patients with macular or retinal disease,[15,24,25] which may skew the perception of CBS prevalence amongst different types of vision loss.

Theories

The exact pathophysiological process of CBS remains a mystery. Researchers have converged on the idea that CBS is linked to central changes within cortical areas of the brain following vision loss,[6] and have developed several theories over the years in attempts to elucidate the biological connection between vision loss and CBS hallucinations.

Irritative theory. The irritative theory states that visual hallucinations may arise from erroneous generalised spontaneous discharge within the brain resembling seizure activity.[26] This theory arose from observations that patients with brain irritation either from solid lesions, such as meningiomas,[27] or vascular dysfunction, such as cranial arteritis,[28] could experience hallucinations. These hallucinations would in theory be intermittent and generally stereotypical since the same brain areas would be more prone to such erroneous misfiring.[29] Patients would also often experience other motor and sensory sensations. However, proponents of this theory have failed to identify any definitive 'irritative foci' in CBS.[30] Furthermore, hallucinations in CBS can vary significantly in complexity and form, and appear in the absence of motor or sensory symptoms. Due to these discrepancies, the irritative theory has declined in popularity.

Release theory. The release theory, put forward initially by West and built upon by Cogan, is similar to the irritative theory in that it revolves around increased spontaneous discharge within the brain.[31] However, the release theory states that the spontaneous discharge is not erroneous, but rather is the 'baseline' state of the brain in the absence of afferent sensory input.[30] According to this theory, in people with normal vision, afferent input suppresses spontaneous discharging. However, vision loss can lead to 'release' of these impulses in the form of memory traces ('engrams'), manifesting as hallucinations.[27] Indeed, Merabet et al. performed a blindfolding study in people with normal vision and found that 10/13 experienced simple and complex visual hallucinations.[32] While participants in the study wore blindfolds for 5 days, the hallucinations appeared after the first day and ceased either immediately, or several hours after removal of the blindfold.[32] This study suggests that it is the absence of input through the retina at baseline, rather than damage per se, that leads to hallucinations, consistent with the release theory. However, this and other similar studies[33] examine short-term vision deprivation only, which may not correlate well to CBS hallucinations in those with permanent vision impairment.

Deafferentation theory. The deafferentation theory is currently the dominant theory of CBS development. The reason why it surpassed the release theory is not clear but was likely influenced by numerous studies at the time investigating denervation hypersensitivity in various parts of the body such as skeletal muscle,[34] the gastrointestinal tract,[35] the anterior segment of the eye (including cornea and iris), the oropharynx and even cerebral arteries.[36]

In some ways, the deafferentation theory is a combination of the irritative and release theories. It states that the increased spontaneous discharge within the central nervous system develops not as a default state, but is an adaptation caused by the loss of feedforward inhibition. Feedforward input is usually provided by intact peripheral sensation but is lost in the presence of peripheral deafferentation.[6] With regards to vision loss, this would cause increased excitability of the visual cortex. Indeed, a study using electroencephalography showed that patients with CBS exhibited increased cortical responses to peripheral visual field stimulation compared to visually impaired controls without CBS.[37] Interestingly, Hahamy et al., in an fMRI study, demonstrated a unique build-up of cortical activity within the visual cortex of actively hallucinating CBS patients compared to blind and sighted controls, both when presented with external images and during internal visual imagery.[38] A study by daSilva Morgan et al. used active inhibitory stimulation of the visual cortex of CBS patients to demonstrate a significant decrease in visual hallucinations.[39] These studies provide support for the role of abnormal excitation and inhibition in CBS.

While vision loss is widely accepted as the main driver of CBS, some studies have shown that patients with relative preservation of visual acuity, such as patients with advanced glaucoma, can still experience complex visual hallucinations.[15,40–42]

Vision consists not only of visual acuity but a complex amalgam of different aspects of visual function. If any of these aspects are affected, CBS can occur. One of the key factors highlighted as contributing to the presence of CBS has been symptoms of depression and negative thinking.[43]

Psychology

Investigations into the psychological overlay in CBS have been neglected in favour of elucidating its neural mechanisms,[43] which have been documented in several reviews.[6,7,44,45] Many of the studies on the psychology of CBS are qualitative, involving questionnaires and interviews.[46] These types of studies provide greater insight into the patient's lived experience and guidance towards how better practitioners could support patients to improve quality of life.

Patients' reactions to the hallucinations, whether positive, negative or neutral,[47] may be influenced to some extent by the form of the hallucinations. For example, certain types of complex hallucinations, such as prosopometamorphopsia (distorted facial features), may generate more severe adverse reactions.[48] Negative emotional states such as fatigue and stress can trigger hallucinations,[47] and extremely stressful or emotionally impactful life events may directly influence the form of the hallucinations. For example, Cameron et al. described a survivor of the Black Saturday bushfires in Southern Australia in 2009, whose CBS hallucinations morphed from blue designs on white backgrounds to unpleasant facial hallucinations.[49] Another study showed negative changes to hallucinations triggered by media coverage of the COVID-19 pandemic.[50] These examples seem to suggest that CBS patients may experience a self-propagating cycle of negative emotions causing and being caused by worsening hallucinations, which may contribute to persistence of symptoms and, by extension, detrimental implications on health and wellbeing through effects on sleep, diet, and work.[17] A negative feedback loop may also provide an explanation for the link between CBS and depression.[48] Patients with visual hallucinations are more likely to report feelings of depression and score more poorly than those without hallucinations using metrics such as the General Health Questionnaire even when visual acuity was mostly preserved.[51,52] However, vision loss, even if mild, often presents with depression as a comorbidity,[53] and so it may be difficult to accurately determine the extent to which the presence of CBS influences the prevalence of depression in visual impairment.

Higher cognition

Hallucinations are a feature of many conditions characterised by temporary or permanent cognitive impairment, such as delirium and Lewy Body dementia.[54] CBS patients characteristically exhibit retained insight and cognition,[43] though some argue that CBS is associated with cognitive impairment.[47,55] It is possible that the answer lies somewhere in between.

A novel approach was utilised by Collerton et al., who defined and synthesised eight existing models of hallucinations into a model for aspects of visual perception relevant to hallucinations.[56] These existing eight models included not only sensory deafferentation but also memory, attention, perception and emotions. According to this framework, memory, emotions and motivation influence expectancies which contribute to a subjective perception. The subjective perception is compared to the objective data seen through the eye, which are themselves modulated by attentional processes assigning different levels of significance to different parts of a static visual field.[56] However, this framework still leaves several unanswered questions, such as the most important factors determining the influence of objective and subjective perceptions in forming or preventing hallucinations, or the interplay between expectations and sensory data in forming hallucinations.[56]

Despite efforts over the last few decades, clearly there is much about CBS that remains a mystery, including its manifestation in certain patients but not others. It may be helpful, therefore, to investigate similar conditions with larger evidence bases to target resources and research efforts more efficiently, such as phantom limb syndrome and tinnitus. As discussed earlier, they are both 'phantom' conditions, following sensory deprivation, that share many of the same investigatory challenges, such as the heterogeneity of the cause of sensory loss, and difficulties with objectively quantifying the severity of subjective experiences.[57]

Lessons from phantom limb syndrome

Overview

PLS was first described in 1872 by Silas Mitchell.[58] It refers to the aberrant sensation of the presence

of a missing limb following limb amputation (i.e. a phantom limb). PLS has also been seen in non-amputees with spinal cord or peripheral nerve injuries.[59–61]

PLS most commonly affects the limbs, but similar sensations have been described with other body parts including the breast, penis, testicles and tongue.[3]

Many also experience painful shooting, burning or cramping sensations in their phantom limb, known as 'phantom limb pain' (PLP).[62] This pain can be very difficult to manage for patients. PLP has therefore become the main focus of investigation of phantom limb sensations. Phantom eye syndrome – encompassing 'phantom vision' (hallucinations analogous to those in CBS), phantom pain and phantom eye sensations (resembling those of a phantom limb) – has been described in patients undergoing evisceration, enucleation and/or exenteration.[63] This is a form of expanded CBS with additional features of PLS.

It is estimated that lifetime prevalence among amputees of PLS is anywhere between 30% and 90%,[64] which is higher than the prevalence of CBS amongst the visually impaired. The reasons for this are unclear but may relate to the physical mechanism of sensory loss, which is often more abrupt and physically traumatic in amputation compared to vision loss. Indeed, recent work has also suggested that features related to amputation, such as pre-amputation pain, stump pain, sleep disturbances and/or diabetic/traumatic causes of amputation, may be associated with pain development in PLP.[65]

Neurology

The first notable theory for the development of PLP was the peripheral theory, which suggested that phantom sensations were triggered by stimulation of the nerves in the stump previously innervating the amputated portion of the limb.[66] Indeed, intraneural recordings have shown that stimulation of the stump of amputees can generate action potentials in the remnants of axons.[66] Interestingly, anaesthetising the cell bodies of these nerves significantly reduced PLP.[67] Furthermore, targeted muscle reinnervation (TMR), a technique initially developed to enhance prosthesis control in amputees, involves connecting remnant nerves cut during amputation to surrounding muscles and has been shown to reduce PLP.[68]

In more recent times, the peripheral theory has been neglected in favour of central theories. The most popular central theory currently is that of maladaptive cortical plasticity, which combines ideas from both the deafferentation theory and the 'neuromatrix' theory, an early theory of PLP championed by Melzack and colleagues.[69] In PLP, it is believed that the peripheral deafferentation from amputation induces central sensitisation, involving neuronal receptive field expansion and hyperexcitability of spinal neurons.[23,70] This in turn induces both an increase in the quantity of spinal cord receptors and a decrease in descending modulatory inhibition.[71] These changes culminate in cortical reorganisation[72,73] and an alteration in the 'neurosignature' – the pattern of impulses within the brain in response to constant sensory feedback.[69] This theory was popularised in the wake of a non-invasive magnetoencephalography study performed by Flor et al., which showed a highly positive correlation between the degree of cortical reorganisation and the severity of PLP.[74] Further studies have demonstrated that in amputees, the cortical areas representing the amputated limb are assimilated into adjacent areas of the motor and somatosensory cortices.[71,73] Indeed, recent evidence suggests that TMR may reduce PLP not by preventing aberrant stimulation of peripheral nerves but by preventing cortical reorganisation. A recent study by Li et al., on 32 major limb amputees showed that the pain-reducing benefits of TMR were greater when performed soon after amputation (within days) rather than months to years after the amputation.[75]

Cortical reorganisation in PLP could be thought of as a physiological manifestation of the theoretical concept of '*body schema*', an idea first originating in the late 1800s but solidified by Head and Holmes in the early 20th century.[22,76] '*Body schema'* refers to the internal representation of an individual's own body based on the combination of input from different sensory modalities. This representation would be dynamic, as sensory inputs are constantly changing. With regards to PLP, this would involve afferent innervation from the proprioceptive, somatosensory, visual and vestibular systems and integration of motor and sensory input by the parietal cortex.[22,77] In a similar way, a *'visual schema'* for CBS may integrate afferent visual input from the eyes with

information from other areas. An interesting review by Pennartz et al. proposes a view of the visual pathway as 'constructive' rather than 'replicative'. It hypothesises that rather than copy directly, the brain builds a view of the outside world influenced by the sensory pathways mentioned above in addition to working memory.[78] For example, upon closing our eyes, our brain is often able to reconstruct what we have previously seen. This bears a resemblance to the harmonised framework for CBS discussed earlier. The support for their hypothesis stems from studies showing that auditory and proprioceptive inputs can modulate responses in the primary visual cortex, forming the basis of feedback input to the visual system.[79,80] However, much of this evidence comes from animal studies and therefore the applicability to humans is difficult to ascertain.

In theory, cortical reorganisation should predict that patients with PLP lose cortical representation of their amputated limbs over time. However, more recent work using high-resolution human neuroimaging has cast some doubt on the role of cortical reorganisation in PLP. Kikkert et al. utilised neuroimaging on unilateral upper limb amputees and found that these amputees retained cortical representation of individual digits of the amputated hand within the primary somatosensory cortex even despite decades of lost afferent sensory input.[81] This evidence calls into question the extent to which the reorganisation of the somatotopic map is influenced by changes to afferent input. It is possible that cortical reorganisation and retention of the somatotopic map are not mutually exclusive.[82] For example, reorganisation may not be within the primary somatosensory cortex itself but rather in the inputs received from subcortical areas.[81] However, in a recent review, Makin and Krakauer argue that the lack of pluripotency of cerebral neurons precludes any form of significant anatomical reorganisation, and proposes instead that remapping of existing synapses causes the effects seen in PLP.[83]

Therefore, many questions still remain regarding the brain regions that contribute most to the presence of phantom limb syndrome and the extent to which the condition is caused by maladaptive plasticity.

Psychology of PLS and PLP

Compared to CBS, there is more research on the influence of PLS patients' psychological states on their symptoms. Loss of a limb is in itself psychologically traumatic,[84,85] though compared to vision loss there is more likely to be painful trauma at the site of the amputation than there would be in the eye. Most of the evidence concerning the psychology of PLS comes from cross-sectional or retrospective studies which suggest that psychological states are indeed linked to the intensity of sensations in PLS, particularly pain.[70] For example, Arena et al. found a significant stress-pain relationship in 74% of amputees over 180 days.[86] Interestingly, in 37% of participants, changes in stress preceded changes in pain, and in 44% pain preceded stress.[86] This provides evidence for a bidirectional relationship between stress and pain in PLP,[87] and may support the concept of a negative feedback loop between negative emotions and worsening symptoms mentioned previously in reference to CBS. In addition to psychological stress and other negative emotions, it has been suggested that cognitive factors including attention, memory, coping mechanisms and expectations can modulate pain in PLP.[88,89]

Teachings of tinnitus

Unlike CBS, knowledge of tinnitus dates back millennia, as far as ancient Mesopotamia.[90] Tinnitus refers to the aberrant, or 'phantom', perception of sound. *Objective* tinnitus, which is exceedingly rare, is caused by legitimate transduction of sounds or vibrations originating within the body (such as carotid aneurysms), while *subjective* tinnitus occurs in the absence of any sound or vibratory stimulus.[20,91] For the purposes of this review, 'tinnitus' will refer to subjective chronic tinnitus.

Tinnitus is most commonly associated with high-frequency hearing loss, likely because it is the most common form of hearing loss.[92] However, tinnitus can develop from damage anywhere along the auditory pathway.[91] Reports differ, but tinnitus affects anywhere between 30% and 80% of adults with hearing loss,[93–96] being more prevalent in older adults,[97] though again this may be because hearing impairment becomes more common with age.

The sound of tinnitus can vary, from simpler monotonous tones or ringing to more complex sounds like pulsing, buzzing, crickets and even melodies or features of music or indistinct speech (so-called 'auditory imagery tinnitus').[20,98] Very complex and meaningful sounds like coherent

speech or fully formed music are classified as auditory hallucinations, which are clinically distinct from tinnitus.[99] Of those affected by tinnitus, around one-third, can be significantly disturbed by tinnitus,[96] and therefore may experience negative effects on sleep, mood, and – by extension – day-to-day functioning.[100]

Though some sufferers of tinnitus have hearing within the normal range, there may still be damage to the sensorineural hearing apparatus (i.e. supra-threshold).[101,102] In these people, tinnitus may manifest in later life as seemingly idiopathic tinnitus years after the initial insult to their ears since hearing tends to decline naturally with age.[103]

Pathophysiology

Development of tinnitus. The current prevailing theory is that tinnitus is caused by central reorganisation induced by peripheral deafferentation,[20] in this case caused by damage to the hair cells of the cochlea, which are the sensory receptors of the inner ear.

Physical damage. The pathophysiological mechanisms of tinnitus were initially studied mainly in animal models, including cats, rats and chinchillas, in whom hair cells within specific frequency ranges could be selectively damaged with loud noises or chemical agents.[104–106] These studies showed that cochlear damage correlated with increased spontaneous firing rates in the dorsal cochlear nucleus (DCN) and auditory cortices, and increased neural synchrony in the central cortical areas.[20] Changes in spontaneous firing rates and neural synchrony have been hypothesised to induce reorganisation of the cortical tonotopic map,[20,107] which then leads to tinnitus.

While these changes in animal models appear to be consistent with the maladaptive plasticity seen in patients with PLP, results of animal studies demonstrating the importance of tonotopic reorganisation have not yet been replicated in humans.[108] Furthermore, given that tinnitus is a subjective phenomenon, it is difficult for us as humans to quantify its presence or severity in animals. Given these limitations, it is very important that tinnitus be investigated in humans.

Effects on the brain. In a recent study echoing blindfolding studies in CBS, Brotherton et al. demonstrated that short-term earplug-mediated auditory deprivation in participants with undamaged auditory systems can lead to a perception of tinnitus.[109] Studies such as these are useful in connecting tinnitus to hearing loss at a rudimentary level, but in humans investigations such as functional neuroimaging play a more important role in better delineating the neural mechanisms of tinnitus.

Early neuroimaging in humans with tinnitus indicated little change in the tonotopic organisation in the cortex compared to those with normal hearing.[108] However, a recent study used ultra-high field strength fMRI in participants with comparable hearing loss, with and without tinnitus.[110] In this study, there was a loss of selectivity for frequency in the tinnitus patients that was frequency non-specific. In addition, there was a reduction in auditory system functional connectivity measured in resting state data, both thalamo- and cortico-cortical. This study suggests that, like PLP, tinnitus is associated with reduced inhibition in the auditory pathway, potentially leading to increased neural noise and reduced functional connectivity.

Outside of auditory-specific, tonotopically organised regions, fMRI studies have implicated that several other brain regions may be affected by tinnitus. The most frequently identified regions include the dorsolateral prefrontal cortex, cingulate cortex, parahippocampus and insula.[21] This suggests that tinnitus is a complex condition that involves abnormalities in brain regions concerned not only with hearing but also more general perception, salience, memory and attention. This is, in some ways, similar to the concept of '*body schema*' proposed for PLP, and the harmonised framework in CBS.

In any case, it is perhaps not surprising that understanding the origin of tinnitus is challenging. These challenges are compounded by heterogeneity of samples, small populations and challenges in presenting auditory stimulation in MRI scanners, which are very noisy.

Persistence of tinnitus

While the initial development of tinnitus is thought to be caused by peripheral deafferentation, the persistence of tinnitus can be perpetuated or aggravated by psychological and cognitive factors.[111]

Psychological model. The psychological model of tinnitus suggests that the persistence or recurrence of tinnitus relates to a neural connection between tinnitus and emotional events – both positive and negative – through conditional learning.[112] Events or emotions that draw attention to the presence of tinnitus such as mood disorders, or distract from it (positive engagement with tasks) can increase or decrease distress respectively.[112] The psychological model has been expanded into the neurophysiological model of tinnitus by Jastreboff.[113] This model suggests that tinnitus arises from a culmination of sensory input from all levels of the sensory pathway that is integrated by various other cortical areas. This model also highlights the importance of subconscious rather than conscious processing of the tinnitus percept.[114] It, therefore, prompted interest in Tinnitus Retraining Therapy (TRT) – a combination of counselling and sound therapy that combats the salience and perception of the tinnitus to accelerate habituation.[115]

Such psychological modulation of tinnitus is supported by evidence showing that the subjective severity of tinnitus (and subsequent psychological impact) is not strongly correlated to objective assessments of tinnitus loudness.[116] Furthermore, there have been studies involving structured psychiatric interviews conducted in patients with tinnitus, which, similarly to CBS, have shown a high prevalence of mood disorders such as anxiety and depression.[117,118] Importantly, people who seek help for tinnitus generally exhibit more psychiatric symptoms than people who do not seek help.[119] Even those with tinnitus who did not seek help exhibited more psychiatric symptoms than controls without tinnitus.[119]

Cognitive model. McKenna and Andersson proposed a cognitive model of tinnitus, in which they suggest that cognition and tinnitus share a bidirectional relationship; the presence of tinnitus can worsen cognitive function,[120,121] and differences in cognitive biases can predispose certain individuals to tinnitus. With cognition and attention affecting both tinnitus and PLS, it is highly likely that there is a cognitive component to CBS as well. Mckenna's cognitive model was built upon by Ghodratitoostani et al.'s neurofunctional tinnitus model[122] and more recently in Ghodratitoostani et al.'s 'Conceptual Cognitive Framework' of tinnitus. The tinnitus Conceptual Cognitive Framework suggests that the distress caused by tinnitus is modulated through multiple cognitive and emotional mechanisms that gradually change the perception and emotional response to the sounds that are heard.[123] According to this model, any treatments should therefore not only target the original tinnitus sound but also influence the perceptual modification. In a similar way, treatments for CBS should target not only hallucinations but an individual's response to hallucinations.

Management

Existing treatments for CBS

CBS has not been effectively treated as it has been poorly understood. Medications have been trialled in patients with severe CBS, including atypical antipsychotics (such as olanzapine), anti-epileptics (like valproate), and cholinesterase inhibitors (like donepezil). However, the evidence in favour of these medications is low quality, coming mainly from case reports of patients with marked heterogeneity in how their CBS manifests.[124–126]

Counselling and talking therapies are also used to manage symptoms of CBS. However, there is a noticeable lack of structured studies investigating the benefits of dedicated talking therapies in CBS patients. As our understanding of the neuroscience of CBS expands,[127] targeted treatments can be developed. Additionally, exploring new and emerging treatments for PLS and tinnitus may provide useful insights.

Inspiration for emerging therapies from PLS and tinnitus

PLS and tinnitus are also notoriously difficult to manage. Sherman et al. identified 68 different methods of treating PLS, many of which have been discontinued over the years due to poor effectiveness.[128] In a more recent three-round Delphi study involving 27 experts in PLS, 7 treatments were deemed effective by consensus.[129] Four of these treatments – graded motor imagery, mirror therapy, sensory discrimination training and use of functional prostheses – rely heavily on visuo-proprioceptive or tactile feedback, so relevance to CBS may be limited. Furthermore, evidence on the efficacy of pharmacotherapy is inconclusive.[130] Many interventions have been investigated in the management of tinnitus, including sound therapy. Like PLS, interventions such as medications and biofeedback have shown

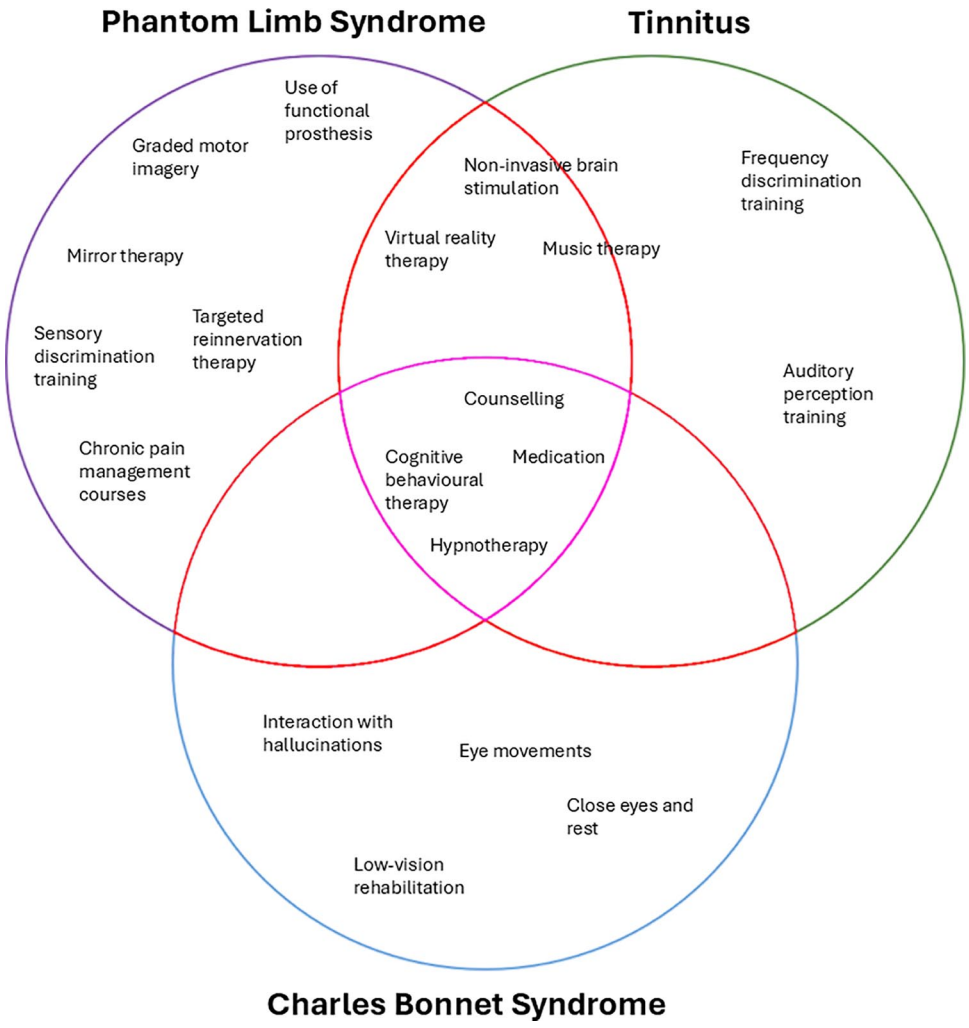

Figure 2. Current available treatment options for Charles Bonnet syndrome, Phantom Limb syndrome and tinnitus.

limited or inconsistent efficacy.[131–134] Of the remaining interventions, there is a significant overlap between those used in PLS and those used in tinnitus (Figure 2).

CBT

Cognitive behavioural therapy (CBT) has become a popular intervention for people suffering from psychiatric conditions, ranging from mood disorders like anxiety, depression and bipolar disorder to addictions, eating disorders and obsessive-compulsive disorder. If implemented effectively, CBT could be a very effective tool in breaking the negative cycles associated with CBS, tinnitus and PLS and therefore lessening the dysregulated emotions and thoughts, providing a coping strategy. Despite the significant dearth of literature validating the application of CBT directly in PLS patients, CBT has become commonplace in clinical practice to manage PLS.[129] In PLS, CBT may in some way modulate the 'body schema' referenced earlier through its contributions to modifying cognitive and behavioural factors that have been proposed to initiate and potentiate PLS,[129] but the exact mechanism is unknown.

Unsurprisingly, CBT has also been used to treat tinnitus. Several early systematic reviews and meta-analyses have shown that CBT in tinnitus patients reduces patient distress and improves quality of life.[135–137] Another recent network meta-analysis demonstrated that face-to-face CBT showed significant improvements in health-related quality of life in tinnitus sufferers.[138] However, a recent Cochrane review published

around the same time has highlighted a paucity of evidence detailing the long-term benefit of CBT on health-related quality of life and associated psychological comorbidities.[139] More research into the long-term benefits of CBT for tinnitus, as well as PLP and CBS, may therefore be warranted and may generate transferrable principles that help inform best practice across the three conditions.

There is a more significant dearth of literature relating to the efficacy of CBT in CBS. However, there are isolated case studies demonstrating beneficial effects. For example, Issa et al. described the case of an 87-year-old man blind man with CBS who was reassured that his hallucinations were not real, and was taught techniques on preventing hallucinations such as blinking or closing his eyes.[140] Perhaps techniques like these could be investigated in larger-scale studies to provide more reliable evidence of the efficacy of CBT.

Hypnotherapy

Hypnotherapy has been investigated as a potential treatment of PLS as far back as the 1970s due to its efficacy in managing other forms of chronic pain refractive to conventional management.[141,142] While hypnosis has been offered in clinical practice to manage CBS, there are no studies to date to demonstrate its efficacy.

Compared to other forms of chronic pain, evidence of hypnotherapy in PLS is lacking. Much of the evidence supporting hypnotherapy comes from case studies[143–145] rather than systematic research,[23] but these case studies do suggest that hypnotherapy can be effective.

The evidence for the effects of hypnotherapy on tinnitus is more concrete. For example, a prospective longitudinal study of Ericksonian hypnotherapy demonstrated improved scores on the Tinnitus Handicap Inventory questionnaire before and after therapy.[146] Similar results have been demonstrated in other studies,[147,148] particularly for self-hypnosis. Self-hypnosis has the intrinsic ability to be performed whenever needed and therefore could be very beneficial in CBS patients, whose hallucinations are often intermittent and appear without warning.

The main drawback of hypnotherapy is that its success is dependent on how 'hypnotisable' a patient is,[23] which appears to differ intrinsically between individuals at a cortical level.[149] There is evidence to suggest that hypnotisability can be trained or temporarily enhanced with chemicals such as alcohol,[150] though the latter may not be ethical or sustainable. A very recent study by Perri et al., however, showed that transcranial direct current stimulation (tDCS) applied to the dorsolateral prefrontal cortex increased the hypnotisability of participants,[151] possibly presenting a safe and sustainable way to enhance the effectiveness of hypnosis. Further research into perfecting the clinical technique for hypnosis in both PLS and tinnitus may guide the investigation of and clinical viability of hypnosis for CBS.

Non-invasive brain stimulation

A form of non-invasive brain stimulation, transcranial direct current stimulation (tDCS), has been used to achieve therapeutic relief of chronic conditions. Non-invasive brain stimulation has received a surge in popularity over the last couple of decades and has been used both in investigatory and therapeutic capacities. tDCS has been tested on several areas of the brain, including the motor, prefrontal and posterior parietal cortices and cerebellum, and some studies have shown that pain in PLS is reduced by tDCS,[152–154] though often there was no significant reduction in pain on follow-up several weeks later.[155] The effects of tDCS are also difficult to discern in tinnitus, with a study by Teismann et al. showing no additional benefit of tDCS applied to the left auditory cortex in people with tinnitus also treated with sound therapy.[156] In CBS a recent placebo-controlled crossover trial performed by daSilva Morgan et al. involving tDCS to the visual cortex of 16 CBS participants showed a significant reduction in hallucinations.[39] However, the duration of the improvement was not assessed.

Transcranial magnetic stimulation (TMS) is another form of non-invasive brain stimulation that disrupts neural signalling.[157] It has demonstrated significant short-term reduction of pain in PLP studies.[155,158] It has also been used on tinnitus sufferers by Plewnia et al. in two studies, with both demonstrating an immediate subjective decrease in the volume of tinnitus after stimulating the left temporo-parietal cortex.[159,160] Unfortunately, this effect appears to be transient, as improvements in tinnitus were not detectable when retested two weeks after the last treatment session.[160] Therefore, the feasibility of non-invasive brain stimulation in the management of CBS

may depend on the duration of effects, and so more research incorporating long-term follow-up may be warranted.

Evidence of the efficacy of TMS in CBS is once again limited, though one case report had demonstrated that 1Hz rTMS to the occipital cortex abolished hallucinations in a patient with bilateral visual cortex ischaemic damage.[160,161]

Virtual reality therapy and mirror therapy

The effectiveness of mirror therapy in treating PLS was first demonstrated with the famous mirror-box experiment by Ramachandran et al.[162] Mirror therapy involves using mirrors to reflect an image of an intact limb over a patient's phantom limb, and then performing movements with the intact limb to give the illusion that their phantom limb is moving. In this way, mirror therapy uses constructed visual feedback to attempt to resolve visuo-proprioceptive dissociation experienced by patients.[23] For this reason, as mentioned earlier, its applicability to CBS may be limited.

VR therapy could be thought of as a modern enhancement of mirror therapy since it possesses the ability to generate rather than merely replicate images. For this reason, the efficacy of VR therapy may not be inextricably reliant on visuo-proprioceptive feedback, and therefore may theoretically be useful in CBS. However, much of the evidence regarding the benefits of VR therapy in PLS comes from case studies[163] and trials lacking control groups,[164] highlighting a need for more systematic research.[165,166] For example, a study by Rutledge et al. on 14 amputees showed that VR significantly reduced the number of patients experiencing phantom limb sensations and pain,[164] but the lack of a control group means that the true benefit of VR therapy in this instance beyond a placebo effect is hard to infer. There is one randomised control trial in which VR was compared to mirror therapy and a control condition over a 4-week period. The study showed no improvement in PLP in the VR group at 4 or 10 weeks after the cessation of intervention,[167] which calls into question the efficacy of VR therapy.

VR has also been investigated in tinnitus patients to a lesser extent in more recent years. In a study by Malinvaud et al., patients were placed in a VR simulation in which they could manipulate a representation of their tinnitus in different everyday environments. They showed that the efficacy of VR therapy was comparable to CBT,[168] and remained comparable three months post-treatment. However, their study included only unilateral tinnitus sufferers, and therefore more research is needed to determine if these findings are applicable to other forms of tinnitus.

The application of VR therapy to CBS specifically has not been studied. Drori et al. used VR to study the role of a sense of reality in hallucinations,[169] but this was mainly focused on psychotic conditions in which patients lacked insight. Furthermore, VR therapy would inevitably require some residual vision, and so would most likely be ineffective in completely blind individuals. More knowledge about what causes or triggers CBS hallucinations is required before we know whether VR would have any benefit in alleviating symptoms of CBS.

Sound therapy

Various sound therapies, such as simple sound enrichment, or more complex frequency discrimination training and auditory perception training, have been used to manage tinnitus.[91] These are relatively tinnitus-specific with limited applicability to CBS, and therefore they will not be explored further.

A more 'general' sound therapy – music therapy – has been gaining popularity due to growing evidence of its ability to reduce stress and anxiety, alleviate depression and even improve functioning in conditions such as depression and schizophrenia.[170] The benefits of music therapy extend to tinnitus; a recent systematic review by Niu and You showed that music therapy significantly reduced Tinnitus Questionnaire and Tinnitus Handicap Inventory scores.[171] A tinnitus-specific form of music therapy, tailor-made notch music training (TMNMT), involves playing music with the frequency with no energy at the patient's tinnitus 'spectrum'. It has been shown to decrease auditory cortex activity in areas corresponding to tinnitus,[172,173] though the aforementioned systematic review did not show a significant difference in score reduction between TMNMT and regular music therapy.[171]

An equivalent therapy that may be of use in CBS is visual art therapy. The limited research into the application of visual art in investigating experiences associated with hallucinations is summarised by Melvin et al.[174] They describe empirical

studies employing art-based research methods, such as participants taking photos of things resembling their hallucinations or using visual diaries to facilitate introspection into thoughts and feelings surrounding hallucinations. In this way, visual art therapy is thought to serve as an outlet for patients to express in art what they cannot in words.[174] As a next step, further investigation with control comparisons may be warranted to further investigate any clinical benefits of visual art therapy in CBS. Patient-produced artistic representations of their hallucinations may also serve as a powerful information source to those at risk of CBS as to what they may experience.

Discussion

CBS, PLS and tinnitus share remarkable similarities in their inception and persistence. Given the relative paucity of CBS research to date, studying conditions such as PLS and tinnitus could provide beneficial insights that could inform theoretical and clinical practice. Unfortunately, conflicting and inconclusive evidence regarding both pathogenesis (e.g. the debate surrounding cortical reorganisation) and management (e.g. conflicting evidence on the benefits of VR therapy and CBT) highlights the challenges in investigating these conditions. Indeed, treatment studies are difficult to compare due to lack of standardised methodology and use of different outcome measures.

All three conditions are thought to arise, in the majority of cases, from significant sensory deafferentation (vision loss in CBS, amputation in PLS and hearing loss in tinnitus). This loss causes central sensitisation and the emergence of an abnormal percept which is reinforced through negative feedback loops spurred on by stress, anxiety, depression and maladaptive coping mechanisms (Figure 1). Other features investigated in PLS and tinnitus may also bear relevance to CBS, such as cognition, attention, and contribution of other sensory modalities to '*body schema*'.

The prevailing pathophysiological theory for CBS, PLS and tinnitus involves cortical reorganisation. Reorganisation has been shown to arise following denervation[175–177] which is the key mechanism underlying all three conditions. Much of the human evidence for the contribution of cortical reorganisation to these phantom conditions has come from neuroimaging studies in PLS and tinnitus.[38,81,110,178] Neuroimaging studies in CBS are lacking, and therefore future research could be directed here. Importantly, there is no single standardised method of quantifying cortical reorganisation. It would be beneficial for working groups to come together and discuss further standardisation of techniques and develop methods to be used across studies, which would allow easier and more consistent comparisons between different studies. Furthermore, there is limited evidence regarding factors increasing susceptibility to cortical reorganisation. If cortical reorganisation is the true pathological mechanism, then one may postulate that potential risk factors for CBS, PLS and tinnitus like higher cognitive functioning and psychological health may work by increasing susceptibility to developing symptoms in the presence of the required physical condition. Other predictors are yet to be determined but are likely to relate to attentional state or a person's extrapolated use of senses (for example, to what extent people 'hear' (verbal) or 'see' (visual) thoughts). Perhaps more research into the psychosocial context of participants may allow 'grouping' of participants together to produce more standardised results.

However, it is important to remain open to explanations other than cortical reorganisation. In a thought-provoking commentary on PLP, Makin makes the pertinent point that many of the management techniques devised for PLP have not been shown, under scientific scrutiny, to have long-term benefits to PLP beyond placebo effect.[66]

Although there is much to be gained from PLS and tinnitus for CBS research, it is also important to remember that the three conditions remain distinct, and therefore there may be some unreconcilable differences. For example, while CBS is usually intermittent, tinnitus can often be continuous.[179] Each may also have multiple mechanisms of action, further fragmenting the applicability of learning across the conditions. Indeed, in PLP, there are still mechanisms by which pain can be perceived from peripheral nerves that were damaged. Further research into the effects of modulation of other sensory modalities, including the auditory, vestibular, proprioceptive and somatosensory pathways on CBS could provide some useful answers, particularly as dual sensory loss will increase in the ageing population.

Briefing patients with CBS, PLS and tinnitus has been shown to be important in reducing distress and suffering,[47,91,180] and helping people cope. Indeed, many patients with symptoms of, but no

knowledge about, CBS may misinterpret the hallucinations as a sign of mental illness. Practitioners unfamiliar with the condition may also misdiagnose these hallucinations as mental illness. VR technologies may prove an incredibly useful tool in raising awareness about CBS and what it is like to live with hallucinations. Early intervention and better social support in some form may be key to managing the negative psychological responses that reinforce CBS. For those already suffering from CBS, focus could be shifted to interventions effective in both PLS and tinnitus that require further investigation in CBS, such as non-invasive brain stimulation, or more prospective treatments like visual art therapy. Furthermore, inspiration to enhance the efficacy of interventions already used in CBS, such as hypnotherapy and CBT, could be drawn from modifications tried in PLS and tinnitus.

Given the nature of 'phantom conditions', outcome measures in treatment studies tend to be subjective, relying on standardised symptom questionnaires. To date, only one CBS-specific questionnaire exists[181] but is not widespread owing to its recent development and more recent translation into English. This or future CBS-specific questionnaire should be used in studies moving forward to facilitate the development of a standardised protocol for studying treatment benefits in CBS.

Limitations

While this review aims to be as comprehensive as possible, since it is a literature review it did not employ a structured search strategy, which may limit the range of information covered in the review. Furthermore, the broad scope of the review limited the extent of in-depth discussion of all three conditions.

Conclusion

In summary, combining the knowledge of CBS, PLS, tinnitus and other similar conditions may facilitate more efficient allocation of research time and effort and subsequently more effective treatments, as well as a greater understanding of the underlying mechanisms.

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Not applicable.

Consent for publication

Not applicable.

Author contributions

Kwame A. Baffour-Awuah: Conceptualisation; Formal analysis; Methodology; Visualisation; Writing – original draft.

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