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Hallucinations in schizophrenia, sensory impairment, and brain disease: A unifying model

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Abstract: Based on recent insight into the thalamocortical system and its role in perception and conscious experience, a unified pathophysiological framework for hallucinations in neurological and psychiatric conditions is proposed, which integrates previously unrelated neurobiological and psychological findings. Gamma-frequency rhythms of discharge activity from thalamic and cortical neurons are facilitated by cholinergic arousal and resonate in networks of thalamocortical circuits, thereby transiently forming assemblies of coherent gamma oscillations under constraints of afferent sensory input and prefrontal attentional mechanisms. If perception is based on synchronisation of intrinsic gamma activity in the thalamocortical system, then sensory input to specific thalamic nuclei may merely play a constraining role. Hallucinations can be regarded as underconstrained perceptions that arise when the impact of sensory input on activation of thalamocortical circuits and synchronisation of thalamocortical gamma activity is reduced. In conditions that are accompanied by hallucinations, factors such as cortical hyperexcitability, cortical attentional mechanisms, hyperarousal, increased noise in specific thalamic nuclei, and random sensory input to specific thalamic nuclei may, to a varying degree, contribute to underconstrained activation of thalamocortical circuits. The reticular thalamic nucleus plays an important role in suppressing random activity of relay cells in specific thalamic nuclei, and its dysfunction may be implicated in the biological vulnerability to hallucinations in schizophrenia. Combined with general activation during cholinergic arousal, this leads to excessive disinhibition in specific thalamic nuclei, which may allow cortical attentional mechanisms to recruit thalamic relay cells into resonant assemblies of gamma oscillations, regardless of their actual sensory input, thereby producing an underconstrained perceptual experience.

Keywords: Charles Bonnet syndrome; gamma oscillations; hallucinations; late paraphrenia; Lewy body dementia; perception; schizophrenia; thalamocortical system

1. Introduction

Gestalt psychologists in the first half of the last century argued that perception cannot be broken down into patterns of sensory stimulation and is not a derivative of the richness of stimulation from the external world (e.g., Koehler 1940). Instead, they maintained that perceptual experience is an *active* achievement of the nervous system. More recently, Llinas and Pare (1991) suggested that conscious perception is subserved by intrinsic activity in thalamocortical circuits, involving cortical pyramidal neurons and relay cells in specific thalamic nuclei. They pointed out that most of the connectivity in thalamocortical circuits is geared to the generation of internal functional modes, which can principally operate in the presence or absence of sensory input; only a minor part of thalamocortical connectivity is devoted to the transfer of sensory input. Cells in thalamocortical circuits are intrinsically active and sensory input may only modulate their activity. Llinas and Pare (1991) viewed consciousness as a closed-loop property of the thalamocortical system, and not a by-product of sensory input. Accordingly, they regarded wakefulness and paradoxical sleep as fundamentally equivalent states. The main difference between perception in wakefulness and dream imagery in paradoxical sleep would lie in the weight given to sensory afferents. In the state of wakefulness, but not in paradoxical sleep, the intrinsic functional mode underlying consciousness is modulated by sensory input (Llinas & Pare 1991).

In their implication for the relationship between conscious experience and physical reality, these views are consistent with the philosophical position of transcendental idealism (Kant): The world that we see around us is internally created and a fundamentally subjective experience that in the state of normal wakefulness is merely constrained by external physical reality (Fig. 1). Transcendental idealism predicts that normal perception, dream imagery, and hallucinations are principally manifestations of the same internal process. They differ only with respect to the degree to which they are constrained by physical reality represented by sensory input. Thus, hallucinations can

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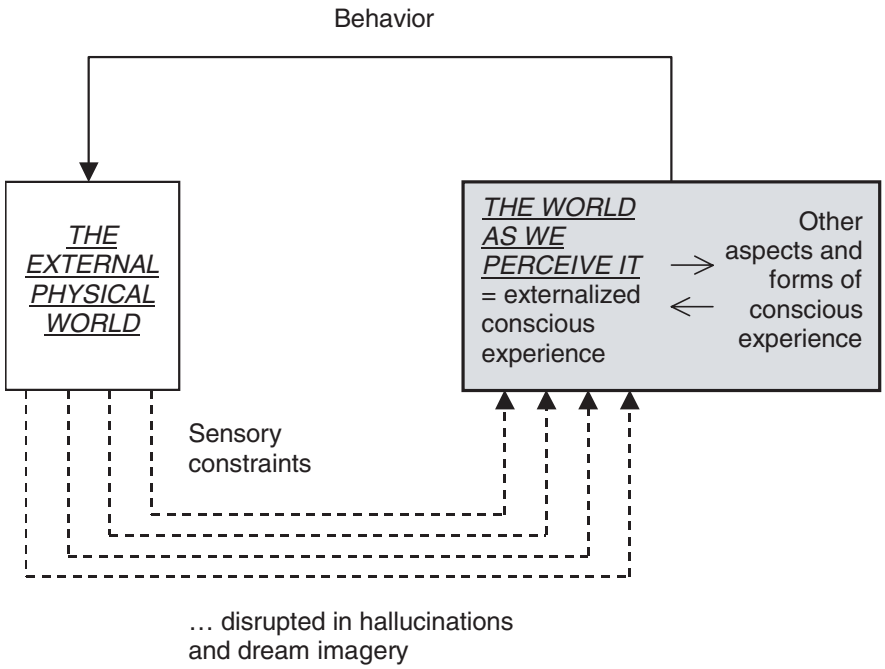

Figure 1. According to transcendental idealism, a crucial distinction has to be made between the world that we perceive around us and the external physical world with which we interact. What we perceive as being around us is not the external physical world; instead, it is a part of our mind that is projected outside. In order to be adaptive, the subjective image of the world has to be constrained by external physical reality, and this is where sensory input plays its role. Thus, in the state of normal wakefulness, there *is* a relationship between the external physical world and the world that we perceive, but *it is not the physical world that we see*.

be conceptualised as perceptual experiences in the state of wakefulness that are *underconstrained* by sensory input (and it is suggested that in schizophrenia and some organic conditions this can be caused by peripheral sensory impairment or increased random neural activity in specific thalamic nuclei). Otherwise, there should be no difference: hallucinations arise in the focus of attention, just like any other perception, and they should involve activity in the same physiological systems that subserve normal perception. In hallucinations, attentional factors determine the content of conscious experience in a manner that is unrestricted by external sensory stimulation (although in some organic conditions focal cortical hyperexcitability may substitute prefrontal and limbic input to the cortex mediating attention).

In contrast, psychopathology usually adopts a philosophical position of *realism* (in the form of dualism or materialism), which assumes that the world we perceive around us is an objective reality. The world is thought to exist independently of ourselves and not to be a product of our mind (Hamilton 1974). Accordingly, hallucinations are defined as false perceptions that arise in the absence of an external object or event. They are thought to differ from true perceptions in that they come from within the person's mind, as opposed to from outside the mind (Hamilton 1974). The realist approach to hallucinations is intuitive and practical, however it suggests that hallucinations differ fundamentally from normal perception with respect to their source and mechanism of generation. Here, we suggest that in order to better understand the nature of hallucinations and integrate accumulating data pertaining to these phenomena, we need a shift in paradigm from regarding the world around us as an objective reality to recognising it as a fundamentally subjective experience. In other words, normal perception, dreaming, and hallucinations are equivalent, because even normal perception in wakefulness is fundamentally a state of hallucinations, one however that is constrained by external physical reality. The adaptive state of wakefulness certainly does depend on changes taking place in the outside world, but we do not *see, hear, feel, or smell*

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physical reality itself; instead physical reality *constrains* the internal and fundamentally subjective process of perception, which is all that is necessary to ensure its adaptivity. From an evolutionary perspective, perception did not develop to copy the external world; the world that we perceive around us is as complex and differentiated as is necessary for the organism's adaptive interaction with the external world in pursuit of its physiological needs.

In the following sections, we outline specific and nonspecific factors that influence intrinsic thalamocortical activity, such as attentional mechanisms, sensory input, and cholinergic control. A review of the thalamocortical system, as it subserves perception, enables us to relate the proposed general perspective on hallucinations to a specific pathophysiological model. Then we show how this model relates to clinical and neurobiological findings in conditions that are associated with hallucinations, including schizophrenia, visual and hearing impairment, as well as some cortical lesions and neurodegenerative disorders. What emerges is a theme of disruption of sensory constraints and determination by attentional factors, supporting the specific pathophysiological model and the general approach to hallucinations.

1.1. Resonance in thalamocortical networks

Projection neurons in specific and nonspecific thalamic nuclei and inhibitory neurons in the adjacent reticular thalamic nucleus form neuronal circuits with interneurons and pyramidal neurons and in the cerebral cortex. In *specific thalamocortical circuits*, thalamic relay cells send axons to interneurons in layer IV of the cortex, which in turn connect to pyramidal neurons in cortical layer VI. Pyramidal neurons send glutamatergic projections back to the thalamus. These corticofugal (corticothalamic) projections exert a direct excitatory influence on thalamic relay cells, as well as an indirect inhibitory influence that is mediated by the reticular thalamic nucleus (reviewed in Llinas & Ribary 1993). In *nonspecific thalamocortical circuits*, neurons in intralaminar thalamic nuclei project to layer I of the cortex; pyramidal cells in cortical layers V and VI project back to intralaminar nuclei both directly and indirectly via collaterals to the reticular thalamic nucleus (reviewed in Llinas & Ribary 1993). The reticular thalamic nucleus, which forms a sheet along the outer surface of the thalamus, plays an important part in thalamocortical connectivity. It consists of GABAergic inhibitory neurons that project to all other thalamic nuclei in a topographically organised manner and that receive collateral terminals from both thalamocortical and re-entrant corticofugal axons passing through the nucleus (reviewed in Saper 2000). Reticular thalamic neurons establish synaptic connections predominantly with dendrites of thalamic projection neurons and, to a lesser extent, with inhibitory interneurons in thalamic nuclei (Liu et al. 1995).

Thalamic projection neurons and neurons in the reticular thalamic nucleus can be in one of two electrophysiological response modes: a tonic-firing mode, in which cells are partly depolarised and respond to afferent stimulation with firing of single action potentials, and a burst-firing mode, in which cells are hyperpolarized and respond with bursts of action potentials. In the tonic-firing mode, thalamic relay cells generate action potentials in a manner that is related to afferent sensory input, whereas in burst-firing mode sensory information is not transmitted effectively (McCormick & Feeser 1990). During wakefulness, thalamic relay neurons are predominantly in tonic mode; burst-firing mode becomes more prevalent in states of inattentiveness and drowsiness and predominates in slow-wave sleep.

Partial membrane depolarisation in thalamic neurons, not only enables tonic firing of action potentials, but also produces subthreshold gamma (around 40 Hz) oscillations of membrane potential (Steriade et al. 1991; 1993). With further depolarisation, membrane potential oscillations can give rise to spikes or spike-bursts of action potentials that recur at gamma rhythms (Steriade et al. 1993). Subthreshold membrane potential oscillations that depend on partial depolarisation were also demonstrated in cortical neurons (Nunez et al. 1992; Steriade et al. 1996). They may predispose cortical and thalamic neurons to fire at gamma frequencies and synchronously in response to sensory input during wakefulness or internal input during paradoxical sleep (Steriade et al. 1996).

Rhythmic discharges from thalamic or cortical neurons can entrain oscillatory activity in connected neurons, whereby resonance occurs at a preferred frequency of synaptic input. Synchronised firing of several neurons will elicit temporally overlapping excitatory postsynaptic potentials in other cells and increase their chance of firing, as well. Thus, "single cell oscillators" and the conduction time of the intervening pathways can resonate to generate "large functional states" in the thalamocortical system (Llinas & Ribary 1993). Reverberating activity in local assemblies of interconnected thalamic and cortical neurons can manifest in gamma oscillations of magnetic or electrical field potentials recorded over the neocortex (Ribary et al. 1991).

Neocortical gamma oscillations of electrical or magnetic field potentials are more likely to occur in states of increased alertness and focused attention (Bouyer et al. 1981; Herculano-Houzel et al. 1999) and are also characteristic of paradoxical sleep (Llinas & Pare 1991; Llinas & Ribary 1993). Stimulation of cholinergic nuclei in the brainstem enhances neocortical 40-Hz oscillations in the electroencephalogram (Curró Dossi et al. 1991; Steriade et al. 1991) and facilitates their synchronisation in response to sensory stimulation (Munk et al. 1996; Herculano-Houzel et al. 1999). Electroencephalographic activation is mediated by acetylcholine that is released in the thalamus from cholinergic projections where it acts on muscarinic receptors (Steriade et al. 1991) to induce delayed and prolonged membrane depolarisation in thalamic projection neurons (Curró Dossi et al. 1991), thus enabling gamma discharge activity – most strongly in intralaminar thalamic nuclei (Steriade & Amzica 1996; Steriade et al. 1993).

Neocortical gamma oscillations during wakefulness or paradoxical sleep show a coherent rostrocaudal phase shift from the frontal to the occipital pole of the hemisphere (Ribary et al. 1991). Rostrocaudal sweeps of cortical activation may be caused by internal waves of neural activity in intralaminar thalamic nuclei (Llinas & Ribary 1993). Intralaminar thalamic nuclei are organised as a circular mass and project to superficial layers of all neocortical areas in a spatially continuous manner (Llinas & Ribary 1993). Neurons in these nuclei have a particularly strong intrinsic 40-Hz rhythmicity that may entrain oscillatory discharge activities in cortical neurons (Steriade et al. 1993). By distributing gamma rhythms over the neocortex, intralaminar thalamic nuclei can facilitate the synchronisation of gamma reverberations in *specific* thalamocortical circuits

that are activated by sensory input and attentional mechanisms. Llinas and Ribary (1993) suggested that conscious experience might be based on coherent 40-Hz coactivation of specific and nonspecific thalamocortical circuits. Although the *content* of consciousness may lie in specific thalamocortical circuits, nonspecific thalamocortical circuits may ensure the temporary *binding* of activated specific thalamocortical circuits towards the creation of a unitary conscious experience (Llinas & Pare 1991; Llinas & Ribary 1993).

Neocortical 40-Hz oscillations have been recorded simultaneously with normal perception (Joliot et al. 1994) and hallucinations (Baldeweg et al. 1998) and are thought to underlie conscious experience in dreaming (Amzica & Steriade 1996; Llinas & Ribary 1993). Neocortical 40-Hz oscillations recorded magnetoencephalographically during paradoxical sleep are similar in distribution, phase shift, and amplitude to those recorded during wakefulness (Llinas & Ribary 1993). During wakefulness, sensory stimulation can reset and enhance 40-Hz oscillatory activity recorded from the neocortex (Ribary et al. 1991). Such resetting is not observed during paradoxical sleep when random bursts of 40-Hz oscillations occur in a manner unrelated to sensory stimulation (Llinas & Ribary 1993). This is thought to represent the central difference between wakefulness and paradoxical sleep; neocortical 40-Hz oscillations and conscious experience are generated during both wakefulness and paradoxical sleep; however, during paradoxical sleep the external world is mostly excluded from conscious experience (Llinas & Ribary 1993).

1.2. Nonspecific regulation of thalamocortical activity

Thalamic relay cells and reticular thalamic neurons are regulated nonspecifically by cholinergic, noradrenergic, and serotonergic systems ascending from the brainstem. During wakefulness, brainstem regulatory systems globally facilitate or inhibit fast oscillatory and resonance capabilities of thalamic neurons and modulate their responsiveness to afferent sensory input. Thus, afferents from brainstem neurotransmitter centres adjust the impact of sensory information on resonance in the thalamocortical system, or, in other words, regulate the capacity of specific thalamic nuclei to transmit sensory information to the cortex. The neuromodulatory effects of serotonergic, noradrenergic, and cholinergic input on spontaneous and evoked activity of thalamic relay cells have been studied mostly in the dorsal lateral geniculate nucleus of the cat. Noradrenaline released from fibres originating in the locus coeruleus produces a delayed enhancement of spontaneous firing in lateral geniculate relay cells and enhances their responsiveness to afferent synaptic excitation (Rogawski & Aghajanian 1980). Serotonin released from terminals of dorsal raphe nucleus neurons induces a delayed and prolonged suppression of spontaneous firing in lateral geniculate relay cells (Kayama et al. 1989). It also suppresses responses of lateral geniculate neurons to weak retinal stimulation (Kemp et al. 1982). Serotonergic suppression of relay cell activity is associated with augmentation of slow waves in the electroencephalogram (EEG) (Kayama et al. 1989).

The laterodorsal tegmental nucleus and the pedunculopontine nucleus in the mesopontine region of the brainstem are the main cholinergic nuclei that project to the thalamus. Mesopontine cholinergic neurons provide high concentrations of acetylcholine to the thalamus during both wakefulness and paradoxical sleep and much less so during slow-wave sleep (Williams et al. 1994). Acetylcholine released in the thalamus plays a crucial role in electroencephalographic activation during wakefulness and the generation of paradoxical sleep. In the lateral geniculate nucleus, acetylcholine exerts a facilitatory influence over the transfer of visual information. Mediated by a muscarinic receptor mechanism, cholinergic activation during arousal facilitates visually evoked responses (McCormick & Pape 1988), but also enhances spontaneous discharge activity of geniculate relay cells (Francesconi et al. 1988). In thalamic relay cells and cortical neurons, cholinergic activation induces sustained muscarinic depolarisation, characterised by subthreshold oscillations of membrane potential, which enables tonic firing of action potentials at 40-Hz rhythms and predisposes neurons to participate in reverberations of gamma oscillations (Curró Dossi et al. 1991; Steriade & Amzica 1996).

Acetylcholine activates thalamic relay cells in the lateral geniculate nucleus both directly and indirectly, the indirect effect being mediated by activation of muscarinic receptors on local GABAergic inhibitory neurons (Francesconi et al. 1988; McCormick & Pape 1988). By mediating a reduction in the release of GABA in specific thalamic nuclei, muscarinic receptors on interneurons play an important role in increasing the efficacy of signal transmission in states of arousal and increased attention (Carden & Bickford 1999).

The reticular nucleus is among the thalamic nuclei with the highest density of cholinergic input (Heckers et al. 1992). Nicotinic receptors, particularly those with the alpha-7 subunit, are concentrated on reticular thalamic neurons (Agulhon et al. 1999; Quik et al. 2000; Spurden et al. 1997). Cholinergic input from the brainstem inhibits spontaneous activity of GABAergic neurons in the reticular nucleus, contributing to disinhibition of thalamic relay cells (Murphy et al. 1994). However, in response to certain patterns of sensory stimulation, reticular thalamic neurons can mediate inhibition of thalamic relay cells during arousal (Murphy et al. 1994). Stimulus-specific inhibition of thalamic relay cells may be a result of activation of presynaptic nicotinic receptors on GABAergic terminals, such as those from reticular thalamic neurons (Lena & Changeux 1997). Thus, whereas inhibition of GABAergic neurons in the thalamus mediated by muscarinic receptor activation may contribute to the global increase of relay cell activity during arousal, nicotinic facilitation of GABAergic transmission may, at the same time, improve the signal-to-noise ratio of thalamic activity (Lena & Changeux 1997).

The reticular thalamic nucleus assists in organising activity in specific thalamic nuclei according to characteristics of sensory input. In the auditory modality, for example, the reticular nucleus participates in time-dependent analysis of the auditory input, with different neurons of the auditory part of the reticular nucleus being sensitive to different latencies of stimulus presentation (Villa 1990). Dysfunction of the reticular thalamic nucleus would lead to loss of sensory-specific inhibition in specific thalamic nuclei. This may manifest particularly at times of arousal when thalamic relay cells exhibit increased spontaneous activity. Then, random activity may predominate over stimulus-specific activity, and relay cells may become recruited into thalamocortical reverberations without receiving adequate sensory input.

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1.3. Attentional modulation of thalamocortical activity

The pattern of gamma oscillations that underlies conscious perception results from thalamocortical self-organisation and does not derive from purposeful sensory information processing (Fig. 2). Following activation by arousal mechanisms, populations of neurons synchronise their gamma-frequency discharge activity through reciprocal interaction via re-entrant loops, while the thalamocortical system, as a whole, converges towards a state of transient stability, an attractor state that is determined by the current constellation of external and endogenous constraints imposed on the system (Varela et al. 2001). Sensory input imposes specific patterns of depolarisation on specific thalamic nuclei. At the same time, endogenous activity from the prefrontal cortex and limbic system, reflecting attention, current behavioural goals, and recent memories, modulates cortical activity in primary and secondary sensory areas (reviewed in Varela et al. 2001). Prefrontal cortex neurons can sustain their activity for short periods of time despite ongoing behaviour and changes in sensory stimulation (Bodner et al. 1996; Fuster 1991), which may allow them to constrain self-organisation of gamma oscillatory activity in posterior sensory areas via long-distance corticocortical projections.

Neuroimaging studies show that attention modulates regional cerebral activity in primary and secondary sensory areas of the neocortex (O'Leary et al. 1996; Shulman et al. 1997; Woodruff et al. 1996), which are thought to be concerned with different stages of analysis of sensory information. Attention-dependent activity changes (despite identical sensory stimulation) can be seen even in parts of sensory systems that are believed to subserve the earliest stages of sensory processing, such as parts of the lateral geniculate nucleus of the thalamus and the retinotopically organised striate cortex (Vanduffel et al. 2000). It appears that activity in early sensory systems depends, to a large extent, on attentional factors and does not just reflect the pattern of external sensory stimulation. This challenges the notion, implicit in cognitive or information-processing accounts of perception, that sensory information is analysed to create a meaningful representation of the world, from which attentional mechanisms then select relevant stimuli. Instead of being derived from hierarchically processed sensory information, perception appears to be created in the very focus of attention.

1.3.1. Corticofugal control of relay cells. Sherman and Koch (1986) suggested that sensory relay plays only a minor role in the activity of thalamocortical circuits, compared with re-entrant activity from the cortex and reverberating activity. Numerically, the largest input to thalamic nuclei does not derive from sensory organs, but from layer VI of the cerebral cortex. Cortical neurons establish abundant excitatory synaptic connections with both thalamic relay cells and neurons in the reticular thalamic nucleus. In the lateral geniculate nucleus, only 10–20% of synapses on thalamic relay cells stem from the retina, about one-third of synapses are from inhibitory terminals of local interneurons or neurons in the perigeniculate section of the reticular thalamic nucleus, and roughly half of all synapses are from neurons in cortical layer VI (reviewed in Sherman & Koch 1986). Attentional modulation of thalamocortical transmission may be a major function of these corticofugal projections (Montero 2000; Sherman & Koch 1986).

Through corticofugal projections, the cortex can adjust thalamic sensory-related activity and control the emerging pattern of synchronized gamma oscillations that underlies perception. Steriade (1997) reported that cortical pyramidal neurons discharging at 30–40 Hz rhythms are effective in synchronising gamma oscillations in thalamocortical networks. Enhanced excitability of cortical pyramidal cells, which can be induced by noradrenaline or acetylcholine, may increase the spatiotemporal coherence of oscillatory activity in the thalamus (Destexhe et al. 1999). As proposed by Destexhe et al. (1999), a more excitable cortex may generate a more powerful feedback onto the thalamus, resulting in highly coherent oscillations.

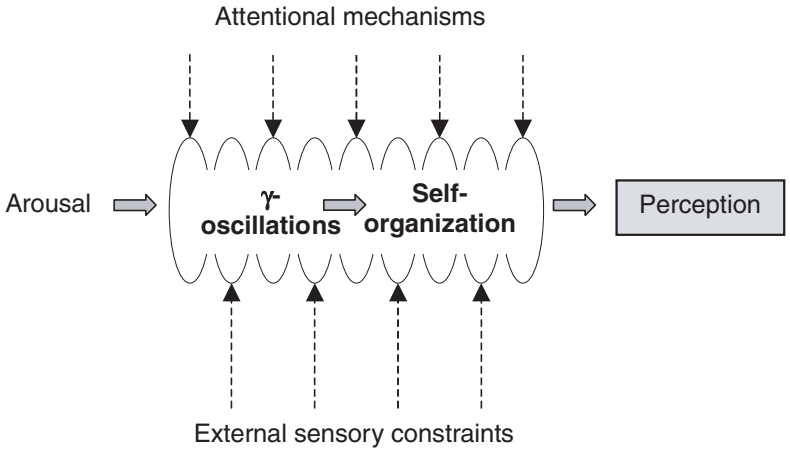

Figure 2. Perception may be a manifestation of intrinsic self-organisation of neural activity. Fast oscillatory activity in the thalamocortical system that is facilitated by cholinergic arousal self-organises into coherent assemblies under constraints of attentional mechanisms and sensory input. If sensory constraints are weak, then attentional mechanisms may become the dominant modulatory influence on thalamocortical self-organisation and hallucinations may arise.

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The excitatory effect of cortical input to thalamic relay cells may be similar to that of afferent sensory input (Destexhe 2000). If thalamic relay cells are in tonic-firing mode, corticothalamic excitatory postsynaptic potentials may contribute to depolarisation of relay cells, alongside accumulating sensory-induced excitatory potentials, until the firing threshold is reached. In this manner, corticofugal input may complement or predict afferent sensory input (Destexhe 2000). It is therefore conceivable that strong corticofugal input, in combination with increased spontaneous activity pre-existing for various reasons, can induce fast rhythmic discharges in relay cells despite insufficient or absent sensory input to these cells.

To resonate with cortical pyramidal neurons discharging at gamma rhythms, thalamic relay cells have to be in tonic-firing mode. Sherman and Koch (1986) suggested that, as part of some attentional mechanisms, corticothalamic input might modulate thalamocortical sensory transmission by altering the electrophysiological response mode of thalamic relay cells. McCormick and von Krosigk (1992) showed that corticothalamic glutamatergic input can induce slow depolarisation in thalamic relay cells through activation of *metabotropic* (as opposed to ionotropic) glutamate receptors. This switches the response mode of relay cells from burst firing to tonic firing and facilitates thalamocortical transmission (McCormick & von Krosigk 1992).

1.3.2. Reticular thalamic nucleus. The reticular thalamic nucleus has been recognised to play a role in attentional mechanisms (e.g., Brunia 1993; Montero 1997). McAlonan et al. (2000) found attention-dependent activation in sectors of the reticular thalamic nucleus in rats despite identical sensory input. Montero (2000) reported that the visual sector of the reticular thalamic nucleus in rats was activated by attentional exploration of a new environment, and that this activation depended on corticofugal inputs from the primary visual cortex. According to Montero's (2000) hypothesis, a focus of attention in primary sensory cortex generates a column of increased thalamocortical sensory transmission by corticofugal glutamatergic activation of thalamic *relay* cells, in conjunction with input to the *reticular* thalamic nucleus mediating the inhibition of surrounding relay cells. Thus, to a large extent, the pattern of thalamic relay-cell activity depends on cortical feedback. Instead of being "transmitted" to the cortex, sensory input may only play an adjuvant role in thalamocortical activation.

Destexhe (2000) considered that attentional mechanisms might involve control of the electrophysiological response mode of reticular thalamic neurons. Their hyperpolarisation, for instance, can be achieved through muscarinic receptor mechanisms. Once reticular thalamic neurons are hyperpolarised, glutamatergic input from the cortex can trigger in these neurons a burst of action potentials. This would lead to hyperpolarisation of connected thalamic *relay* cells (Destexhe 2000), switching their response mode to burst-firing, as well, and preventing them from generating action potentials in accordance with incoming sensory and corticothalamic excitatory postsynaptic potentials.

1.3.3. Nucleus basalis of Meynert. Acetylcholine is involved not only in global brain activation during arousal but it also mediates attentional mechanisms based on the nucleus basalis of Meynert. The nucleus basalis represents the sole source of cholinergic input to the cerebral cortex. It receives terminals from the limbic system and the cholinergic pedunculopontine and laterodorsal tegmental nuclei (among others) and projects to all cortical areas. The nucleus basalis also sends cholinergic input to the reticular thalamic nucleus. Arousal is associated with increased tonic firing of nucleus basalis neurons and the release of acetylcholine to the cortex (reviewed in Smythies 1997). Activation of muscarinic cholinergic receptors on cortical neurons leads to increased neuronal excitability and facilitation of synaptic transmission from thalamic projections (Metherate & Ashe 1993), thus enhancing cortical sensory-evoked activity.

The nucleus basalis is involved in shifting attention to environmental stimuli that are behaviourally significant (e.g., in predicting a reward; Wenk 1997). For this purpose, the nucleus basalis receives information about the behavioural significance and reinforcement value of stimuli via afferents from the limbic system. Cholinergic projections from the nucleus basalis, in turn, modulate cortical excitability appropriately in order to facilitate perception of the significant stimulus (Wenk 1997). Apart from sending direct excitatory projections to the cortex, the nucleus basalis may modulate thalamocortical activity *indirectly* via projections to the reticular thalamic nucleus. Unlike most other thalamic nuclei, the reticular nucleus receives a substantial cholinergic innervation from the basal forebrain (Heckers et al. 1992).

To briefly summarise, cholinergic input from the brainstem enhances evoked and spontaneous activity of thalamic relay cells and facilitates fast rhythmic discharges and their synchronisation in thalamocortical networks. Attentional mechanisms based on prefrontal cortex, limbic system, and nucleus basalis provide specific patterns of activation to cortical neurons in sensory areas and indirectly participate in activation of thalamic relay cells. Activation of thalamic

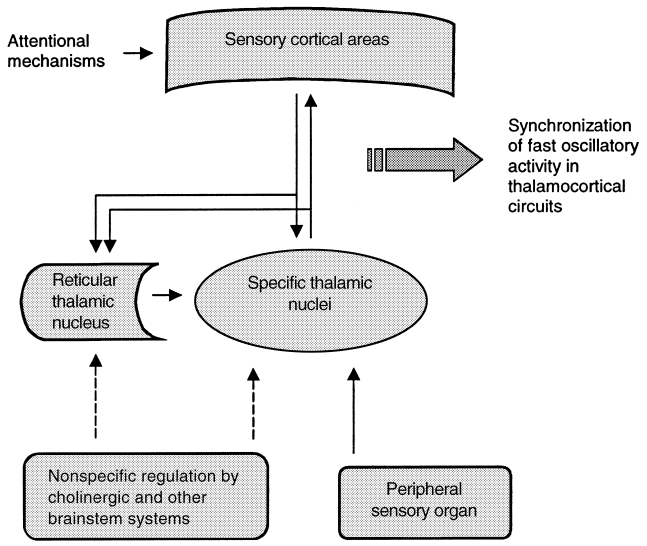

Figure 3. Gamma oscillations in thalamocortical circuits depend on the depolarisation of thalamic and cortical cells. Attentional mechanisms activate neurons in cortical sensory areas, and via corticothalamic projections, contribute to depolarisation of thalamic relay cells. Sensory input complements activation of thalamic relay cells. Globally, the level of fast oscillatory activity (and therefore perceptual productivity) is regulated by input from brainstem neurotransmitter systems.

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relay cells is balanced by general inhibitory input from serotonergic brainstem centres and sensory- and attention-specific inhibition from the reticular thalamic nucleus (Fig. 3). A disturbance in mechanisms that maintain inhibition in specific thalamic nuclei may cause increased levels of noise in thalamic activity, particularly at times of arousal. This would allow oscillatory input from cortical pyramidal neurons to establish resonance with thalamic relay cells more easily – regardless of the pattern of sensory input to specific thalamic nuclei. Alternatively, or in addition, pathological activation of thalamocortical circuits may be caused by more powerful corticofugal input from cortical foci of hyperexcitability or under conditions of general cortical hyperexcitability.

Normally, sustained thalamocortical activation and perception may ensue if the pattern of thalamocortical circuits that is pre-activated by prefrontal attentional mechanisms is matched by the pattern of sensory input to specific thalamic nuclei. In hallucinations, attentional mechanisms alone may produce sustained assemblies of thalamocortical activation, regardless of the pattern of sensory input. In sensory imagery, which is a nonsubstantial and fleeting experience, attentional mechanisms may initiate patterns of thalamocortical resonance that would normally lead to perception but cannot be sustained in the absence of supporting sensory information. Indeed, activity in early sensory processing areas during sensory imagery resembled that observed during selective attention (reviewed in Frith & Dolan 1997), again emphasising the importance of attention in the modulation of sensory systems.

2. Schizophrenia

Schizophrenia is characterised by episodes of hallucinations and other psychotic symptoms in clear consciousness that are usually accompanied by lack of insight and occur in the absence of a primary mood disturbance or identifiable brain disease. Hallucinations in the auditory modality and particularly verbal hallucinations appear to prevail in schizophrenia and affective psychoses. Nevertheless, visual hallucinations are not uncommon in schizophrenia; in contrast to some organic conditions, they typically occur without prodromata and in a psychological setting of intense affect (Asaad & Shapiro 1986). Tactile, kinaesthetic, olfactory, and gustatory hallucinations are also reported in schizophrenia. Asaad and Shapiro (1986) suggested that the development of hallucinations in mental illness might represent a final common pathway involving biological vulnerability and psychological influences. Although the biological vulnerability to hallucinations is likely to be indiscriminate of perceptual modality (affecting either all modalities or affecting them randomly), it may be that *psychological influences* can explain the apparent predominance of *verbal* hallucinations in mental illness. First, human communication and interpersonal relationships are largely mediated by language, and verbal hallucinations may reflect social experiences or fulfil defensive functions in people with enduring social anxiety and problems in relating to others. Verbal hallucinations may be employed "unconsciously" to project social fears, confirm suspicions, or fulfil social desires, bypassing open interaction with the social environment. Second, subvocal speech may provide a mechanism to unconsciously modulate and maintain the experience of verbal hallucinations once they have started to develop.

In schizophrenia, the development of hallucinations, and possibly other psychotic symptoms, may represent the outcome of a general *biological predisposition* towards hallucinations that interacts with psychological distress or anxiety arising from different constellations of personality problems, limited social coping skills, and current interpersonal conflicts or social problems. Gruzelier (1999) proposed that schizophrenia might be a partial disorder of consciousness involving dysregulation in specific and nonspecific thalamocortical systems. It is argued here that failure of sensory input to modulate intrinsic thalamocortical activity may be the core biological disturbance in schizophrenia that predisposes schizophrenics to hallucinations at times of arousal and heightened attention. In the first instance, such failure could manifest in relative uncoupling of perception from sensory input across modalities – that is, if perception were generally subserved by reverberating activity in thalamocortical circuits. The olfactory system, which departs from organisational arrangements common to other sensory systems, may not be an exception in this respect because olfactory pathways between thalamus and orbitofrontal cortex appear to be critical for the perception and discrimination of odours (reviewed in Buck 2000).

Antipsychotic drugs are effective in controlling hallucinations, almost regardless of the underlying etiology. Their effectiveness is established not only in mental disorders, such as schizophrenia, late paraphrenia, and severe depression or mania, but also in psycho-organic syndromes and drug-induced psychoses. Although psycho-organic and substance-induced psychoses classically present with visual hallucination, this may nevertheless indicate (1) that all hallucinations result from a common pathophysiological mechanism regardless of their etiology and (2) that other symptoms of acute psychosis, such as disorders of the possession of thought and disturbances of self-experience, may share a common mechanism with hallucinations or be secondary to hallucinations. The effectiveness of antipsychotic medication across a variety of psychotic symptoms and across etiological conditions testifies against there being a specific mechanism for hallucinations in schizophrenia. Cognitive or neuropsychological theories of hallucinations in schizophrenia tend to focus on verbal hallucinations and neglect the fact that hallucinations in schizophrenia can occur in other modalities. What would be desirable is a more *general theory* of hallucinations that provides a common framework for understanding the content, form, and meaning of these experiences, regardless of modality or etiology.

Neuropsychological and cognitive theorists regard auditory verbal hallucinations as self-generated mental events, such as inner speech, thoughts, retrieved memories, or verbal images that are mistaken for external events (i.e., misattributed to an external origin), because they arise without intention and/or are experienced as alien to the self (e.g., David 1994; reviewed in Behrendt 1998). Consequently, the cause of hallucinations is attributed to a disorder of a hypothetical mechanism that controls or "monitors" the corresponding self-generated mental phenomenon. Unfortunately, cognitive theories do not show convincingly why and how internally generated mental events can acquire the substantiality, richness, and clarity that characterise normal perception. As long as perception is conceptualised as an experience that derives from external objects or events, and as long as these external objects or events are required to be absent in hallucinations, we have to look for mental phe-

nomena outside the normal process of sensation and perception that could become a source of hallucinations. Cognitive theories tend to suggest that the absence of a correspondence to external reality, which is thought to exclusively characterise self-generated mental events, has to be complemented by a conviction of their external origin to yield hallucinations. However, it is doubtful that thoughts, inner speech, verbal images, or retrieved memories can be transformed into experiences with perceptual qualities just by virtue of their misattribution to an external origin.

Once we recognise that both hallucinations and normal perceptions are fundamentally subjective experiences that are externalised into a virtual space surrounding oneself, we can eliminate questions about how hallucinations acquire perceptual qualities. Hallucinations and normal perceptions would differ only with respect to the degree to which they are constrained by external physical reality, and we can now move on from hypothesising about sources of hallucinations and mechanisms of "inner" mental phenomena to considering factors that lead to a disruption of sensory constraints normally imposed on the process of perception. Functional neuroimaging studies of actively hallucinating patients have confirmed that verbal hallucinations involve activity in cortical areas that are normally concerned with perception of external speech (David et al. 1996; Lennox et al. 2000; Woodruff et al. 1997), which is consistent with the notion of underconstrained perception. The model predicts that further similarities will be found in brain activation; for example, with the appropriate technology, it should be possible to detect correlated patterns of activity in auditory sensory cortex and auditory sections of the thalamus during both normal speech perception and verbal hallucinations.

2.1. Impaired response synchronisation

In visual backward masking tasks, detection of a briefly presented target stimulus is prevented by a mask stimulus that is presented shortly after the target (at interstimulus intervals of less than 100 msec). Compared to normal subjects, target identification by schizophrenic patients is prevented more easily by presentation of an early masking stimulus. Visual backward masking deficits were also demonstrated in schizophrenic patients who were in clinical remission (Green et al. 1999) and unaffected siblings of schizophrenic patients (Green et al. 1997), suggesting that these deficits are a marker of predisposition to schizophrenia rather than the presence of active illness (Green et al. 1999). Green et al. (1999) related visual backward masking deficits in patients with schizophrenia to failure to establish cortical oscillations in the gamma range in response to sensory stimulation. Kwon et al. (1999) found delays in entrainment of the electroencephalogram to 40-Hz auditory stimulation in patients with schizophrenia, which the authors interpreted as failure to entrain intrinsic gamma-frequency oscillators. These findings are consistent with the prediction by Llinas and Ribary (1993) that impaired resetting of 40-Hz oscillations by sensory stimulation characterises conditions that are accompanied by hallucinations.

The auditory evoked potential P50, which may be a subcomponent of the synchronised gamma response to sensory stimulation (Basar et al. 1987 1991; Clementz et al. 1997), tends to be reduced in patients with schizophrenia. As pointed out by Gruzelier (1999), P50 amplitude reduction in patients with schizophrenia is associated with the presence of auditory hallucinations, although this is controversial. In experiments that involve repeated presentation of paired auditory stimuli and averaging of the electroencephalographic responses, most normal subjects show an amplitude reduction of mid-latency evoked-potential components, such as P50, in response to the second stimulus (S2) as compared to their response to the first stimulus (S1). This amplitude reduction of the P50 response to S2 is absent in most schizophrenic patients, as expressed in an increase of their P50 S2/S1 amplitude ratio (so-called gating ratio). Lack of suppression of S2 P50 in auditory paired-stimulus paradigms can be found both in acutely psychotic and medicated clinically stable patients (Adler et al. 1990; Freedman et al. 1983), and is also present in many relatives of schizophrenic patients (Adler et al. 1992; Clementz et al. 1998). There is some controversy as to whether the increase in the P50 S2/S1 ratio is associated with perceptual abnormalities among patients with schizophrenia (Jin et al. 1998; Light & Braff 2000), however there is no doubt that this abnormality is associated with a vulnerability to schizophrenia, which – to a large extent – may represent a vulnerability to hallucinations (Asaad & Shapiro 1986).

Clementz et al. (1997) suggested that amplitude suppression of the P50 response to the second stimulus S2 that is normally observed in auditory paired-stimulus paradigms might be a proxy for suppression of the gamma-band response to S2. Although at short interstimulus intervals synchronisation of the electroencephalogram is impaired normally only in response to S2, in patients with schizophrenia, response synchronisation is impaired also in response to S1 (Zouridakis et al. 1997), which may explain their reduced S1 P50 amplitudes and increased P50 S2/S1 amplitude ratios. Evoked potentials are averaged from electroencephalographic recordings of many individual trials, and the amplitudes of evoked-potential components, such as P50, can therefore be influenced by the temporal variability of the evoked response. Jin et al. (1997) and Patterson et al. (2000) showed that the lack of relative suppression of S2 P50 (i.e., increase in P50 S2/S1 amplitude ratio) in patients with schizophrenia was related to increased temporal variability of the P50 response to S1. Recognising that neuronal synchrony can be affected when the rate of background firing is too high, Patterson et al. (2000) hypothesised that increased temporal variability of S1 P50 in schizophrenic patients may be the result of "erratic neuronal firing" in a "hyperactive nervous system." Increased random neuronal activity in schizophrenia could mask stimulus-specific activity, leading to deficient synchronisation in response to sensory stimulation or greater temporal variability of the synchronised response with consequences of reduced mid-latency evoked potentials and increased S2/S1 P50 ratios.

It may be added here that, despite also showing an increase in their P50 S2/S1 amplitude ratios, clinically unaffected *relatives* of schizophrenic patients did not show a marked reduction in their P50 amplitudes in response to S1 (Clementz et al. 1998). Therefore, increased temporal variability of evoked potentials to S1 is unlikely to explain the increase of the S2/S1 P50 ratio in schizophrenic patients' relatives. Even in *patients* with schizophrenia, increased temporal variability may not provide the sole explanation for increased P50 S2/S1 ratios. Although Patterson et al. (2000) showed that correction for temporal variability elim-

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inated the significant difference in P50 S2/S1 ratios between patients with schizophrenia and control subjects, there still appears to have been a trend towards greater S2 P50 amplitudes in patients with schizophrenia (3.92 vs. 3.08 μV). It could be hypothesised that the increase in S2 P50 in relatives of schizophrenic patients is a manifestation of the same process that, with greater severity, leads to amplitude reduction of mid-latency evoked potentials, including reduction of S1 P50. At lower levels of neural noise – as may be the case in *relatives* of schizophrenic patients – sensory input (S1) may have a reduced impact on neural activity in specific thalamic nuclei and evoke less sustained thalamocortical synchronisation, which would result in less phase opposition at S2, and therefore increased S2 P50 amplitudes and S2/S1 ratios. At higher levels of neural noise – as may be the case in *patients* with schizophrenia – changes in afferent sensory input to thalamic nuclei may be of similar magnitude to fluctuations of noise, which would render the impact of sensory input on thalamocortical activity unpredictable. As a result, the latency variability of stimulus-induced thalamocortical responses would increase, leading to amplitude reduction of the averaged S1 P50 (and a further increase in the S2/S1 ratio). This is consonant with suggestions that the increased P50 S2/S1 ratio (in relatives partly a result of increased S2 P50) represents a vulnerability factor for schizophrenia, and additional factors, such as reduction of auditory-evoked potentials (including reduction in S1 P50 – not found in relatives), are involved in active schizophrenia (Adler et al. 1990).

2.2. Implication of the reticular thalamic nucleus

Administration of nicotine transiently restored amplitude suppression of P50 in response to S2 in patients with schizophrenia (Adler et al. 1993) and relatives of schizophrenic patients (Adler et al. 1992), which implicated nicotinic cholinergic receptors in schizophrenia. S2 P50 amplitude suppression in schizophrenic patients also normalised after brief periods of slow-wave sleep (Griffith et al. 1993), suggesting that nicotinic receptors might undergo abnormally rapid desensitisation during cholinergic arousal and resensitise only after a period of absence of cholinergic stimulation (Griffith et al. 1998). Genetic linkage analysis established that the increase in the P50 S2/S1 amplitude ratio in patients with schizophrenia and their relatives was linked to a polymorphic marker at chromosome locus 15q13–14, which is the site encoding the alpha-7 subunit of the nicotinic cholinergic receptor (Freedman et al. 1997). Altered expression or function of the alpha-7 nicotinic receptor may therefore be responsible for failure to suppress the auditory-evoked P50 response to the second of paired auditory stimuli in patients with schizophrenia and their relatives.

Nicotinic cholinergic receptors with the alpha-7 subunit are particularly concentrated in the reticular thalamic nucleus (Agulhon et al. 1999; Quik et al. 2000; Spurden et al. 1997). Interestingly, expression of alpha-7 nicotinic receptors was moderately reduced in the reticular thalamic nucleus in postmortem tissue from patients with schizophrenia (Court et al. 1999). Activation of nicotinic receptors on terminals from reticular thalamic neurons facilitates GABAergic transmission in the thalamus, which may contribute to an increase in the signal-to-noise ratio of neural activity in specific thalamic nuclei during arousal (Lena & Changeux 1997). Rapid desensitisation and/or reduced expression of alpha-7 nicotinic receptors on reticular thalamic neurons would therefore result in decreased stimulus-specific or attention-specific inhibition and increased random activity in specific thalamic nuclei. This is consistent with the hypothesis by Patterson et al. (2000) that greater temporal variability of auditory evoked responses reflects erratic neuronal activity in schizophrenia.

In electroencephalographic recordings from a patient with recurrent somatic hallucinations, Baldeweg et al. (1998) observed gamma oscillations that occurred simultaneously with hallucinations. It appears that, on the one hand, sustained patterns of thalamocortical gamma resonance can occur in the absence of sensory input and give rise to hallucinations; on the other hand, as indicated above, thalamocortical gamma rhythms are less modifiable by external sensory input in schizophrenia. The notion of increased random activity or noise in specific thalamic nuclei may explain this apparent paradox. Increased noise in specific thalamic nuclei could both mask changes in sensory input and, particularly at times of arousal, facilitate the recruitment of thalamic relay cells by cortical attentional mechanisms into assemblies of coherently activated thalamocortical circuits, regardless of their sensory input. Thus, not only would an impaired signal-to-noise ratio predispose a person to hallucinations, it would also dampen the impact of sensory input on thalamocortical activity and perception. More intensive or prolonged sensory stimulation would be necessary to induce or modulate patterns of coherent thalamocortical oscillations, with the consequence of reduced perceptual responsiveness to changes in sensory input. This may manifest in elevated thresholds for tone discrimination (Rabinowicz et al. 2000) and reduced auditory acuity (Mathew et al. 1993) that were demonstrated in patients with schizophrenia.

2.3. Dopaminergic hyperactivity

Lack of amplitude suppression of P50 in response to the second of paired auditory stimuli, or increased P50 S2/S1 amplitude ratio, appears to be more related to a predisposition to schizophrenia rather than the presence of active illness. Waldo et al. (1994) suggested that an increase in the P50 S2/S1 amplitude ratio might be a necessary factor, but not, in itself, sufficient to cause schizophrenia. For schizophrenia to become clinically manifest, a pre-existing increase in the P50 S2/S1 ratio may have to be complemented by other abnormalities, such as diminished hippocampal volume or increased dopamine metabolism (Waldo et al. 1994).

Dopamine activates D2 and D4 dopamine receptors on GABAergic neurons in the reticular thalamic nucleus (Khan et al. 1998). D2 and D4 are metabotropic receptors that are negatively coupled to adenylate cyclase, and their activation on reticular thalamic neurons – among other effects – may suppress activation or expression of glutamic acid decarboxylase, which is the rate-limiting enzyme in the synthesis of GABA. This would reduce the synthesis of GABA and reduce the release of GABA to specific thalamic nuclei during arousal. D2 and D4 receptors are common targets for antipsychotic drugs. By blocking these receptors, different antipsychotic drugs have consistently been found to increase the expression of glutamic acid decarboxylase in Sprague Dawley rats, particularly in the reticular thalamic nucleus (Sakai et al. 2001). This would restore the release

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of GABA to specific thalamic nuclei. As a result, chronic administration of antipsychotic drugs would increase the level of inhibition in specific thalamic nuclei, which was indeed demonstrated for haloperidol (Lukhanina 1989). Clozapine, which is known to be particularly effective in the treatment of symptoms of schizophrenia, is characterised by a high affinity for the D4 receptor. Interestingly, D4 receptors are expressed particularly on GABAergic neurons (including those in the reticular thalamic nucleus), suggesting that the antipsychotic effect of clozapine, and antipsychotics in general, may be achieved by modulation of GABAergic transmission (Mrzljak et al. 1996).

The hypothesis that emerges is that while dopaminergic hyperactivity results in excessive noise in specific thalamic nuclei, and thus impaired thalamocortical response synchronisation to sensory stimulation, antipsychotic agents may reverse this process. Indeed, the use of indirectly acting dopamine *agonists*, such as cocaine or amphetamine, was associated with amplitude reduction of the auditory-evoked potential P50 (Boutros et al. 1993) and failure of relative amplitude reduction of auditory P50 (Light et al. 1999) in response to the second of paired stimuli. In patients with schizophrenia, the amplitude reduction of evoked potentials that is observed during exacerbation of schizophrenia may similarly be mediated by excessive dopamine (Adler et al. 1990). Treatment with antipsychotics, on the other hand, can normalise reduced P50 amplitudes in patients with schizophrenia (Boutros et al. 1993). However, conventional antipsychotics cannot reduce the increased P50 S2/S1 amplitude ratio in schizophrenia (reviewed in Gruzelier 1999), which is a more enduring abnormality that is independent of clinical state (Adler et al. 1990).

A constitutionally elevated P50 S2/S1 amplitude ratio in schizophrenia, which appears to be related to rapid desensitisation of nicotinic receptors on reticular thalamic neurons, may indicate increased baseline levels of random thalamic activity. Additional factors, such as dopaminergic hyperactivity, which can manifest in reduced amplitudes of mid-latency evoked potentials, may contribute to further random disinhibition of thalamic activity, until eventually perception becomes underconstrained by sensory stimulation and psychosis emerges. To suppress hallucinations, antipsychotic drugs may only have to reverse excessive dopaminergic inhibition of reticular thalamic neurons and restore an appropriate release of GABA to specific thalamic nuclei. In addition, antipsychotic drugs may prevent pathological activation of thalamocortical circuits by blocking D2 or D4 receptors on inhibitory *cortical* interneurons, thus restoring the release of GABA onto cortical pyramidal neurons (Sharp et al. 2001).

A similar mechanism to the one proposed for dopaminergic hyperactivity and exogenous dopamine agonists (i.e., inhibition of reticular thalamic neurons, reduction of the release of GABA onto thalamic relay cells, disinhibition of thalamic relay cells, and pathological activation of thalamocortical circuits) was suggested by Tomitaka et al. (2000) and Sharp et al. (2001) to underlie the capacity of noncompetitive NMDA (N-methyl-D-aspartate) receptor antagonists, such as phencyclidine and ketamine, to cause psychosis in humans. Particularly in schizophrenia, excessive disinhibition of thalamic relay cells alone may not be enough to produce psychotic symptoms. Corticofugal attentional mechanisms may be involved in the formation of coherent assemblies of pathologically activated thalamocortical circuits by providing additional specific depolarisation to cortical and thalamic neurons. Under conditions of excessive disinhibition of thalamic relay cells, corticofugal attentional mechanisms may recruit thalamic relay cells into temporarily sustained assemblies of thalamocortical circuits in a manner that is unrestricted by the pattern of sensory input. Such assemblies of pathologically activated thalamocortical circuits may underlie hallucinations and other psychotic symptoms.

2.4. Hyperarousal

Tonic electrodermal hyperactivity was regarded as a state indicator of acute psychosis, because tonic electrodermal activity in patients with schizophrenia was abnormally elevated during psychotic states but not during remission (Dawson et al. 1994). Tonic electrodermal hyperactivity may even precede psychotic relapse (Dawson et al. 1992). Moreover, in schizophrenic patients with intermittent hallucinations, the onset of hallucinatory periods was associated with an increase in the rate of spontaneous fluctuations of skin conductance (Cooklin et al. 1983). Tonic electrodermal activity is a measure of autonomic arousal, and these findings may indicate that hyperarousal contributes to the development of psychosis and the production of hallucinations.

Central cholinergic activation during arousal results in electroencephalographic activation with an excess of fast activity. Electroencephalographic recordings from patients with schizophrenia tend to show increased beta activity, particularly in postcentral regions, and less alpha activity but also excessive slow-wave activity, particularly in frontal areas (Morihisa et al. 1983). On its own, the excess of fast activity in the EEG would indicate hyperarousal (Gruzelier 1999). Among schizophrenic patients, excessive fast beta activity and less alpha-wave and slow-wave activity in the resting EEG were associated with more florid psychotic symptoms and better response to neuroleptic treatment (Itil et al. 1975), further supporting an association between hyperarousal and acute psychosis. Acute psychosis may itself contribute to hyperarousal, but hyperarousal may also be the result of excessive stress and anxiety in schizophrenia, or it may indicate that cholinergic brainstem centres are excessively responsive. The number of neurons in the pedunculopontine nucleus was shown to be increased in most schizophrenic patients, which suggests that increased cholinergic output from the midbrain reticular formation can overdrive the thalamus to produce schizophrenic symptoms, such as hallucinations (Garcia-Rill et al. 1995).

In a biopsychosocial model of schizophrenia, environmental stressors, such as life events and ongoing social stress, can precipitate psychotic episodes by interacting with preexisting biological vulnerability factors (Nuechterlein & Dawson 1984). Premorbid limitations in social competence and coping skills would influence the likelihood of adverse life events and social problems and thereby determine the extent to which the individual's biological vulnerability is stressed. Asaad and Shapiro (1986) predicted that the neurobiological basis for the vulnerability to hallucinations is also the basis for the vulnerability to schizophrenia. The biological vulnerability to hallucinations may be given by excessive random activity in specific thalamic nuclei, which can be caused by reticular thalamic nucleus dys-

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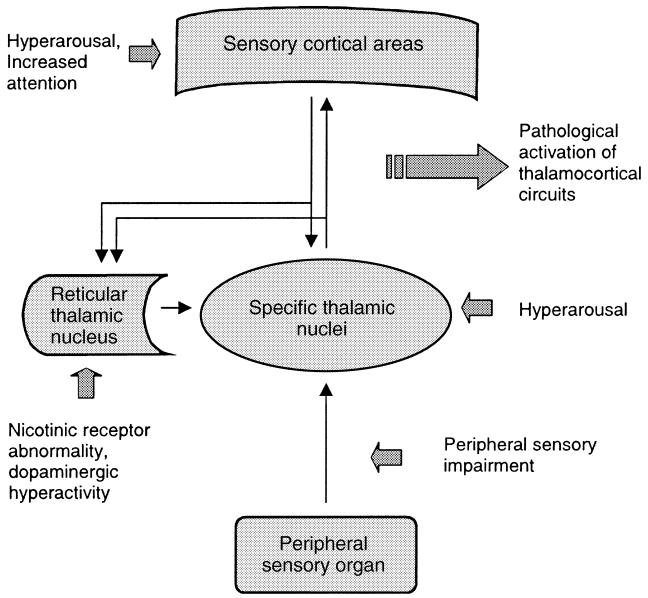

Figure 4. Neurobiological factors suggested to be involved in the generation of hallucinations in schizophrenia. Disruption of sensory constraints may be a result of disturbed function of the reticular thalamic nucleus, leading to lack of specific inhibition in specific thalamic nuclei, or peripheral sensory disorder. Reticular thalamic nucleus dysfunction, in turn, may be caused by nicotinic receptor abnormalities or dopaminergic hyperactivity. During arousal, relay cells in specific thalamic nuclei may be activated by attentional mechanisms alone and induced to participate in reverberations of gamma activity that underlie hallucinations.

function or random sensory input from disordered sensory organs (Fig. 4). Cholinergic arousal that accompanies psychological stress and anxiety may mediate between environmental stressors and acute psychosis in a predisposed individual by further increasing thalamic background activity to a point where sustained pathological activation of thalamocortical circuits becomes possible. Dopaminergic hyperactivity may also play a mediating role. Once hallucinations have started to occur, a vicious circle of anxiety and psychotic defences may develop, with accompanying hyperarousal maintaining thalamic random background activity at a level compatible with ongoing hallucinations throughout the psychotic episode.

Based on the proposed neuroanatomical model of perception, one should expect the emergence of further evidence in schizophrenia that shows a dysbalance between the impact of sensory input on activity in specific thalamic nuclei and the general level of arousal. Either thalamocortical systems are activated by arousal mechanisms normally, and sensory input is less effective in consistently modulating activity in thalamic relay cells, or sensory input modulates activity in the thalamus normally, but hyperactive arousal mechanisms excessively facilitate thalamocortical gamma oscillations, and thus perceptual productivity. Both mechanisms may play a role in schizophrenia.

2.5. Psychological factors

One of the benefits of an approach that conceptually unifies normal perception and hallucinations is that hallucinations can be recognised as arising in the focus of attention, just like any other perception. This means that, once the process of perception loses its external constraints, unconscious and conscious attentional factors become the main determinants of content and form of perceptual experience. Contemporary cognitive theories of verbal hallucinations fail to explain why hallucinatory voices tend to resemble voices of particular people rather than the hallucinator's own voice, and why hallucinatory voices characteristically make statements in the second- or third- person grammatical form rather than in the first-person form. These facts are not easily reconcilable with theories that hypothesise that hallucinations derive from self-generated mental events, such as verbal imagery and inner speech, where the self is usually the one who is observing or discussing rather than the one who is being observed or being discussed.

In schizophrenia, patients may perceive hallucinations under pressure of increased attention to environmental cues and events that relate to their social fears. Personality deficits and enduring social anxiety may be core problems that precede symptomatic illness. Premorbid feelings of inferiority can be found in at least a subgroup of patients with schizophrenia (Kendler & Hays 1982). Poor social adjustment and lack of social confidence are common characteristics in children and adolescents who later develop schizophrenia (Jones et al. 1995). If there is an additional biological predisposition to underconstrained perception, hallucinations and other psychotic symptoms may develop at times of insurmountable social stress and rising interpersonal anxiety. Despite their withdrawn state, patients with established schizophrenia are still sensitive to social factors, as suggested by observations that psychotic episodes often follow an insult to the patient's self esteem (Gabbard 1990) and tend to develop in circumstances of high levels of critical comments and hostility (Brown et al. 1972). Patients with social anxiety and low self-esteem are likely to observe their social environment intensely for hints that allow them to make inferences about their social value and acceptance. In particular, patients may pay increased attention to how other people think and talk about them. In biologically predisposed subjects, this increased attention could result in underconstrained perceptions; and according to what the patient attends to, hallucinations would take the form of voices that discuss them or comment on them, thereby confirming social suspicions and allowing unconscious projections. The fact that schizophrenics, among all possible hallucinations, predominantly perceive hallucinatory voices, and that these voices are in the second or third person, is likely to be of value for understanding the mechanism of hallucinations in schizophrenia.

With regard to their content, clinical observations suggest that verbal hallucinations are context-dependent and have a predictable quality (Nayani & David 1996). They reflect the patient's beliefs about his subordination, disparagement, and marginalisation in social relationships (Birchwood et al. 2000; Linn 1977). Verbal hallucinations may represent parental authority (Nayani & David 1996) and reveal psychodynamic influences such as guilt, wish fulfilment, or gratification of repressed impulses (Asaad & Shapiro 1986). In short, rather than being symptoms that randomly afflict the patient, verbal hallucinations appear to be intricately linked to the patient's psychological condition, reflecting his experiences, preoccupations, and anxieties, both on a conscious and unconscious level. The role of attentional factors in the generation of hallucinations is further confirmed by the fact that attention-commanding

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properties in stimulation from the environment can suppress hallucinations (Margo et al. 1981). The role of attentional factors can also be demonstrated in bereavement. People without mental illness can hallucinate their dead relative's voice or presence in the context of intense yearning and searching for the deceased. This may seem obvious, but only a perspective that accepts that perception is generally a subjective creation, whether or not it is currently constrained by sensory information, allows us to explain the content of these hallucinations with reference to normal attentional mechanisms.

3. Hearing impairment

Sensory impairment may contribute to random background activity in specific thalamic nuclei. Noise is, to some extent, inherent in the flow of sensory information. For instance, retinal dark discharge, which is the maintained discharge of retinal ganglion cells, constitutes the background noise from which the visual signal must be discriminated. The proportion of noise in sensory input would be expected to increase as a result of pathology of peripheral sensory organs. Hypothetically, thalamic relay cell excitability may be up-regulated in an attempt to enhance or recover lost information. Such compensatory up-regulation or, indeed, simply up-regulation by cholinergic mechanisms during arousal would amplify noise in specific thalamic nuclei, again predisposing to underconstrained thalamocortical activation.

3.1. Auditory hallucinations and acquired deafness

Acquired hearing impairment is associated with auditory hallucinations. This is particularly clear in the case of musical hallucinations in nonpsychotic patients. Musical hallucinations, which include the hearing of instrumental and vocal music, are predominantly found in elderly female patients with progressive hearing loss (Berrios 1990; Pasquini & Cole 1997). Psychiatric illness or personality factors are thought to play a minimal role (Berrios 1990; Wengel et al. 1989). However, psychiatric illness, mostly depression, can contribute to the development of musical hallucinations in patients with hearing loss, and in this case musical hallucinations tend to respond to the appropriate psychiatric treatment (Pasquini & Cole 1997; Wengel et al. 1989). Male gender, acute onset, and the absence of deafness or psychiatric illness are factors suggesting the presence of brain disease usually affecting the nondominant hemisphere (Berrios 1991).

Nonmusical auditory hallucinations, such as tinnitus, irregular sounds, or voices, can also occur in association with hearing impairment in the absence of any psychiatric disturbance or organic condition (Hammeke et al. 1983). Additional, central disinhibiting factors often contribute to the development of auditory hallucinations in patients with ear disease (Gordon 1987), even in the case of musical hallucinations (Aizenberg et al. 1987) wherein the contribution of sensory impairment is particularly prominent. Central disinhibiting factors that have been implicated include cerebrovascular disease, organic changes related to aging and alcoholism, as well as psychological factors such as paranoia, persistent anxiety, and depression (reviewed in Gordon 1987). Although auditory hallucinations are less likely to occur without independent evidence of neurological or psychiatric disorder, the contribution made by deafness appears to be crucial, as hallucinations often vanish after remission of ear disease (Gordon 1987).

It is often believed that auditory hallucinations in patients with hearing loss result from sensory deprivation leading to central disinhibition and *release* of past memories (reviewed in Asaad & Shapiro 1986; Hammeke et al. 1983). The release theory of hallucinations does not explain hallucinations unrelated to sensory deprivation, and it remains elusive which mechanisms are to be disinhibited and how past memories are to be perceived. Alternatively, it is proposed that peripheral otopathic conditions, such as otosclerosis or chronic otitis media, disrupt sensory constraints normally imposed on the process of perception, whereas central disinhibiting factors may contribute to pathological activation of thalamocortical circuits by enhancing cortical excitability.

3.2. Sensory impairment in late paraphrenia

There is a well-established association between deafness and late paraphrenia, a form of schizophrenia occurring in late life that is characterised by prominent paranoid delusions and auditory hallucinations. Pure-tone audiometric assessment of elderly psychiatric patients revealed a greater degree of hearing loss among patients with paranoid psychosis than those with affective psychoses (Cooper et al. 1974). Hearing impairment among patients with paranoid psychosis was most commonly a result of chronic middle ear disease and had usually begun well before the onset of paranoid illness (Cooper et al. 1974). Paranoid patients with deafness of early onset tended to have relatively intact premorbid personality, suggesting that in these patients deafness could have played a relatively specific role in causing psychosis (Cooper et al. 1976). Furthermore, chronic deafness was identified as one of several independent premorbid characteristics that successfully differentiated between paranoid and affective psychoses in a group of patients of age over 50 (Kay et al. 1976). Thus, chronic hearing loss may play an important role in the etiology of paranoid-hallucinatory psychoses of later life (Kay et al. 1976).

Almeida et al. (1995) found that patients with late paraphrenia were four times more likely than matched elderly control subjects to have hearing impairment. Patients were also more likely than controls to exhibit neurological soft signs, but there was no difference between patients and controls in the frequency of a family history of schizophrenia (Almeida et al. 1995). Patients with late paraphrenia are also more likely to have visual impairment. Cooper and Porter (1976) found major ocular pathology (predominantly cataracts) in more than half of patients with late paraphrenia, significantly more than in elderly patients with depression. Pearlson et al. (1989) established that, among elderly schizophrenic patients, those with illness onset after the age of 45 had more auditory and visual sensory impairment than those with illness onset before age 45. Howard et al. (1994) confirmed the high prevalence of auditory and visual sensory impairment among patients with late paraphrenia and found that visual impairment was associated with the presence of visual hallucinations.

3.3. Hearing impairment and schizophrenia

Similarly, hearing impairment in childhood or early adulthood was found to be a risk factor for the later development

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of schizophrenia (David et al. 1995; O'Neal & Robins 1958). In a case-control study, Mason and Winton (1995) found an association between middle ear disease and schizophrenia. The odds ratio of middle ear disease in patients with schizophrenia was increased further when patients with ear disease occurring after the onset of schizophrenia were excluded or when those patients were excluded who had a family history of schizophrenia or a history of brain damage, which suggested that middle ear disease may be a predisposing factor for the development of schizophrenia (Mason & Winton 1995). Gordon (1996) suggested that inner ear hypersensitivity might explain the link between middle ear disease and development of schizophrenia. Hypersensitivity to noises (possibly an indication of compensatory up-regulation) is common in incipient ear disease and may be the basic symptom on which psychotic phenomena are later constructed (Gordon 1995).

Auditory sensory impairment may also result from a disturbance affecting auditory nuclei or pathways in the brainstem. Evoked potentials to brief clicks occurring within 10 msec of auditory stimulus presentation reflect the conduction of sensory information through auditory brainstem pathways and nuclei. Abnormal brainstem auditory-evoked potentials characterised by reduced amplitudes and missing peaks were found particularly in schizophrenic patients with prominent negative symptoms (Hayashida et al. 1986; Igata et al. 1994). On the other hand, Lindstrom et al. (1987) reported that, among schizophrenic inpatients, abnormal auditory-evoked brainstem responses were associated with the presence of auditory hallucinations and suggested that interference with auditory brainstem pathways might be causally related to auditory hallucinations.

3.4. Progression of auditory hallucinations in hearing impairment

Gordon (1987) suggested that postotitic middle ear deafness is an important cause of paranoid hallucinatory psychoses of later life. He described how hallucinations might start with tinnitus, gradually assuming more definite forms, until complex verbal hallucinations and finally persecutory delusions arise (Gordon 1987). Marneros et al. (1997) reported a patient with otosclerosis whose hallucinations underwent a progression from tinnitus to musical hallucinations, and, finally, to unilateral auditory verbal hallucinations and other psychotic symptoms (symptoms disappeared completely after surgical treatment for otosclerosis).

Tinnitus and other unformed hallucinations that are perceived in a state of peripheral sensory loss may not necessarily lead to the development of complex verbal hallucinations and psychosis. The relative absence of psychological disturbances in patients with musical hallucinations that result from hearing impairment may be important in this respect. Psychosis may develop only if the person fails to gain insight into the abnormal nature of these experiences. An anxious or paranoid person may more readily attribute the source of a sudden unusual voice to the social environment, because such perception may already confirm fears and suspicions that he harbours about other people. Not surprisingly therefore, paranoid personality traits and social isolation are frequent premorbid characteristics of elderly patients who develop late paraphrenia. Under conditions of chronic fear or social isolation, the person may increasingly pay attention to utterances from the social environment. Lack of insight would ensure that the psychotic patient continues to focus attention on the presumed external source of voices, and in the focus of attention verbal hallucinations would continue to be generated.

4. Charles Bonnet syndrome

The Charles Bonnet syndrome refers to complex visual hallucinations that are usually recognised as unreal and develop in the absence of a disturbance of consciousness or major psychopathology (Gold & Rabins 1989; Schultz & Melzack 1991). The Charles Bonnet syndrome is commonly associated with impaired vision or blindness resulting from ocular pathology, such as macular degeneration (Holroyd et al. 1992), retinal haemorrhage, and cataracts (Gold & Rabins 1989). However, any lesions of the visual system can cause the condition, including destructive lesions of the optical nerves or chiasm (Gold & Rabins 1989; Lepore 1990).

The content of hallucinations has no localising value, in contrast to the more elementary hallucinations resulting from irritative lesions of the cortex (Lepore 1990). Complex visual hallucinations experienced by patients with Charles Bonnet syndrome are usually vivid, clear, and compelling, and often feature scenery, people, animals, buildings, or plants (Gold & Rabins 1989; Schultz & Melzack 1991). Images tend to be static, but may be described as moving or animated (Schultz & Melzack 1991; Schultz et al. 1996). The hallucinations tend to appear suddenly without any obvious triggers or voluntary control, typically last for seconds, and then suddenly disappear (Schultz et al. 1996). They usually occur while the patient is alert with his eyes open and disappear when eyes are closed (Schultz et al. 1996; Teunisse et al. 1994).

Brain disorder coexisting with impaired vision is often implicated in the Charles Bonnet syndrome (Gold & Rabins 1989; Taylor et al. 1986). In particular, the syndrome has been associated with cognitive impairment (Holroyd et al. 1992) and early dementia (Pliskin et al. 1996). Gold and Rabins (1989) proposed to view visual system pathology and cerebral pathology as two risk factors, each of which being sufficient to cause the syndrome. A possible contribution by psychological disturbances is more controversial, having been suggested by some (Taylor et al. 1986), but de-emphasized by others (Schultz & Melzack 1993; Teunisse et al. 1994).

4.1. Disruption of sensory constraints

It is intriguing that circumscribed lesions at different levels of the visual system can cause a single syndrome characterised by rich hallucinatory phenomena. The perceptual release theory proposes that, as a consequence of reduced sensory input, cortical activity representing memories of past perceptions is released and experienced as hallucinations (Schultz & Melzack 1991). Alternatively, visual hallucinations in the Charles Bonnet syndrome can be viewed as a manifestation of intrinsic thalamocortical activity in the visual system that is externally underconstrained.

Teunisse et al. (1996) reported that low levels of arousal and additional sensory deprivation favoured the occurrence of visual hallucinations in patients with Charles Bonnet syndrome. Reduced levels of sensory stimulation may perhaps

play a complementary role in further increasing noise in retinal input to the lateral geniculate nucleus. Accordingly, an increase in sensory stimulation can suppress complex visual hallucinations (Lalla & Primeau 1993). This effect resembles the suppression of illusionary misperceptions in dim surroundings by stronger or more consistent sensory input.

Although Teunisse et al. (1996) reported an association of hallucinations with low levels of arousal, some reports have suggested that sudden arousal occurring as part of the startle reaction may contribute to the production of visual hallucinations in patients with peripheral visual system pathology. Jacobs et al. (1981) described a series of patients with partial deafferentation of the eye, resulting from lesions of the optic nerve or chiasm, in whom sounds could induce simple or complex visual hallucinations under circumstances that would normally promote a startle reaction to sound. In some patients with visual impairment, elementary visual hallucinations could be elicited by a noise only under conditions of darkness or dim illumination (Lessell & Cohen 1979).

4.2. Role of psychological factors

The Charles Bonnet syndrome is associated with living alone (Holroyd et al. 1992) or social isolation (Teunisse et al. 1994), which may suggest that psychological factors are still relevant, despite the lack of association with psychiatric disorder. Weinberger and Grant (1940) noticed that the content of complex visual hallucinations is unrelated to the level of lesion in the visual system and proposed using a psychological perspective to understand the content and meaning of these experiences; whereas Taylor et al. (1986) suggested that conflicts, wishes, and past memories influence the content and form of visual hallucinations in patients with impaired vision (reviewed in Gold & Rabins 1989).

Using questionnaires and factor analysis, Santhouse et al. (2000) identified three clusters of hallucinatory phenomena in patients with Charles Bonnet syndrome: (1) extended landscapes with small figures in costumes and hats, (2) distorted faces with prominent eyes and teeth, and (3) perseveration and delayed palinopsia. These clusters may be consistent with the involvement of attentional mechanisms in the formation of the content of visual hallucinations. If perception is not constrained by external sensory input, then objects that are attended to would become bigger or brighter, or occur repeatedly or multiply. Objects that are of secondary importance within a particular context would become smaller. For example, when looking at faces, one tends to focus at a person's eyes and mouth, which may then become bigger if the perception is not constrained. When looking at particular objects, these may keep reappearing as attention fluctuates, similarly to the figure-ground conversions in ambiguous pictures discussed by Gestalt psychologists.

While attentional mechanisms may shape the content of visual hallucinations in Charles Bonnet syndrome, similarly to hallucinations in mental illness, psychological concerns may be less important. For most patients, the content of hallucinations lacks personal meaning (Teunisse et al. 1996). Patients usually have full insight into the unreal nature of their experiences (Teunisse et al. 1996). Insight into the unreality of visual experiences may develop quickly, and once patients recognise that they are hallucinating, they may become concerned about the possibility of a mental illness. These concerns are common in Charles Bonnet syndrome, and patients usually respond to reassurance (Teunisse et al. 1996). Indeed, it would be lack of concern resulting from lack of insight that would raise the possibility of psychosis.

Hallucinations in all modalities occur in the normal population at an annual incidence of 4–5%, with visual hallucinations being more common than auditory ones (Tien 1991). Initially, occasional hallucinations may be mistaken as real, but in some people the initial lack of insight may provide the ground on which psychosis develops. People who are suffering from high levels of psychological distress, perhaps because of limited coping skills or enduring personality problems, may be more likely to maintain lack of insight because their hallucinations could soon prove to be useful as ego-defensive or anxiety-reducing mechanisms. A psychological need to reappraise "reality" and a persistent lack of insight may go hand in hand in promoting elaboration of hallucinations and further social withdrawal. Hallucinations occurring in the auditory modality may be more suitable for such progression into psychosis because they can adopt a verbal form and, hence, become more relevant for the patient's interpersonal anxieties. Secondly, auditory perception is less accurate in locating the source of a stimulus; stimuli can be perceived as coming from behind walls. Therefore, auditory hallucinations may be less likely than their visual counterparts to appear as being inconsistent with behaviour or experience. It may be more difficult not to develop insight into the unreality of visual hallucinations, which may be why visual hallucinations are less frequently associated with mental illness.

5. Brain disease

The cerebral irritation model suggests that hallucinations arise from abnormal excitation in cortical sensory areas. This model is based on Penfield's work on electrical brain stimulation (Penfield & Perot 1963). Electrical brain stimulation was found to induce hallucinations that in modality, content, and complexity depended on the site of stimulation (Penfield & Perot 1963). For example, stimulation in primary auditory areas resulted in the experience of noises, whereas stimulation in secondary associative areas induced more complex sounds. Electrical stimulation of the right superior temporal gyrus near the insula could produce musical hallucinations (Penfield & Perot 1963). Electrical stimulation in the occipital lobe induced visual hallucinations that varied in complexity from light flashes to formed objects. These observations supported the view that abnormal brain excitability may be responsible for hallucinations in some patients with organic brain disease. The cerebral irritation model is particularly applicable to hallucinations experienced by patients with temporal or parietal lobe epilepsy or migraine (reviewed in Asaad & Shapiro 1986).

Penfield's work on electrical brain stimulation provides some insight into the nature of perception. Stimulation of the cerebral cortex alone can produce an experience that appears to be located in external space. The brain can create the illusion of a surrounding world, whether or not the senses are stimulated, and what we accept as external reality, even during normal wakefulness, may just represent

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such an illusion. Furthermore, Penfield's work suggests that coherent activation in thalamocortical circuits, which is thought to underlie perceptual experience, can be achieved by cortical excitation alone. From a focus of cortical hyperexcitation, corticofugal input to thalamic relay cells can activate thalamocortical assemblies without regard for current sensory input. Thus, electrical brain stimulation or excitation from a focus of pathological excitation in the cortex may mimic cortical attentional mechanisms. In contrast to hallucinations arising under conditions of peripheral sensory impairment, attention and psychological factors would be less relevant in hallucinations arising from cortical excitation.

5.1. Cortical lesions

Visual hallucinations can occur in scotomas caused by infarction in the territory of the posterior cerebral artery (Brust & Behrens 1977). Kolmel (1985) reported a series of patients with occipital lobe damage and homonymous hemianopia who experienced complex visual hallucinations in the hemianopic field. Hallucinations appeared after a latent period and were stereotypical in content and weak in colour (Kolmel 1985). These hallucinations were considered to be release phenomena; specifically, occipital lobe lesions were thought to cause loss of inhibition in other cortical areas, resulting in the release of cortical activity there and the experience of hallucinations (Brust & Behrens 1977; Peroutka et al. 1982). However, the cerebral irritation model may be equally plausible. Hallucinations in patients with occipital lobe lesions may result from irritation of intact or partly damaged visual cortical areas by pathological or regenerational processes. Wunderlich et al. (2000) attributed complex visual hallucinations in a patient recovering from cortical blindness to electrophysiological hyperexcitability in the recovering, partially damaged visual cortex.

Pathological processes that involve temporal lobe areas may be accompanied by auditory hallucinations. These may lead to development of psychosis, for reasons suggested previously, particularly if left-sided auditory-language areas are affected. In a retrospective study, Fujii and Ahmed (1996) reviewed psychiatric records of 15 patients with a history of hallucinations or delusions and evidence for traumatic brain injury before the onset of psychiatric illness. The majority of patients had evidence for bilateral lesions on imaging studies; lesions in the right and left temporal region were documented most frequently (Fujii & Ahmed 1996). Fujii and Ahmed (1996) pointed out that most studies of patients with psychosis secondary to traumatic brain injury, reported in the literature, found a preponderance of left-sided lesions and all indicated a preponderance of temporal lobe lesions.

Peroutka et al. (1982) described the case of a 72-year-old woman with sudden onset of complex auditory and visual hallucinations, including third-person verbal hallucinations, following a *right* temporoparietooccipital infarction. A *left* focal seizure preceded the onset of her psychotic symptoms. Electroencephalography revealed excessive slowing over the right hemisphere (Peroutka et al. 1982). Levine and Finklestein (1982) reported the development of paranoid delusions and well-formed auditory and visual hallucinations in a series of eight patients after damage to the *right* temporoparietooccipital region, identified by computed tomography. Electroencephalography showed right hemisphere slowing in almost all of these patients (Levine & Finklestein 1982). In addition, most patients had *left*-sided focal seizure activity. The relationship between seizures and hallucinations was not clear. Seizures were usually brief and occurred in clouding of consciousness, whereas hallucinations tended to last longer and occurred in clear consciousness (Levine & Finklestein 1982). Cortical hyperexcitability (which in these patients may have been caused by loss of inhibition from the contralateral hemisphere) may have different consequences for thalamocortical self-organisation, depending on the predominant electrophysiological response mode of thalamic relay cells. During arousal, a hyperexcitable cortex may recruit tonically active thalamic relay cells into synchronous gamma-frequency oscillations, underlying hallucinations (and if left-sided language regions are affected, these would include verbal hallucinations). In states of drowsiness, when most thalamic relay cells are in burst-firing mode, cortical hyperexcitability may force slow reverberations upon thalamocortical networks, and these may manifest as seizures.

5.2. Peduncular hallucinosis

Peduncular hallucinations are typically vivid and bright visual images of sceneries, people, animals, or geometric figures. They are more likely to occur at the end of the day or during drowsiness and are associated with vivid dreams and sleep disturbances, suggesting involvement of the ascending reticular activating system (reviewed in Manford & Andermann 1998). In most cases, peduncular hallucinosis is caused by circumscribed vascular, neoplastic, or other lesions in the upper brainstem (Dunn et al. 1983), but similar hallucinations have been reported with lesions in the thalamus (Serra Catafau et al. 1992). The most frequent lesion location is in the midbrain close to the level of the raphe nuclei; lesions do not directly involve the visual system, but appear to damage the ascending reticular activating system, including serotonergic pathways (reviewed in Manford & Andermann 1998). Damage to serotonergic pathways can explain sleep-wake-cycle disturbances and alterations of arousal associated with peduncular hallucinosis (reviewed in Manford & Andermann 1998).

Serotonergic input from the raphe nuclei antagonises cholinergic activation and inhibits spontaneous and evoked activity of thalamic relay cells in the dorsal lateral geniculate nucleus. Therefore, lesions of the raphe nuclei may cause disinhibition in the dorsal lateral geniculate nucleus and reduce the fidelity of retinogeniculate sensory transmission (Manford & Andermann 1998). Again, disinhibition of thalamic relay cells may lead to their recruitment into resonant thalamocortical assemblies, regardless of sensory input, leaving the process of perception without external restrictions and free to adopt hallucinatory forms under the direction of attentional mechanisms.

Similarly to visual peduncular hallucinosis, limited brainstem lesions can give rise to *auditory* hallucinations. Auditory hallucinations have been reported in patients with lesions of the tegmentum of the pons, for example (Cambier et al. 1987; Cascino & Adams 1986; Murata et al. 1994). Complex auditory hallucinations resulting from brainstem lesions are associated with hearing loss (Murata et al. 1994), and the disruption of brainstem auditory pathways is thought to play a role in their causation (Cambier et al.

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1987; Douen & Bourque 1997), in contrast to the mechanism envisaged for *visual* peduncular hallucinosis.

5.3. Neurodegenerative disease

Like peduncular hallucinations, visual hallucinations in Parkinson's disease and Lewy body dementia typically occur at the end of the day and are associated with sleep disturbances, vivid dreams, and episodes of altered arousal (Manford & Andermann 1998). The clinical picture in Lewy body dementia is characterised by prominent hallucinations and fluctuating level of consciousness. Hallucinations in Parkinson's disease are less common. Visual hallucinations and other hallucinations not associated with delirium can also occur in Alzheimer's disease.

5.3.1. Cholinergic dysfunction. Pathological brainstem changes in Parkinson's disease include loss of noradrenergic neurons in the locus coeruleus, loss of serotonergic neurons in the dorsal raphe nucleus, and loss of cholinergic neurons in the pedunculopontine tegmental nucleus. In Lewy body dementia, these brainstem changes are more severe. In contrast to Parkinson's disease, Lewy body dementia is also characterised by extensive cortical abnormalities (reviewed in Manford & Andermann 1998).

Patients with Lewy body dementia or Parkinson's disease who hallucinate are especially sensitive to anticholinergic agents, indicating marked cholinergic dysfunction. Postmortem studies of brain tissue from patients with Lewy body dementia revealed selective reductions in presynaptic cholinergic activity in the reticular thalamic nucleus, and these were associated with hallucinations and fluctuating consciousness (reviewed in Perry et al. 1998). Alpha-bungarotoxin is a selective antagonist at nicotinic cholinergic receptors with the alpha-7 subunit. In the human thalamus, receptors with high affinity for alpha-bungarotoxin are concentrated in the reticular thalamic nucleus (Spurden et al. 1997). Court et al. (1999) examined binding of radio-labeled alpha-bungarotoxin in thalamus tissue obtained postmortem from patients with schizophrenia and patients with Lewy body dementia. Alpha-bungarotoxin binding was moderately reduced in the reticular thalamic nucleus in patients with schizophrenia and more extensively reduced in patients with Lewy body dementia (Court et al. 1999).

As a consequence of reduced cholinergic activity or reduced concentration of nicotinic receptors in the reticular thalamic nucleus, there would be a lack of nicotinic activation of GABAergic inhibitory neurons. This would reduce specific inhibitory influences in specific thalamic nuclei (with impairment of the signal-to-noise ratio) and thus allow pathological activation of thalamocortical circuits. Deficient nicotinic-receptor mechanisms may undergo abnormally rapid desensitisation during wakefulness (re-sensitising only during slow-wave sleep), which would explain why hallucinations in Lewy body dementia tend to occur in the evenings.

5.3.2. Visual impairment. Hallucinations in patients with dementia may result from involvement of sensory and association cortical areas in the general neurodegenerative process. Patients with Alzheimer's disease and visual hallucinations showed more extensive occipital lobe atrophy in magnetic resonance imaging (MRI) than did patients without visual hallucinations (Holroyd et al. 2000). In Alzheimer's disease, there is also impairment in contrast sensitivity and visual acuity (Cormack et al. 2000). Impaired visual acuity and cataracts in patients with Alzheimer's disease were associated with visual hallucinations (Chapman et al. 1999). Hallucinations may improve with prescription of glasses or cataract surgery (Chapman et al. 1999), which highlights the contribution of visual impairment to visual hallucinations in patients with Alzheimer's disease.

Holroyd et al. (2001) established that visual hallucinations in patients with Parkinson's disease were associated with reduced visual acuity, among other factors. This suggested that visual system pathology plays a role in visual hallucinations in Parkinson's disease, as well (Holroyd et al. 2001). Even among patients with Parkinson's disease whose visual acuity was normal, those with visual hallucinations performed worse on tests of colour vision and visual contrast sensitivity than did those without visual hallucinations (Diederich et al. 1998). Such abnormalities in colour and contrast discrimination indicate retinal dopamine deficiency and/or visual cortex involvement (Rodnitzky 1998).

6. Summary

The cerebral cortex and thalamus constitute a unified oscillatory system. Thalamic and cortical neurons that are connected in thalamocortical circuits have intrinsic resonance rhythmicity that is released by cholinergic arousal. In the depolarised state, these cells exhibit subthreshold oscillations of membrane potential around 40 Hz, predisposing them to fire at gamma rhythms in response to synaptic excitation. In response to arousal and under constraints of external sensory input and endogenous input from prefrontal cortices and limbic regions, gamma activities in populations of thalamocortical circuits synchronise to form coherent assemblies that underlie conscious perception. It may be important to understand that sensory input merely constrains self-organising processes in parts of the thalamocortical system that subserve perception.

General activation of thalamic relay cells during arousal is normally balanced by sensory-specific and attention-specific inhibitory input from GABAergic neurons in the reticular thalamic nucleus. The reticular thalamic nucleus, in turn, is under cholinergic control by the mesencephalic reticular formation and basal forebrain nuclei. In schizophrenia and Lewy body disease, deficient nicotinic activation of reticular thalamic neurons during arousal may lead to loss of specific inhibition and excessive random activity or noise in specific thalamic nuclei. This would mask sensory input to the thalamus and weaken its impact on thalamocortical self-organisation, resulting in impaired gamma response synchronisation to sensory stimulation. On the other hand, it may permit the recruitment of thalamic relay cells into assemblies of activated thalamocortical circuits without regard for the actual pattern of sensory input. Inhibition of the reticular thalamic nucleus and disinhibition in specific thalamic nuclei may also result from dopaminergic hyperactivity, as may be the case in schizophrenia, or exogenous NMDA-receptor antagonists, such as phencyclidine.

Peripheral sensory impairment may constitute another cause for excessive noise in specific thalamic nuclei predisposing to pathological activation of thalamocortical circuits. It is suggested that this mechanism contributes to musical

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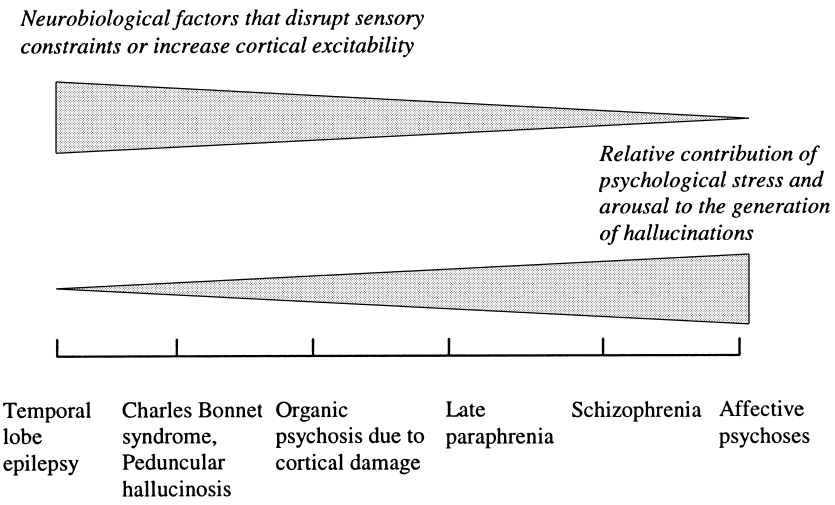

Figure 5. Disorders that feature hallucinations could be placed along a continuum, depending on the balance between neurobiological and psychological factors that contribute to the generation of hallucinations. Mediated by general arousal or attentional mechanisms, psychological factors may contribute to pathological activation of thalamocortical circuits alongside any disruption of sensory constraints. Alternatively, or in addition, pathological lesions may cause cortical hyperexcitability and increase the cortical drive on the thalamus. Psychological concerns are unimportant in the generation of hallucinations in temporal lobe epilepsy and Charles Bonnet syndrome, although attentional factors may shape their content. In schizophrenia and late paraphrenia, increased attention and arousal under psychological stress may be crucial for the generation of hallucinations, with a relatively moderate biological vulnerability given in the form of reticular thalamic nucleus dysfunction or peripheral hearing impairment. In affective psychoses, there may be a minimal biological predisposition to hallucinations.

hallucinations, the Charles Bonnet syndrome, late paraphrenia and schizophrenia, and perhaps plays a role in Parkinson's disease and Alzheimer's dementia. A disorder of serotonergic raphe nuclei, as may be the case in peduncular hallucinosis, may also cause global disinhibition in specific thalamic nuclei.

Neurobiological and psychological aspects are essential and complementary in understanding the nature of hallucinations, particularly in mental illness. In patients with a predisposition to underconstrained perception, *verbal* hallucinations may develop at times of heightened arousal and increased attention to *social* stimuli. In musical hallucinations and the Charles Bonnet syndrome, psychological disturbances are less important, although – in the absence of effective sensory constraints – attentional mechanisms may still shape thalamocortical self-organisation and determine the content of the perceptual experience. In hallucinations resulting from cortical lesions, intrinsic cortical hyperexcitability may complement attentional mechanisms in generating corticofugal input to thalamic relay cells. In hallucinations resulting from temporal lobe seizures, attentional mechanisms are irrelevant (Fig. 5).

In conclusion, the notion that normal perception and hallucinations are essentially equivalent, both being manifestations of intrinsic thalamocortical resonance in sensory areas, and the consequential reappraisal of the relationship between sensory input and physiological processes underlying perception, may provide a framework for the integration of neurobiological and clinical findings relating to hallucinations in schizophrenia and other disorders.

Open Peer Commentary

Underconstrained perception or underconstrained theory?

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Abstract: Although the evidence remains tentative at best, the conception of hallucinations in schizophrenia as being underconstrained perception resulting from intrinsic thalamocortical resonance in sensory areas might complement current models of hallucination. However, in itself, the approach falls short of comprehensively explaining the neurogenesis of hallucinations in schizophrenia, as it neglects the role of external attributional biases, mental imagery, and a disconnection between frontal and temporal areas.

According to the theory proposed by Behrendt & Young (B&Y), hallucinations and normal perception are essentially equivalent, both being manifestations of intrinsic thalamocortical resonance in sensory areas. Their approach is presented as an alternative to existing cognitive models of hallucination, which are criticized because they seem to suggest that the absence of a correspondence to external reality (which is thought to characterize self-generated mental events) has to be complemented by a conviction of their external origin to yield hallucinations. However, as the authors rightly point out, it is doubtful that thoughts, inner speech, or retrieved

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