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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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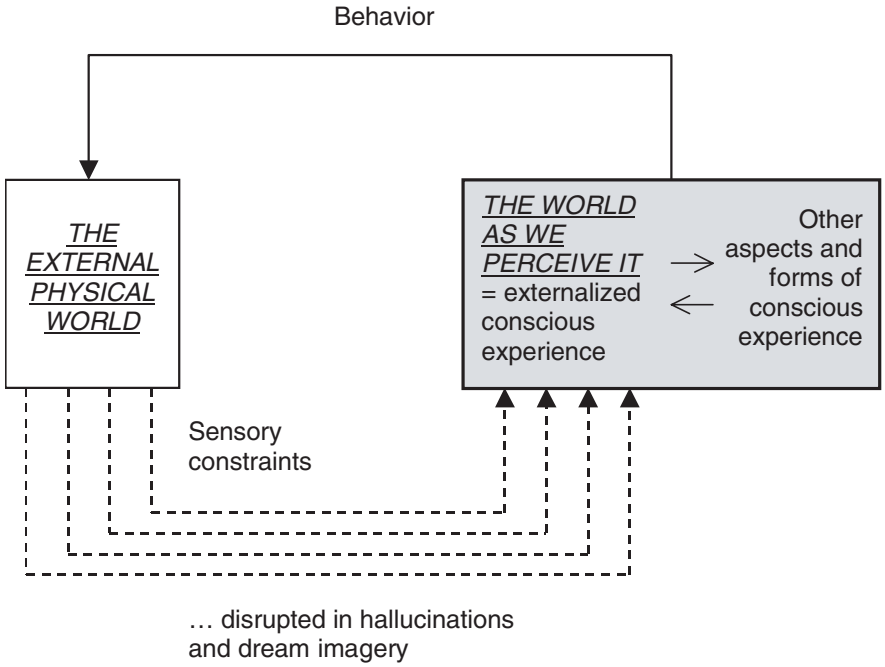

Figure 1. According to transcendental idealism, a crucial distinction has to be made between the world that we perceive around us and the external physical world with which we interact. What we perceive as being around us is not the external physical world; instead, it is a part of our mind that is projected 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.

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.

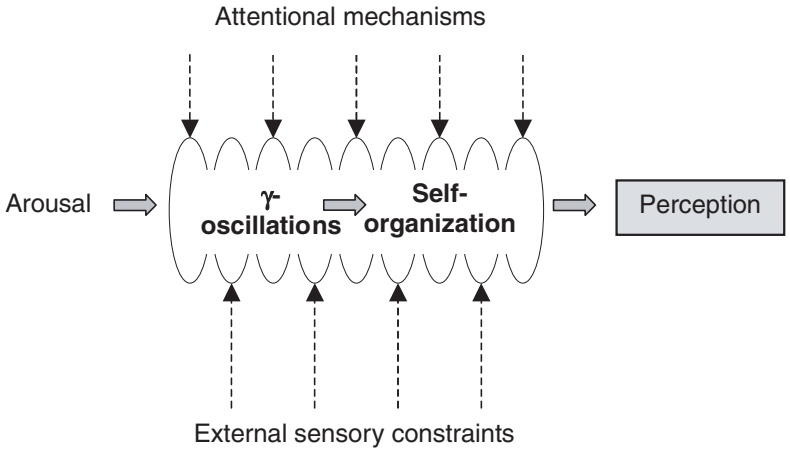

Figure 2. Perception may be a manifestation of intrinsic self-organisation of neural activity. Fast oscillatory activity in the thalamocortical system that is facilitated by cholinergic arousal self-organises into coherent assemblies under constraints of attentional mechanisms and sensory input. If sensory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

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

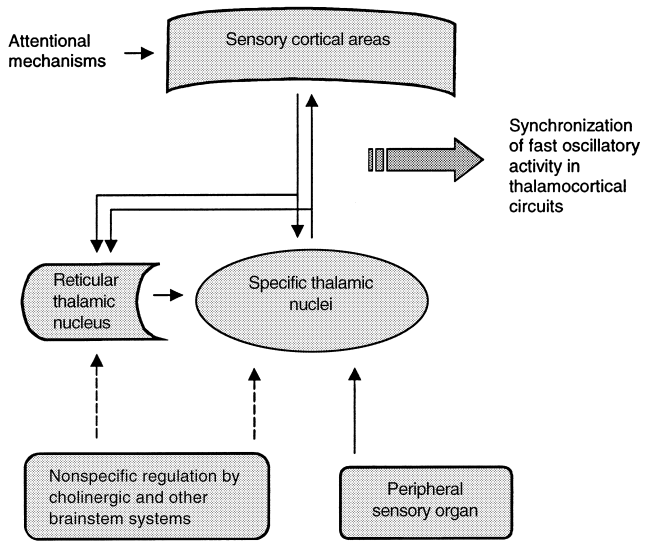

Figure 3. Gamma oscillations in thalamocortical circuits depend on the depolarisation of thalamic and cortical cells. Attentional mechanisms activate neurons in cortical sensory areas, and via corticothalamic projections, contribute to depolarisation of thalamic relay cells. Sensory input complements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

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-

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

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-

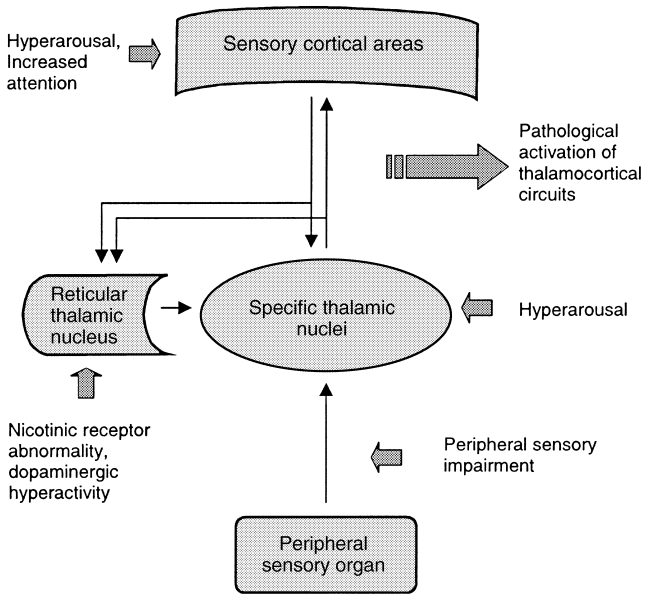

Figure 4. Neurobiological factors suggested to be involved in the generation of hallucinations in schizophrenia. Disruption of sensory constraints may be a result of disturbed function of the reticular thalamic nucleus, leading to lack of specific inhibition in specific thalamic nuclei, or peripheral 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

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

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

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.

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

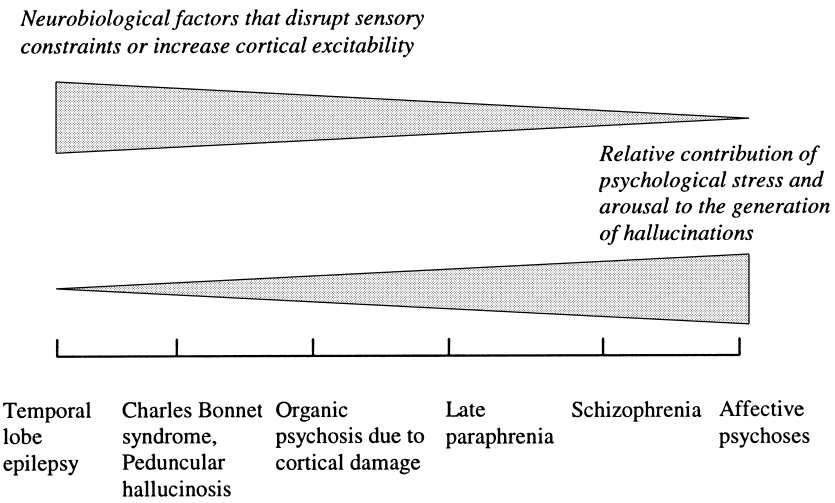

Figure 5. Disorders that feature hallucinations could be placed along a continuum, depending on the balance between neurobiological and psychological factors that contribute to the generation of hallucinations. Mediated by general arousal or attentional mechanisms, psychological factors may contribute 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

memories can be transformed into experiences with perceptual qualities just by virtue of their misattribution to an external origin.

Unfortunately, in their critique, the authors neglect a large body of evidence in favor of the external attribution bias hypothesis (for reviews, see Bentall 1990 and Seal et al. 2004). Any comprehensive account of the neurocognitive basis of hallucinations in schizophrenia should incorporate these findings. Nonetheless, we agree with B&Y that an external attribution bias cannot explain the sensory characteristics of hallucinations. However, attempts to address this issue have been extensively reported in the literature. Therefore, it is surprising that the authors seem to be unaware of the *imagery hypothesis* of hallucination. This is arguably the first scientific hypothesis of hallucinations: Sir Francis Galton proposed, more than a hundred years ago, that hallucinations result from an increased vividness of mental imagery (Galton 1883). He also devised introspective questionnaires to test his hypothesis and concluded that the evidence was in favor of his hypothesis. Indeed, an approach that focuses on mental imagery may have considerable explanatory power, as mental imagery has been shown to share important characteristics with bottom-up perception (Kosslyn 1994).

Most previous studies that investigated the imagery hypothesis of hallucinations (e.g., Mintz & Alpert 1972; Roman & Landis 1945; Starker & Jolin 1982) relied on subjective and introspective scales of imagery vividness, which may explain the inconsistent results reported in those studies. However, a number of recent studies have assessed the relationship between mental imagery and hallucination with objective, behavioral measures (Böcker et al. 2000; Evans et al. 2000;). Evans et al. (2000) used only auditory measures and failed to find differences between 12 hallucinating and 7 nonhallucinating patients. Böcker et al. (2000) assessed imagery and perception in the auditory and visual modalities in 13 hallucinating and 19 nonhallucinating patients. Consistent with Evans et al. (2000), no between-group differences were observed. However, regarding within-group comparisons, Böcker et al. observed a stronger influence of imagery on perception in the auditory compared to the visual modality in patients with auditory hallucinations. That is, imagining a stimulus enhanced subsequent detection of that stimulus to a larger extent in an auditory task than in an analog visual task. This significant difference was not evident for the nonhallucinating group. Moreover, in a recent cognitive neuropsychiatric case study (Aleman et al. 2002), we observed a modality-specific imbalance between imagery and perception in a patient with continuous auditory hallucinations, compared to five nonhallucinating patients. Specifically, whereas control subjects always performed better on a perception condition than on an imagery condition of the same task (the perception-superiority effect), this patient showed the reverse effect (imagery > perception) in the auditory but not the visual modality.

More recently, we investigated performance of 77 subjects on multiple behavioral measures of auditory and visual mental imagery and perception, and also on a measure of reality monitoring (Aleman et al. 2003). Our approach to the behavioral assessment of imagery-perception relations started from the assumption that, in normal conditions, mental images are less vivid; that is, they have fewer sensory and contextual characteristics than percepts. Kosslyn et al. (1999) and Aleman et al. (2000) recently provided evidence for this assumption in nonpsychiatric samples. According to the theory of Johnson and Raye (1981), increased vividness of images will make them less distinctive from percepts, which may lead to reality-monitoring errors. To test the imagery hypothesis, we assumed that a reduced distinctiveness of mental images with respect to bottom-up generated percepts would be observable differences in performance on tasks of imagery-perception relations. Therefore, we investigated whether patients with hallucinations would show smaller differences in performance on imagery and perception conditions of the same task, after controlling for nonspecific attentional variables. Comparisons were made between performance of schizophrenia patients with ($N = 22$) and without ($N = 35$) hallucinations and matched normal comparison subjects ($N = 20$), after controlling for attentional factors. No differences emerged on any of the mental imagery measures or on reality monitoring accuracy. This suggests that there is no stable disposition toward abnormal mental imagery associated with hallucinations. However, for patients with active hallucinations ($N = 12$), hallucination severity correlated positively with a measure of imagery-perception interaction in the auditory modality. Although preliminary, this finding is consistent with recent theoretical proposals in which hallucinations have been suggested to result from a larger influence of top-down sensory expectations (imagery) on conscious perception, and is therefore consistent with the approach taken by B&Y.

Top-down generated images can be confused with bottom-up percepts when there is a disconnection between prefrontal areas (involved in consciously generating an image) and temporal areas (involved in decoding the image, e.g., "image inspection" or "listening to the inner voice"). Evidence that such a disconnection is present in schizophrenia, and moreover, is associated with the occurrence of hallucinations, is accumulating at a rapid rate (Hubl et al. 2004; Lawrie et al. 2002; Shergill et al. 2003; Silbersweig & Stern 1996). In contrast, there is a lack of empirical data from patients with schizophrenia supporting the thalamocortical model proposed by B&Y. For example, a study by McKay et al. (2000) failed to find basic sensory impairment in patients with hallucinations as compared to patients without hallucinations, whereas deficits in perception of complex auditory stimuli were associated with hallucinatory status.

Nevertheless, we concur with B&Y that subcortical mechanisms may play an important role in the neurogenesis of hallucinations, as is apparent from studies reporting brain activation patterns during hallucinations (Shergill et al. 2000). Therefore, 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.

Underconstraint and overconstraint in psychiatry

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Abstract: Hallucination lies at an intriguing border between psychiatry and philosophy. Although Behrendt & Young (B&Y) tie their proposal to Kantian transcendental idealism, other philosophical positions are equally consistent. Cognition is underconstrained by reality not only in hallucination but also in autism and dreaming. Sensory underconstraint is insufficient to encompass schizophrenia. There is also a breakdown in integrative capacity on the cognitive side. From a wider clinical perspective than schizophrenia, there can be underconstraint or overconstraint in sensory and cognitive functionalities.

The problematic of hallucination brings psychiatry and philosophy up close. What adamantly *is* for the hallucinating patient, does not appear to the observer. This is a bona fide Being in itself, despite being hallucinated. What appears, the phenomena that onrushing experience discloses, is no basis for ontology, given the honest conviction of the hallucinator, who finds himself already thrown amidst a world in which, for example, voices may emanate from the shut-off television. And what if the non-schizophrenic world, too, is *maya*, illusion? Could non-schizophrenics in some deep ontological sense be hallucinators too? After all, Descartes meditating, seated by the fire, could find no certain truth that he was not dreaming it.

Behrendt & Young (B&Y) explicitly tie their theory of brain functioning to Kantian "transcendental idealism." "The world that we see around us is internally created and a fundamentally sub-

jective experience that in the state of normal wakefulness is merely constrained by external physical reality" (target article, sect. 1, para. 2). Here, Being is a function of knowing. Our perceptions do not mirror reality but are shaped by it: "we do not *see, hear, feel, or smell* physical reality itself; instead physical reality *constrains* the internal and fundamentally subjective process of perception" (sect. 1, para. 3, emphasis in target article).

The difference between normal perception, dreaming imagery, and hallucination is only the degree to which they are constrained by sensory input. Hallucination is "*underconstrained* by sensory input" (sect. 1, para. 2, emphasis in original). The primacy of subjectivity, which is "merely constrained" by external physical reality, is clear. Kant's transcendental idealism is grounded in the subject. This is not Berkeley's solipsistic idealism. Kant's *ding an sich* is a reality that in itself is unknowable, but knowable via our subjective appropriation of it.

B&Y's theory is not necessarily tied to Kantian philosophy, however. In Neisser's *Cognition and Reality* (1976), perception is where cognition and reality meet. Subjectivity (in the form of schemata with conditions of satisfaction) and reality are at parity, but only in the normal case. In the psychopathology of schizophrenia, reality may underwhelm subjectivity, per B&Y. In Neisser, the balance shifts subjectivity from Kantian dominance over external reality to parity with external reality. When the particular schemata's conditions are satisfied, there is perception of a particular world. In schizophrenia, the schemata are underconstrained. So B&Y's theory is consistent with both Kant's transcendental idealism and Neisser's scientific realism.

Yet, another philosophical position quite consistent with B&Y's brain theory is monadological (Globus 1987; 2003; Globus & Bezzubova 2001). (See Nakagomi [2004] for a monadological interpretation of fundamental physics.) Here, world "thrownness" – to use Heidegger's term – rather than perception, is where cognition and reality meet. But the meeting is no longer one in which abstract conditions are satisfied. The meeting is instead a match – a belonging-together – some match between reality and cognitive attunement, which may be repeated across monadological brains. The mechanism is the same here – cognition and reality meet – but the result is no longer reflective perception *of* the world, but finding oneself already amidst it, in parallel with other world thrownnesses. In this view, reality is no longer the ground of the perceivable, but "is" instead a defaulting unknowable abground (more Heidegger; see Globus 2003). So there is no exclusive philosophical connection between Kantian transcendental idealism and B&Y's conception of brain functioning.

B&Y's theory can be clinically more broadly applied. For autistic mental activity, which is exaggerated in schizophrenia but is by no means confined to that condition, the inner life predominates over the external world. Autism, too, can be conceived of as underconstrained by reality. The Freudian unconscious mind is underconstrained by reality during dreaming. So underconstraint by input explains more than hallucination.

The key explanatory brain mechanism exploited by B&Y involves dysregulation in thalamocortical systems, so that reality underconstrains relative to cognition. The difference between normal perception and hallucination is only a matter of degree. In hallucination, "sensory constraints normally imposed on the process of perception" (sect. 2, para. 5) are disrupted. This explanation is restricted, however, leaving out primary pathology of the cognitive processes in schizophrenia. Bleulerian splitting (Bleuler 1968), so characteristic of schizophrenia, is a breakdown of integrative capacity, which disrupts experience, cognition, and action.

So a richer context for B&Y's account of brain functioning in hallucination is called for. Input may be underconstraining in schizophrenic hallucination and underconstrained in post-traumatic stress disorder. The subjective attunement may be overconstraining in obsessive-compulsive disorder and underconstraining in impulse control disorders. There is a variable imbalance in psychiatric disorders between constraints of the internal attunement and constraints from external reality. In the case of bipolar disorder, the shifts in attunement between depression and mania are striking.

We applaud B&Y for bringing in a philosophical framework, which is rare outside the phenomenological tradition in continental psychiatry (e.g., Jaspers 1962), and their approach to the relationship between symptoms and brain functioning is worth pursuing. We suggest that a broader clinical context would be beneficial to the development of their ideas.

Thalamocortical dysfunction and complex visual hallucinations in brain disease – Are the primary disturbances in the cerebral cortex?

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Abstract: Applying Behrendt & Young's (B&Y's) model of thalamocortical synchrony to complex visual hallucinations in neurodegenerative disorders, such as dementia with Lewy bodies and progressive supranuclear palsy, leads us to propose that the primary pathology may be cortical rather than thalamic. Additionally, the extinction of active hallucinations by eye closure challenges their conception of the role of reduced sensory input.

We are as dissatisfied as Behrendt & Young (B&Y) with previous models of the genesis of hallucinations. Applying them to complex visual hallucinations (CVH) in neurodegenerative disorders such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), these models struggled to account for who hallucinated, what they saw, and when and where their hallucinations occurred.

We have devised a Perception and Attention Deficit model (PAD; Collerton et al., in press). CVH occur when combined impairments in visual attention and object perception, in the context of a relatively normal scene representation, disturb scene perception. We postulate that these functional impairments result from disturbances in a lateral frontal cortex–ventral stream system. Projections from basal forebrain cholinergic nuclei directly regulate this system, whereas cholinergic projections to the thalamus from the basal forebrain and the brainstem have an indirect influence.

B&Y's emphasis on the primacy of attentional processes in the phenomenology of CVH, and the role of cholinergic regulation, is consistent with PAD. Indeed, as a potential mechanism for synchronizing attention and visual perception, it fills a gap in PAD. Two differences, however, are the role given to the thalamus and the contribution of reduced sensory input to hallucinations.

If hallucinations reflect disruption of thalamocortical synchronized gamma oscillations, then, in principle, the primary locus of dysfunction could be either cortical or thalamic. In support of their thesis, B&Y point to single cases of thalamic lesions with CVH (e.g., Noda et al. 1993; Risser & Powell 1993). However, in group studies, CVH are infrequent in people with massive, but relatively restricted, thalamic damage resulting from infarcts (none reported, del Mar Saez de Ocariz et al. 1996) or fatal familial insomnia (none reported, Gallassi et al. 1996; Tabernero et al. 2000). They are more frequent in AD (average 23%, Ballard et al. 1995; 1999; 2001; Bathgate et al. 2001; Cummings et al. 1987; Holroyd & Sheldon-Keller 1995), Vascular dementia (VaD, average 33%, Ballard et al. 1995; Bathgate et al. 2001; Cummings et al. 1987), DLB (average 55%, Aarsland et al. 2001a; Ballard et al. 1995; 1999; 2001), and Parkinson's disease dementia (PDD, average 40%, Aarsland et al. 2001b; Neimark et al. 1996) – all disorders with more cortical than thalamic pathology. This suggests to us that the primary role that B&Y allocate to thalamic dysfunction cannot be generalized.

Cholinergic function is closely associated with CVH. Pharma-

cological cholinergic manipulations can both induce and treat hallucinations (Perry & Perry 1995). B&Y relate this to the role of brainstem cholinergic projections to the thalamus. However, there are also wide ranging cholinergic projections to cortical areas. Basal forebrain cholinergic cells in the nucleus basalis of Meynert project to both frontal cortex and the ventral visual stream, as well as directly to thalamic nuclei (Mesulam 1995). Basal forebrain projections to the thalamic reticular nucleus have an additional regulating role in the transfer of corticothalamocortical information (Guillery et al. 1998). We propose that cortical cholinergic projections from the basal forebrain, rather than those to the thalamus, are crucially involved in hallucinations. Thus, loss of cholinergic activity in the temporal and frontal cortex correlates significantly with the prevalence of CVH across AD, DLB, VaD, PDD, Parkinson's disease, and progressive supranuclear palsy (PSP) (Collerton et al., in press). Crucially, in PSP, there is substantial loss of brainstem cholinergic nuclei and concomitant loss of cholinergic function in the thalamus, but no or only minimal involvement of basal forebrain cholinergic nuclei or loss of cortical cholinergic function (Javoy-Agid 1994; Kish et al. 1985; Shinotoh et al. 1999). PSP has low levels of CVH (3%; Aarsland et al. 2001b).

Additionally, in the article cited in the target article on the loss of thalamic reticular nucleus alpha-7 nicotinic receptor in schizophrenia (Court et al. 1999), there was greater loss of this receptor in AD and in DLB. AD has a lower average rate of CVH (23%) than schizophrenia (average 37%, Bracha et al. 1989; Cutting 1997; Howard et al. 1994; Ndetei & Singhe 1983; Zarroug 1975), whereas DLB has a higher rate (55%) – indicative of a lack of obvious relation between thalamic pathology and hallucinations. Because basal forebrain nuclei project to both the cerebral cortex and discrete thalamic nuclei, we would, however, not exclude thalamic dysfunction potentiating the effects of cortical cholinergic loss. Imaging of cholinergic function (e.g., Kuhl et al. 1996) in discrete neocortical, as opposed to thalamic, areas would allow this to be assessed.

Unlike B&Y's model, PAD was not developed to account for schizophrenia. However, new evidence of cortical muscarinic receptor abnormalities (German et al. 1999; Karson et al. 1993; Powchik et al. 1998; Raedler et al. 2003), and the effects of neuroleptic agents with antimuscarinic activity, in creating cognitive impairments in schizophrenia (Minzenberg et al. 2004), opens the possibility that intrinsic or iatrogenic cortical cholinergic abnormalities may also be significant in this disorder.

Reduced sensory function is a risk factor for CVH in neurodegenerative illnesses (Ballard et al. 2001; Barnes & David 2001; Chapman et al. 1999; Holroyd & Sheldon-Keller 1995; Holroyd et al. 2001; Murgatroyd & Prettyman 2001), eye disease (Brown & Murphy 1992; Holroyd et al. 1992), schizophrenia (Howard et al. 1994), and the general population (Ohayon 2000; Ohayon et al. 1996). However, further reducing sensory input in hallucinators by closing eyes generally extinguishes, rather than encourages hallucinations (Diederich et al. 2003; Kolmel 1993; Menon et al. 2003; Santhouse et al. 2000; Teunisse et al. 1996). We account for this by suggesting that specific visual environments activate an abstracted scene representation (Henderson & Hollingworth 2003; Rensink 2000) that biases perception toward a specific hallucination. No vision means no activation and hence no hallucination. To our mind, this extinction is inconsistent with B&Y's conceptualization. This would suggest an intensification of the hallucinatory experience when sensory input is reduced further.

Neither model of hallucinations is likely to be wholly correct. Comparisons such as these should stimulate direct tests of their specific predictions.

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Hallucinations and acetylcholine: Signal or noise?

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Abstract: The cholinergic system is a good candidate for the role of determining the relative weight given in cortical information processing to new sensory information versus prior knowledge. We discuss the physiological data supporting this, and suggest that this Bayesian perspective can easily be reconciled with the dynamical framework proposed by Behrendt & Young (B&Y).

Behrendt & Young (B&Y) suggest that the ability of a sensory system to use information from the world to constrain its activity is dependent on the signal-to-noise ratio (SNR) of thalamic processing. Their model accords well with some data on cholinergic actions in thalamus. However, incorporating data on the effects of acetylcholine (ACh) in cortex and refining our understanding of the SNR effects may give a more compelling result.

In engineering terms, SNR is traditionally the ratio between the signal and noise *power* – that is, between the variance in the overall response attributed to signal changes, and that observed when the signal is held fixed, so that fluctuations merely reflect noise. It is noise defined in this way that limits the fidelity of information transmission, and ultimately of sensory performance. In the simple case of a Gaussian channel, SNR is related to the Shannon transmitted information, I, by

$$I = 1/2 \log_2(1 + \mathrm{SNR})$$

Unfortunately, much of the physiological literature (Lena & Changeux 1997; Sato et al. 1987a; Sherman & Guillery 2001; Sillito & Kemp 1983) confuses the issue by, instead, measuring the ratio between signal amplitude and the average level of background activity. The difference between these two measures is illustrated later.

The reason for the confusion is largely historical, and stems from the analysis of situations in which signal detection against a background was the sole requirement. High levels of background activity do not necessarily limit the SNR of transmission. If we think about the receiving neuron's task, average background can simply be subtracted from its input by a thresholding operation set to the level designated "A" in Figure 1. If thalamic relay neurons are so intrinsically active as to swamp evoked input, this is a problem in detection, because subtracting the background will remove the signal as well (i.e., if A = B in Fig. 1). Once the signal exceeds background activity, further changes in background level will not improve the discriminability of responses. If the signal can modulate the thalamic reticular nucleus (TRN) in a stimulus-specific way, as B&Y propose, detection SNR is not at issue. The authors' model does not address discrimination SNR. Additionally, applying a signal/background analysis to sensory processing is problematic because background activity may carry information; that is, it may be a signal.

There are data, however, that suggest ACh can improve the SNR of cortical sensory processing and, from this perspective, the essential elements of B&Y's model still hold. One study has directly examined the trial-to-trial variability (measure "C" in Fig. 1) of neuronal firing under ACh (Sato et al. 1987b) and shows a small decrease in response variability when some cortical neurons are exposed to ACh. Because, without cholinergic modulation, the variance of cortical responses has been shown to increase proportionally to mean firing rate (Tolhurst et al. 1983), this implies that ACh is having a regularizing effect on spiking, such that visually evoked responses are more reliable from trial to trial than would be expected given their magnitude. Unfortunately, in this study

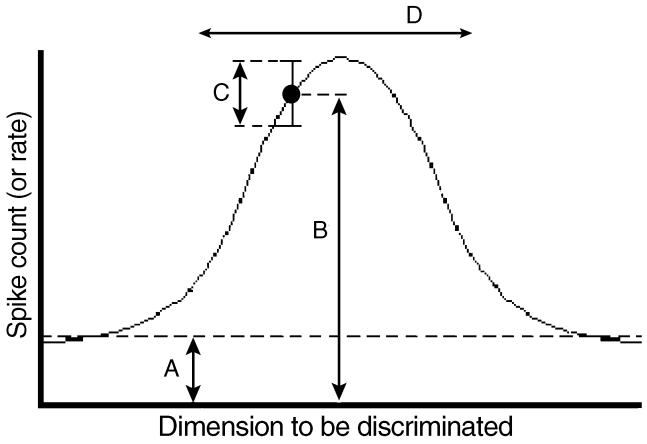

Figure 1 (Disney & Schultz). Two ways to measure signal-to-noise ratio. In this example, the method used in the cited physiological literature measures the SNR at the point indicated by the filled circle as B/A, the evoked divided by the spontaneous activity. SNR in the engineers' sense, however, would be measured as D/C – the variance across the distribution of signals to be discriminated (i.e., across a neuron's tuning curve), divided by the trial-to-trial variability (noise variance) around the point at C.

variance was calculated from only 10 trials per stimulus and the data were recorded from anaesthetized animals with basal forebrain lesions. Data from alert animals with an intact cholinergic afferent system are needed, ideally incorporating measurements of the effect of ACh on the Shannon information transmitted about sensory stimuli.

We can, however, look to other data that suggest what the effect of ACh on thalamocortical transmission may be. There is growing evidence that ACh enables action potentials arriving from the thalamus to elicit relatively larger excitatory postsynaptic potentials (EPSPs) in cortical neurons, compared with EPSPs arising from intracortical input. This effect has been shown in rat piriform (Hasselmo & Bower 1992), visual (Kimura et al. 1999), auditory (Hsieh et al. 2000), and somatosensory (Gil et al. 1997) cortices. The stronger thalamic drive is probably a result of increased glutamate release from thalamic terminals that express high-affinity nicotinic ACh receptors (Disney & Aoki 2003; Lavine et al. 1997; Parkinson et al. 1988; Prusky et al. 1987; Quik et al. 2000; Sahin et al. 1992). If summed EPSP amplitude at the cell soma is considered part of the "signal" to a cortical neuron, then increasing the gain on input from relay nuclei will allow the contribution of sensory input to somatic depolarization to exceed that arriving from intracortical sources.

The effect of thalamic input gain increases would be to give more weight in the cortical representation used by perceptual processes to the current sensory input, and less weight to recurrent, intracortical activity. This accords with both the framework put forward by B&Y and an earlier Bayesian model, which proposed that ACh controls the interaction between prior knowledge and sensory evidence (Yu & Dayan 2002). The chief differences in the two perspectives are: (1) The attractor states traversed by background activity: For B&Y, these are nonevoked gamma band oscillatory discharge cycles in a thalamocortical loop. In the Bayesian perspective, they are cortical recurrent activity representing prior knowledge of the world. (2) Where ACh exerts its critical influence: that is, in the interaction between the TRN and thalamic relay cells (B&Y, target article) or at thalamocortical synapses (Yu & Dayan). In both cases, the effect of sensory input is to constrain the states traversed by the network dynamics to those compatible with the current sensory evidence and, in both, ACh has considerable power to determine the strength of that constraint.

Recent optical imaging results may help us understand what background activity represents. Kenet et al. (2003) showed that activity in primary visual cortex, in the absence of visual stimulation, involves a dynamically switching set of cortical states whose spatial features correspond at above-chance levels to the coherent orientation maps observed with visual stimulation. Additionally, they observed that more time was spent visiting states such as the cardinal orientations, potentially reflecting the prior "knowledge" that arises from previous experience with the statistics of the natural environment (Ringach 2003). These statistics would presumably be represented in the connection strengths between cortical neurons, as a result of Hebbian-type processes. Activity in an individual neuron will then tend to excite neurons with which it is commonly coactive during natural stimulation. So hallucinations, viewed as spontaneous perception, will be like the sensory-evoked states that trained the network.

Good science, bad philosophy

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Abstract: Behrendt's & Young's (B&Y's) persuasive scientific theory explains hallucinations, and is supported by a wide variety of psychological evidence, both normal and abnormal – unlike their philosophical thesis, Kantian idealism. I argue that the evidence cited by the authors in support of idealism actually favors realism. Fortunately, their scientific theory is separable from their philosophy, and is methodologically consistent with realism.

Behrendt & Young's (B&Y's) elegant theory, simply put, is that hallucinations are otherwise normal perceptual processes that are not sufficiently constrained by sensory input. They present an impressively broad range of evidence for it, from microscopic to behavioral, and from normal to abnormal. Lest anyone be tempted to accept the dubious thesis of Kantian idealism on the coattails of this plausible scientific theory, I will argue that the evidence cited does not entail idealism, but instead favors realism. Thus, divorcing the scientific theory from philosophical idealism, I will argue that it be remarried with realistic materialism, its only true, methodologically compatible, partner.

The logical core of B&Y's philosophical thesis is that, "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" (target article, sect. 1, Fig. 1 caption). This is said to be Kantian (transcendental) idealism, though this is in fact the central tenet of idealism of any species, and would be acceptable to Berkeley and Husserl, along with various other phenomenologists, existentialists, poststructuralists, and the like. B&Y adduce four arguments for it.

1. "Perceptual experience is an *active* achievement of the nervous system" (sect. 1, first para., emphasis in original). A parent might challenge a child: Did you really see that, or are you just making it up? Assuming this dichotomy between what we perceive and what we make up, the fact that perception is active (produced, at least in part, by us) seems to entail that we do not really see anything, but just make it up. However, this is not a genuine two-bin dichotomy. Perception need not be either entirely active or entirely passive. All perception requires *some* activity on the part of the perceiver. The only question is whether any external input is also required, and in what way. This is ontologically neutral. We may understand it realistically: Neural activity is necessary to perceive external physical realities. But it applies equally to the *idealist:* Some mental (or spiritual, or soul) activity is necessary to perceive ideas (or phantasms, or whatever). So the fact that perception is active does not favor idealism over realism.

2. "Only a minor part of thalamocortical connectivity is devoted

to the transfer of sensory input" (sect. 1, para. 1). We know (by the previous point) that *some* activity is required by the perceiver, no matter what. Only if *all* perceptual activity were due to the perceiver would it follow that nothing external was being seen. So, the proportionality here tells us nothing. Most of the circuitry and activity in radar is used to generate the outgoing wave and an internal model of the range. The incoming signal makes up only the tiniest bit of the electrical information process, with the rest, including amplification, supplied by the system itself. It does not follow from this that radar does not detect and model external objects.

3. "Even normal perception in wakefulness is fundamentally a state of hallucinations" (sect. 1, para. 3). What is that word, "fundamentally," doing here? If idealism were true, then perception and hallucination would be the same. B&Y *must* distinguish between hallucination and perception – this is presupposed by their theory. And so they do: Perception is constrained by sensory input, hallucination is not. But that is a *fundamental* difference! We know (by point 2) that even a dynamically tiny external input makes a world of difference. Dynamically, there is scant difference between a radar image caused by an unshielded antenna and one caused by an aircraft – but they are fundamentally different in informational terms.

4. "Perception did not develop to copy the external world" (sect. 1, para. 3). True. But copying is not required for realism, and its absence does not entail idealism. Plato hypothesized the *eidos* to explain perception and cognition. *Eidos* means form or shape, and from it we get "video" and "idea." In seeing, thought Plato, the form of a material thing is transported into the immaterial mind: *same* form, different *substances* (material and mental). Cognition was the processing of mental forms. Thus, copying – identity of form – became a ubiquitous part of our theorizing about perception and cognition for the next 23 centuries. Within the last few generations, information theory has shown us how to escape the misdirection of copying theory. Now we can see that realism does not require that our perceptions copy reality, but instead that they provide us with information about it. The ghost of copying still haunts us everywhere, as indicated by B&Y's article, and the very word, in-*form*-ation, itself. But we can escape it, thanks largely to our familiarity with a sister concept: *trans*-formation. We have become conversant with the transformation of (the information in) DNA into an organism – and back again, the transformation of music (a computer program, movie, or whatever) into a CD (or DVD) disk – and back again, and so forth. The forms of external things are not copied in our brains, but rather transformed into neural activity and states. Perception is this transformation, and behavior transforms it back again. Perception is realistic in just those cases where the transformation informs us about its distal causes. Idealism would require *mis*information – that is, the internal creation of forms *as though* they carried information about distal causes, even though they do not. B&Y do not demonstrate, indeed do not even claim, any such misinformation – except for hallucinations.

So deeply ingrained is copying theory, that my admission that brains do not copy external objects – though surely true – might be grasped by some, perchance B&Y, as admitting to idealism itself. Nothing could be further from the heart of the matter, which is not copying itself, but whether our perceptions are causally connected to things in such a way as to carry (via transformation) information about them.

Finally, from a methodological point of view, all of B&Y's neuroscientific evidence would count for nothing if it were fundamentally equivalent to dreams and hallucinations. Idealism, like any philosophically decent metaphysics, can be logically sustained in the teeth of any evidence, if one isn't scared of wild ideas. But, as I have argued more fully elsewhere (Foss 2000), scientific methodology constrains metaphysics more decisively than the scientific evidence as such. Modern science is methodologically materialistic; hence, realism, not idealism, is the only philosophical mate compatible with B&Y's modern, and beautifully scientific, theory.

Perception and psychoses: The role of glutamatergic transmission within the nucleus accumbens septi

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Abstract: In agreement with Behrendt & Young (B&Y), we considered the role of perception disturbances in schizophrenia in our first clinical approaches, using the Bender test with schizophrenic patients. Following this, we reproduced nuclear symptoms of schizophrenia in animal models, showing that perceptual disturbances, acquisition disturbances, and decrease in affective levels can be induced by glutamatergic blockade within the nucleus accumbens septi. Our results link the proposed corticostriatal dysfunction with the thalamocortical disturbances underlying perceptual problems reviewed by B&Y.

The present article by Behrendt & Young (B&Y) is an interesting and strong effort to clarify a very important point: perception disturbances in psychoses. This topic has been recently taken as a central fact of this illness (Holden 2003a), as perceptual cognitive distortions are a core symptom of schizophrenic psychoses (see Costello 1993). One of the main goals of the article is to use biological explanations for illness in a strict sense (psychoses) in psychopathology, and, in this sense, the idea of causality is clearly present. One additional goal is the attempt to establish new relationships between objective study findings (electroencephalograms) and biological disorders underlying the psychoses. The description of and the large amount of evidence cited in support of the concept of a corticothalamic dysfunction in relation to perception, consciousness, neurotransmitters, and clinical entities is quite solid.

Not only hallucinations, but also other disturbances of cognition and perception, are symptoms of schizophrenia. The cognition involved in interpretation of perception is important, particularly in distinguishing facial expressions of emotion (Holden 2003a). Conrad (1966) argued that interpretation of interpersonal communication, because of its subtlety, was more affected than perceptions of external objects, facilitating delusional perceptions. All of these findings, taken together, strongly suggest that cognitive deficits may lie at the heart of schizophrenia (Holden 2003a).

We have studied these topics in the field of perception and psychoses, beginning with the ideas of Conrad about a gestaltic dysfunction underlying delusional perceptions (see Conrad 1966). We used the gestaltic Bender test (Del Vecchio & Gargiulo 1992; Gargiulo & Del Vecchio 1997), which showed that global scores and time employed were significantly different between healthy controls and acute and chronic patients, thereby allowing us to quantify the perceptual alterations resulting from the loss of objective structure of perception in schizophrenic patients (see Gargiulo 2003). Our results are in agreement with the failure of schizophrenic patients to perform well in visual backward masking tasks (Green et al. 1999, cited by B&Y), which are related to a failure to establish cortical oscillations in the gamma range in response to sensory stimulation (Green et al. 1999). Our next goal was to study perception in close relationship with cognition and anxiety in animal models, taking into account the current primary conceptions about the pathophysiology of schizophrenia.

Carlsson has proposed that psychotogenesis depends on an interplay between dopamine and glutamate pathways projecting to the striatum from the lower brainstem and cortex, respectively (see Carlsson et al. 2000). The action of these neurotransmitters on striatal GABAergic projection neurons (indirect striatothalamic pathways) exerts an inhibitory action on thalamocortical glutamatergic neurons, thereby protecting the cortex from a sensory overload and hyperarousal. This protection could be reduced by

hyperactivity of dopaminergic pathways, or hypofunction of the corticostriatal glutamate pathways, leading to psychosis (see Carlsson et al. 2000). The direct pathway exerts an excitatory influence, and both pathways are controlled by glutamatergic corticostriatal fibers, serving as brakes and accelerators, respectively (see Carlsson et al. 2000).

We studied perception in an animal model using pigeons. Pigeons were trained in a visual discrimination task, in which reward was linked to recognition of shapes, requiring a high level of attention. We stimulated dopamine receptors and blocked *N*-methyl-*D*-aspartic (NMDA) glutamatergic receptors within the ventral striatum, nucleus accumbens septi (Acc), which is classically linked to schizophrenia (Grace 2000; Matthysse 1981), with an aim to produce an homologous "psychotic-like state," with loss of "gestaltic" discrimination function (Gargiulo et al. 1998). Negative findings were seen with apomorphine or lidocaine injections, but a significant and reversible performance disruption to near chance levels was obtained after 7-aminophosphonoheptanoic acid (AP-7) injection into the Acc (Gargiulo et al. 1998), and, after it, with another NMDA blocker (5-aminophosphonoheptanoic acid (AP-5; Acerbo et al. 2002).

In rats, we observed that by injecting AP-7 within the Acc, acquisition, which requires a high level of attention, is disturbed, with no effects on consolidation (Gargiulo et al. 1999; Martinez et al. 2002b). In these experiments, fecal boli were also diminished during retrieval, suggesting a decrease in anxiety levels during acquisition. For this reason we used a specific anxiety test, the Plus Maze, and we observed that AP-7 clearly decreases anxiety levels when injected within the Acc, suggesting a homologous fact to affective flattening observed in schizophrenia (Martinez et al. 2002a). Taking all these findings as a whole, it appears that Acc integrates cognition and affective levels, and a dysfunction in this nucleus could underlie schizophrenic illness, giving a basis to the understanding of positive (cognitive) and negative (affective flattening) symptoms.

Recently, Grace proposed an interesting circuitry aiming to explain several schizophrenic symptoms (Grace 2000). His hypothesis is that schizophrenia is related to a dysfunction in afferent projections, glutamatergic in nature, converging onto the Acc. He suggested that goal-directed motor plans produced by the prefrontal cortex, the contextual constraints specified by the hippocampus, and the affective evaluation provided by the amygdala are all integrated in the Acc. This integration leads to goal-directed behavior bounded by contextual information and emotional significance. Conversely, in schizophrenia this integration is disturbed, and this fact leads to an abnormal affective drive with an inadequate utilization of contextual cues, resulting in impulsive and disorganized behavior (Grace 2000).

According to our experimental findings, a glutamatergic deficiency on Acc afferences could be at the base of schizophrenia symptoms because perceptual disturbances (Gargiulo et al. 1998), acquisition disturbances (Gargiulo et al. 1997; Martínez et al. 2002b), and decrease in affective levels (Martínez et al. 2002a) can be induced by glutamatergic blockade within the Acc in animal models. Our results link the proposed corticostriatal glutamatergic dysfunction with the thalamocortical disturbances underlying the perceptual problems reviewed by B&Y. In the same way, drugs acting on particular glutamate receptors could lead to new treatments for schizophrenia (see Holden 2003b).

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Absorption, hallucinations, and the continuum hypothesis

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http://www.biu.ac.il/soc/cr/cv/glicksohn.htm

Abstract: The target article, in stressing the balance between neurobiological and psychological factors, makes a compelling argument in support of a continuum of perceptual and hallucinatory experience. Nevertheless, two points need to be addressed. First, the authors are probably underestimating the incidence of hallucinations in the normal population. Second, one should consider the role of *absorption* as a predisposing factor for hallucinations.

A very thin line differentiates internally generated imagery from externally induced perception (e.g., Mast et al. 1999; Mertz et al. 2000), and this is constantly challenged when one broaches the topic of hallucinatory experience, which is the focus of this target article. There is considerable evidence supporting a continuum of perceptual and hallucinatory, or imaginal, experience (Glicksohn et al. 1999; Mahowald et al. 1998; Savage 1975; Slade & Bentall 1988), and even if one considers as valid the distinction between a hallucination and a *pseudohallucination* (Bentall 1990; Berrios & Dening 1996), one can still be somewhat deceived "naturally" (Barrett & Etheridge 1992), experimentally (Perky 1910; Persinger et al. 2000), and when under stress (Siegel 1984). In fact, this seems to be a natural consequence of the Gestalt notion of *Prägnanz*, which states that "psychological organization will always be as 'good' as the prevailing conditions allow" (Koffka 1935, p. 110). If either the external conditions change or the internal state of consciousness changes (or both), the resulting perceptual organization will change, as will the experience (Glicksohn 1998). Behrendt & Young (B&Y) are thus quite correct in summarizing that hallucinations are "underconstrained perceptions that arise when the impact of sensory input on activation of thalamocortical circuits and synchronisation of thalamocortical gamma activity is reduced" (target article, Abstract), both because this is in line with what we stated earlier, and because there are other reports in the literature supporting this claim (Crawford et al. 1993b; Rainville et al. 2002). They are also correct in suggesting that "normal perception in wakefulness is fundamentally a state of hallucinations, one however that is constrained by external physical reality" (sect. 1, para. 3), because similar arguments have been repeatedly made in the literature over the past 30 years (Neisser 1976; Shepard 1984; Yates 1985). But, I think that they are wrong in sharply criticizing the perceptual-release theory (originally advanced by West 1962), claiming that this theory does not explain hallucinations unrelated to sensory deprivation (sect. 3.1), on two counts. First, because the field of sensory deprivation has evolved since then, with newer conceptualizations relevant to the release of quasi-hallucinatory imagery (Glicksohn 1991; 1993; Suedfeld 1980; Suedfeld et al. 1994); and second, because the same type of theory underlies other experimental work in this and relevant domains (e.g., Stoyva 1973). In fact, B&Y's own Figure 5 seems, to my mind, to be a nice elaboration of Figure 2 appearing in West's chapter, yet there is no mistaking their contribution here, in their proposal that neurobiological and psychological aspects are both required for understanding the nature of hallucinations. There are, however, two caveats to be dealt with.

My first point is that B&Y, while understandably focusing more on those hallucinations associated with pathology, are probably underestimating the incidence of hallucinations in the normal population, citing a single source indicating an annual incidence of only 4–5% (sect. 4.2). A number of recently published studies (Glicksohn & Barrett 2003; Johns et al. 2002; Ohayon 2000) indicate a much higher incidence. In our own study (Glicksohn & Barrett 2003), employing both the Barrett Hallucination Questionnaire (BHQ; Barrett & Etheridge 1992) and the Launay–Slade

Hallucination Questionnaire (LSHS; Launay & Slade 1981), we reported the degree of endorsement of each item. These ranged from 2% ("hearing a conversation in the rear of the car") to 41% ("hearing noises") for the BHQ, with a mean degree of endorsement of 11.8%; and between 4% ("hearing the voice of God") and 76% ("voices in the head") for the LSHS, with a mean degree of endorsement of 35.7%. These data do not detract from the arguments made in the target article, but they certainly suggest that the phenomena under discussion are, by far, not only associated with pathology.

My second point is that it is of paramount importance to consider the *interaction* of trait and context in determining subjective experience (Glicksohn 1987) in general, and in particular, with respect to hallucinatory experience. I single out the trait of *absorption* (for a review, see Roche & McConkey 1990). In a recent paper, we presented data indicative of a common pseudohallucinatory experiential base, and suggested that absorption can serve as the predisposing factor for hallucinatory experience (Glicksohn & Barrett 2003). Absorption might very well be viewed as a *diathesis* for hallucination (for general discussions, see Butler et al. 1996; Monroe & Simons 1991). B&Y have ignored the role of individual differences in developing their model, and yet some authors consider the role of such individual differences to be critical for testing the validity of any model (Underwood 1975). Let me give two examples from the target article. The authors write that "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" (sect. 2, para. 4), but this is exactly what individuals scoring high on absorption seem to do (Destun & Kuiper 1999). Second, the authors argue that when sensory constraints are weak, "then attentional mechanisms may become the dominant modulatory influence on thalamocortical self-organization and hallucinations may arise" (sect. 1.3, Fig. 2 caption). Yet, this is exactly what distinguishes between individuals scoring high and low on absorption (Crawford et al. 1993a). B&Y might well consider the implications of such individual differences for their model.

Paradoxical sleep and schizophrenia have the same neurobiological support

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Abstract: During the paradoxical dreaming sleep stage, characterized by hallucinations and delusions, as in schizophrenia, the increased subcortical release of dopamine, the presynaptic inhibition of thalamic relay nuclei, and serotonergic disinhibition are in accordance with the model for the mechanism of hallucination-induction.

Behrendt & Young (B&Y) develop a highly interesting model based on powerful arguments. Indeed, the thalamus is a crucial step for treatment of sensory information. Moreover, the thalamocortical loop is strongly involved in electrophysiological activities concerned with normal consciousness, in that the gamma rhythm, which is impaired in Alzheimer's disease (Llinas & Ribary 1993), is recorded, most often synchronized, at both levels. The assumption that hallucinations are able to occur in the activated brain when the constraint of sensory afferents is decreased is, of course, very attractive for a sleep researcher, particularly when one is involved in the paradoxical dreaming sleep stage (PS). Indeed, there are strong functional analogies between dreaming and schizophrenic mind disturbances (principally hallucinations and delusions, cognitive impairment). First, already-established results show that there is thalamic postsynaptic activation, but presynaptic inhibition, in relay nuclei during the eye movement bursts of PS (Gandolfo et al. 1980; Steriade 1970), which are in strong relation to dreaming activity (Aserinsky & Kleitman 1953; Dement & Kleitman 1957). These data are in accordance with the hypothesis of sensory deafferentation for PS hallucinatory activity. More recently, the gamma rhythm was discovered in animals (see Maloney et al. 1997) and humans (Llinas & Ribary 1993; Ribary et al. 1991). It occurs during waking as well as during PS, but there is a specific difference when compared to waking. In addition to the absence of reset by sensory stimulation during PS (Llinas & Ribary 1993), recalled by the authors in the target article, which confirms the sensory deafferentation during this sleep stage, the synchronization over the cortical areas disappears during this sleep stage (Perez-Garci et al. 2001). This is an indication of disconnectivity of central structures, which are also repeatedly mentioned for schizophrenia (Meyer-Lindenberg et al. 2001; Tononi & Edelman 2000; Young et al. 1998). Finally, blood flow shows two important facts: (1) Although the associative visual cortex is activated during PS, the primary one is deactivated (Braun et al. 1998), which is also in accordance with some visual deafferentation, the main sensory modality concerned with hallucinatory dreaming activity. (2) There is a prefrontal dorsolateral deactivation both during dreaming (Maquet et al. 1996) and in schizophrenia (Weinberger et al. 1986).

Electrophysiological results related to neurochemistry have shown that noradrenergic and serotonergic neurons that innervate the cortex have mainly inhibitory influences (Araneda & Andrade 1991; Krnjevic & Phillis 1963; Manunta & Edeline 1999; Reader et al. 1979), and that these neurons, active during waking, become silent during paradoxical sleep (Hobson et al. 1975; McGinty & Harper 1976), thus inducing cortical disinhibition during PS (Gottesmann 1999; 2000; 2002). It is worth mentioning that clinical results show a deficit of both transmitters in schizophrenia (Linner et al. 2002; Silver et al. 2000). However, there is one monoamine – dopamine – the activity of which persists during PS (Miller et al. 1983; Trulson & Preussler 1984). It was even hypothesized that these neurons could release more dopamine during PS (Gottesmann 2002), because of firing by bursts (Gonon 1988). Indeed, results have already shown a higher variability of neuron firing in tegmental area neurons during PS (Miller et al. 1983), which implies at least some bursts. Finally, the N_{100} component of the test evoked potential in the prepulse inhibition paradigm shows differences during waking in normal subjects and in schizophrenics; in contrast, an identical increase of amplitude appears during REM sleep, which suggests a disinhibition process in both states (Kisley et al. 2003).

The main neurochemical hypothesis concerning schizophrenia disturbances involves an excess of dopamine functioning, as shown by the improvement by dopamine receptor blockers, and a deficit of glutamate, as shown by NMDA antagonists that induce psychotic symptoms (Grace 2000) and, interestingly, vivid dreaming (Reeves et al. 2001). These dysfunctionings could be responsible for the positive symptoms of schizophrenia (hallucinations, delusions), which mainly concern the nucleus accumbens, whereas a deficit of dopamine at the prefrontal cortex level might induce the negative symptoms of this disease: anhedonia, cognitive impairment (Abi-Dargham & Moore 2003). Moreover, hallucinatory activity and loss of reflectiveness are also observed during PS. Therefore, our laboratory studied dopamine and glutamate release in the medial prefrontal cortex and nucleus accumbens of rats by microdialysis and capillary electrophoresis. The results showed a decrease of dopamine during PS in the medial prefrontal cortex when compared to waking (Gottesmann 2004; Léna et al. 2003). This decrease might cause this transmitter to fall outside the limited range of optimal functioning (Abi-Dargham & Moore 2003) and be responsible for the cognitive impairment observed both during dreaming and in schizophrenia. The level of glutamate was unchanged during sleep–waking stages. In contrast, there was a maximal level of dopamine during PS in the nucleus accumbens, a minimal release during slow wave sleep (SWS), and an intermediate level during waking. Moreover,

glutamate level was maximal during waking and minimal during both slow wave sleep and PS.

Consequently, our results obtained during PS are in close accordance with those postulated for schizophrenia, and this sleep stage seems to offer a good psychological, electrophysiological, and neurochemical model for schizophrenia. In addition, these results could be reconciled with the model of B&Y. First, the increase of dopamine functioning during PS in nucleus accumbens might also occur in thalamic reticular nucleus, inducing decreased GABAergic neuron functioning and indirectly promoting thalamocortical gamma rhythm. Moreover, the silence of serotonergic neurons during PS might create a disinhibition of thalamocortical neurons and also promote the occurrence of gamma rhythm, thereby supporting potential hallucinatory activity because of the presynaptic inhibition of sensory afferents. The silence of noradrenergic neurons probably suppresses some relay nuclei facilitation. However, even if the silences of the two monoamines cancel each other out, the postsynaptic activation would certainly be induced by cholinergic afferents issued from the mesopontine pedonculopontine and tegmental dorsolateral nuclei.

It is fascinating that there are two different kinds of results supporting the same disturbances of schizophrenia – that is, the model presented by B&Y and our neurochemical results. It is possible that new results will soon completely integrate all these convergent, but still slightly different, data and help construct a unitary model.

Hallucinations and antipsychotics: The role of the 5-HT2A receptor

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Abstract: Behrendt & Young's (B&Y's) novel "unifying model" of hallucinations, although comprehensive, fails to incorporate research into the possible role of 5-HT2A receptors in the mode of action of novel "atypical" antipsychotic drugs (which treat hallucinations effectively), and into the role of such receptors, which are located in thalamocortical circuits, in mediating drug-induced hallucinations.

Behrendt & Young (B&Y) have developed a stimulating "unifying model" of hallucinations. This model integrates data from a number of domains; however, it neglects two major interacting research areas related to hallucinations. First, evidence that hallucinogenic drugs act as 5-HT2A receptor agonists; and second, evidence that such receptors may play a key role in the mode of action of many novel "atypical" antipsychotics. Although the authors' model incorporates a number of neurotransmitters, the only reference to serotonergic actions is to inhibitory effects of ascending afferents from the raphé nuclei on actions of thalamocortical circuits. The specific serotonergic receptors involved in such effects are not stated. We suggest that any "unifying model" of hallucinations will have to incorporate the role of 5-HT2A receptors in the actions of hallucinogens and in the mode of action of some novel "atypical" antipsychotics. We briefly review these two areas in turn.

B&Y suggest that all hallucinations, regardless of etiology, arise from one mechanism. Parsimony dictates therefore that any model of hallucinations should also account for drug-induced hallucinations. Indeed, there is a long history of research attempts to understand schizophrenia by analysing hallucinogens. Although such research was popular in the mid-twentieth century, it then went out of favour, but is now showing a resurgence.

Much of our understanding of the mode of action of hallucinogens comes from drug discrimination (DD) studies in animals. In these studies, animals are typically trained to make one of two responses for reward. One response (drug) leads to reward only when drugged, and the alternative response (non-drug) leads to reward only when undrugged. Thus, an animal has to discriminate its internal state to decide which response to make to obtain reward. It is often assumed, although unproven and indeed unprovable, that such states are animal analogs of "subjective" effects of drugs in humans. The DD bioassay has, however, proved to be remarkably specific. When trained to discriminate a hallucinogen, animals typically will only respond on the drug lever when treated with another hallucinogen (Appel et al. 1999). Drug responses can also be blocked by antagonists, and it has been shown that agonist actions at the 5-HT2A receptor mediate the actions of hallucinogens in this model (Winter et al. 1999). Significantly, the ability of risperidone to antagonise LSD in this model played a critical role in the development of the first novel "atypical" antipsychotic to be approved by the FDA (in 1993) for 15 years (see Colpaert 2003 for a review). Furthermore, the actions of hallucinogens in this assay can be blocked by both specific 5-HT2A antagonists and novel antipsychotics (Schreiber et al. 1994). Such data complement findings from other preclinical bioassays that indicate that hallucinogens act as 5-HT2A agonists (e.g., Gresch et al. 2002). Moreover, important studies in humans with psilocybin indicate that its hallucinogenic actions can be blocked by the 5-HT2A antagonist ketanserin (Vollenweider et al. 1998). Collectively, these data suggest that hallucinogens act as 5-HT2A agonists, and that such actions may be valuable in antipsychotic drug development.

5-HT2A receptors are located predominantly on cortical neurons, although some are found on thalamic neurons (see Nichols 2004 for a review). Thus, hallucinogens may act on thalamocortical circuits of the type discussed by the authors. Indeed, Nichols (2004) has suggested specifically (by reference to an earlier article by Behrendt [2003]) that underconstrained perceptions may arise from dual effects of 5-HT2A agonist hallucinogens, involving dysfunction of the reticular thalamic nucleus and concurrent excitation of specific thalamic relay nuclei, leading to marked activation of thalamocortical circuits. Such observations clearly emphasize the need for B&Y's model to include 5-HT2A receptors.

The authors refer to possible actions of novel "atypical" antipsychotics on D4 and GABA receptors, although they do not note that 5-HT2A receptors have been implicated, rather more convincingly, in the mode of action of some of these drugs. Brain imaging studies indicate that some of these drugs occupy 5-HT2A receptors at a high level when used clinically to treat schizophrenia (e.g., Jones et al. 2001; Travis et al. 1998). Importantly, such drugs occupy cortical 5-HT2A receptors at higher levels than striatal D2 receptors (Meltzer 2004), in accord with the hypothesis that a defining feature of "atypical" antipsychotics is that they have higher affinity for 5-HT2A receptors than for D2 receptors (Meltzer 1999). Although this hypothesis is by no means proven as an account of the actions of novel "atypical" agents, it is known that drugs such as clozapine are effective in treating patients who do not respond to other antipsychotics (Meltzer 2004). Significantly, typical agents such as haloperidol do not occupy 5-HT2A receptors (Meltzer 1999), and the enhanced therapeutic actions of agents such as clozapine may result from their ability to block 5-HT2A receptors. This hypothesis is supported by evidence that 5-HT2A systems can modulate the actions of mesolimbic dopamine systems (e.g., Barr et al. 2004), which, it is believed, are hyperactive in patients showing positive symptoms such as hallucinations (Meltzer 2004). A range of preclinical studies designed to detect antipsychotic activity indicate that the selective 5-HT2A antagonist M100907 is effective in reversing behavioural effects associated with hyperdopaminergic states induced by drugs such as amphetamine and cocaine, and by the absence of the dopamine transporter (Barr et al. 2004). Although the precise mechanisms involved in such effects are unclear, they suggest that functional interactions between 5-HT2A and dopamine systems may be of considerable significance in the mode of action of some novel antipsychotics, which may be more efficacious than older agents against symptoms such as hallucinations.

In summary, two related lines of evidence suggest that a "uni-

fying model" of hallucinations will require that attention be paid to 5-HT2A receptors: (1) studies of 5-HT2A receptor agonists that are hallucinogenic in humans; and (2) studies of the possible role of such receptors in the therapeutic actions of novel antipsychotics.

Hallucinations and nonsensory correlates of neural activity

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Abstract: Behrendt & Young (B&Y) suggest that hallucinations occur as a result of decoupling of neuronal populations from sensory control. I propose that such a decoupling is in fact a constant feature of brain activity, even under nonpathological conditions. This position is justified by evidence from recent neurophysiological recording studies. I suggest that hallucinations arise because of a breakdown in segregation of internally and externally generated activity in a neuronal population.

The core of Behrendt & Young's (B&Y's) thesis is that, during hallucinations, neuronal activity in sensory cortex "decouples" from afferent input – rather than reflecting the structure of the outside world, sensory neurons take on a life of their own, forming activity patterns only partially influenced by ongoing sensory stimulation. This is an intriguing explanation for the phenomenon of hallucinations. The aim of this commentary is to suggest that such a decoupling may in fact be a constant feature of brain function, including during nonpathological conditions. The following discussion will describe recent neurophysiological experiments that support this position.

The idea of a decoupling of neural activity from strict sensory control goes at least as far back as the "cell assembly" hypothesis of Hebb (1949). The cell assembly is defined as a subset of neurons among which excitatory connections have been strengthened by repeated coactivation, allowing the assembly to later maintain its activity through reverberant mutual excitation. A cell assembly may be activated by sensory stimulation, or it may also fire as a result of purely internal factors, such as the prior activity of another assembly. The resulting "phase sequence" of active assemblies was Hebb's model for volitional cognitive activity (the "train of thought"). In contrast to contemporaneous "feed-forward" theories of brain function, which concentrate on the production of simple stimulus–response associations, Hebb's theory also allows for behavior resulting purely from internal activity, whereby the phase sequence of active assemblies, decoupled from sensory control, lead eventually to the production of motion.

Although this theory has had a profound effect on thinking about the brain over the last half century, it has only recently become possible to test it directly at the spike-train level. The spike trains of neurons in sensory systems are certainly correlated with the structure of sensory input. However, repeated presentations of identical stimuli lead to varying responses across repetitions (Britten et al. 1993; Mazurek & Shadlen 2002; Shadlen & Newsome 1998; Softky & Koch 1993; Stevens & Zador 1998). This variability may simply be noise (Shadlen & Newsome 1994; 1998; Zohary et al. 1994), or it may reflect an essential element of brain function. Indeed, any division into "signal" and "noise" itself rests on assumptions. The "signal" is typically defined to be the stimulus presented by the experimenter, and the "noise" to be any further variability, assumed random and not helpful for information processing. Alternatively, the variability may also represent a "signal," just not one under experimental control. In particular, variability may reflect participation of neuronal assemblies in cognitive processes not directly related to the stimulus presented by the experimenter.

How might this possibility be tested experimentally? If a cortical region is involved in suprasensory processing, it should happen not only in a single cell, but also at the level of the whole population. To distinguish the involvement of neuronal assemblies in processing nonsensory information from stochastic noise, therefore, requires the recording and analysis of large cell populations, where suprasensory processing will be reflected by coordination of spike trains beyond that predicted by common stimulus modulation.

Recordings from neuronal pairs have revealed that coincident spikes occur frequently in a wide variety of systems. Two types of pairwise synchronization are commonly seen, with characteristic time scales of ~1 msec (Constantinidis et al. 2001; Csicsvari et al. 1998; Usrey & Reid 1999) and ~25 msec (Bair et al. 2001; Constantinidis et al. 2001; DeCharms & Merzenich 1996). It has been hypothesized that 1-msec scale synchronization reflects monosynaptic drive between neurons (Csicsvari et al. 1998; Marshall et al. 2002) or common monosynaptic input from a third cell (Usrey & Reid 1999), whereas 25-msec scale synchrony results from more general network coordination (Constantinidis et al. 2001).

What role might this 25-msec synchrony play in neural processing? In a recent study (Harris et al. 2003), we investigated the hypothesis that this coordination reflects an organization into assemblies whose activity can reflect both external sensory input and internal cognitive processes. One signature of the assembly organization is the existence of anatomically distributed groups of neurons, whose activity is synchronized more than predicted by common sensory modulation. A second postulated signature is that, although individual neurons may participate in many assemblies, not every possible combination of cells comprises a cell assembly. The latter feature should be reflected by a statistical preference in the probability with which a neuron joins its various peers in synchronous firing. A novel "peer prediction method" was used to show that precisely such an organization exists in the hippocampus of rats exploring a spatial environment. Neurons are organized into assemblies, whose timing and composition could not be predicted simply from the animal's trajectory through space (Harris et al. 2003). Furthermore, the time scale of this assembly organization could also be estimated, and was found to be 10–30 msec. This time scale may be of particular physiological significance. Because it closely matches the membrane time constant of pyramidal neurons in the hippocampal region, activity synchronized with this time scale may be optimal for inducing spiking in downstream neurons. Furthermore, this time scale matches the period of the hippocampal gamma oscillation and the effective window for synaptic plasticity. We therefore suggest that assembly activity may be optimal for propagation and storage of information in neuronal circuits.

These results suggest an extension of B&Y's hypothesis. That is, even under nonpathological conditions, neuronal assemblies are equally involved in internal cognitive processes, such as mental imagery, as in the representation of the external world. The question is then: How does the healthy brain keep the internally generated and external worlds separate? When a neuron fires a spike, how do postsynaptic cells know whether that spike coded for an external sensory event or an internally generated one? This task may be harder than we imagine, and the breakdown of this balancing act may be the cause of hallucinations.

Cortico – (thalamo) – cortical interactions, gamma resonance, and auditory hallucinations in schizophrenia

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Abstract: Transcranial magnetic stimulation, EEG, and behavioral studies by our group implicate spurious activation of speech perception neurocircuitry in the genesis of auditory hallucinations in schizophrenia. The neurobiological basis of these abnormalities remains uncertain, however. We review our ongoing studies, which suggest that altered cortical coupling underlies speech processing in schizophrenia and is expressed via disrupted gamma resonances and impaired corollary discharge function of self-generated verbal thought.

Behrendt & Young (B&Y) are to be commended for proposing an integrative and mechanistic model of how hallucinations arise in a variety of clinical contexts. We present comments arising from our past and ongoing studies of auditory hallucinations in schizophrenia. These studies suggest aberrant functional relationships within and between cortical regions involved in speech production and processing that may be, at least in part, organized as gamma resonances.

We have shown that low frequency repetitive transcranial magnetic stimulation delivered to the left temporoparietal cortex – a brain area critical to speech perception – reduces auditory hallucinations (Hoffman et al. 2000; 2003). These findings suggest that auditory hallucinations require activation of speech perception neurocircuitry, consistent with B&Y's model. A study of speech perception capacity of schizophrenic patients with and without auditory hallucinations and normal control subjects provides further insights into this system (Hoffman et al. 1999). Subjects "shadowed" speech that was partially obscured by multispeaker babble. Hallucinating patients were much more likely to misperceive target speech as spurious words and phrases compared to nonhallucinating patients and normal controls. These data suggest that auditory hallucinations may indeed arise from "underconstrained" sensory inputs (resulting from superimposed noise), precisely as postulated by B&Y.

The gamma-based model of hallucinations proposed by B&Y invites speculation regarding alterations of the speech perception system accompanying auditory hallucinations. They refer to the Kwon et al. (1999) study, which demonstrated reduced gamma EEG power in response to stimulation with 40 Hz trains of auditory clicks in patients with schizophrenia. We have replicated and extended this finding by showing that the deficit in evoked-gamma power is specific to hallucinators. The Baldeweg et al. (1998) case study of somatic hallucinations cited by B&Y shows coincident gamma activity. If these gamma findings generalize to auditory hallucinations, then spontaneous (hallucinogenic) gamma activity could blunt gamma shifts in response to external sounds, consistent with our observations.

What does gamma do? A number of writers including B&Y highlight the role of GABA neurons in the resonant activity of thalamocortical networks. Less well known is why the brain needs gamma. We propose that gamma is a field potential indicating the integrity of recurrent local GABA inhibition of neurons that exhibit bistability, such that they can sustain a modulated train of firing, sometimes called reverberatory activity (à la Hebb). GABA input allows these neurons to show "flickering" activity; that is, it allows them to hyperpolarize just enough so that the next excitatory input produces an action potential, but does not depolarize them so much that they become unresponsive to input (Szabadics et al. 2001; Traub et al. 2003; Wang et al. 1996). As such, gamma resonances would maintain the integrity of the functional assembly and serve as a gating mechanism. If so, why would schizophrenic patients, especially those with hallucinated speech, demonstrate spurious gamma responses? Here there is even less certainty, but alterations previously implicated in this disorder – NMDA receptor dysfunction, dendritic spine deficits, GABA interneuron loss, connectivity reductions – could be at fault. A related question is why spontaneous gamma resonances in speech processing neurocircuitry of hallucinators are attracted to verbal content that is vulgar or critical and generally emotion-charged – the characteristic content of schizophrenic "voices." One speculation is that such emotion-linked representations are especially prone to produce neuroplastic changes that predispose to their own recurrence (cf. Packard & Cahill 2001).

B&Y are critical of cognitive models of hallucinations that posit misattribution of inner speech to external sources as the primary mechanism, on the grounds that a misattribution per se cannot readily account for the vividness with which hallucinations are experienced. However, on the plus side, misattribution-based cognitive models of hallucinations can be traced to more fundamental sensory models developed to explain how organisms distinguish between sensory input arising from external sources and sensory input arising as a consequence of self-generated actions. These "forward models" propose that initiation of an action is associated with a "corollary discharge" representing the anticipated sensory consequences of the action (Von Holst & Mittlestaedt 1950). Corollary discharge signals are posited to dampen the sensory cortical response to self-generated acts. While these forward models have mostly been applied to sensory-motor systems (e.g., Angel 1976; Jeannerod 2003; Wolpert & Kawato 1998), they have been extended to the auditory system's response to speech (Curio et al. 2000; Houde et al. 2002) and may also apply to internally generated thoughts and percepts. Thus, the misattribution of inner thoughts and percepts to external sources in schizophrenia may be based on aberrant sensory experiences of these mental events resulting from failures of these forward model/corollary discharge mechanisms to selectively dampen sensory cortex as these events occur. The idea that corollary discharge dysfunction underlies many positive symptoms of schizophrenia, including hallucinations, was first proposed by Feinberg (1978) and was later extended by Frith (1987). Although the mechanisms of these corollary discharge pathways are not established, they may well involve the thalamocortical circuitry and regulation of synchronous oscillatory activity described in the B&Y model.

Consistent with these corollary discharge models, we (Ford & Mathalon 2004) have found that: (1) auditory cortical responsiveness to speech sounds, reflected by the N100 event-related potential (ERP), is dampened during self-production of speech relative to its playback, and (2) modulation of the auditory N100 response to self-produced versus played-back speech is absent in schizophrenic patients. Moreover, dampening of the auditory cortical N100 to sound probes has also been demonstrated during inner speech, and once again, schizophrenic patients engaged in inner speech failed to show this dampening. Although these ERP abnormalities in schizophrenic patients have not been specifically linked to hallucinations, it is possible that they reflect a trait feature of the illness that disinhibits speech production/perception neurocircuitry and permits emergence of spurious gamma dynamics during clinical state exacerbations. We are also conducting studies that directly examine functional relationships between the temporal cortex and frontal regions. Our EEG coherence data (Ford & Mathalon 2004) show greater fronto-temporal coherence in the theta band during talking than during listening in healthy subjects. This was not observed in patients with schizophrenia, especially those with auditory hallucinations.

Deviant patterns of functional coupling between cortical regions in these patients may ultimately lead back to the thalamus,

which has been shown not only to be a relay station for sensory input, but also a center for transmitting and integrating information transmitted between cortical regions (Sherman & Guillery 1996) and plays a key mediating role in gamma-linked processes. B&Y have made an important contribution by highlighting the potential role of anatomically distributed thalamocortical processes and gamma resonances in the emergence of hallucinations.

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A possible role for non-gamma oscillations in conscious perception: Implications for hallucinations in schizophrenia

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Abstract: Behrendt & Young (B&Y) propose a useful theoretical framework for the study of processes underlying perception and hallucinations. It focuses on gamma oscillations in thalamocortical networks and the role of the reticular thalamic nucleus in modulating these oscillations. I suggest that their theoretical model might also be applied to the investigation of temporal encoding deficits in disorders such as dyslexia. I further suggest, however, that a role for slower rhythms, such as theta, might also be considered when investigating perceptual experience.

Behrendt & Young (B&Y) propose that conscious perception is subserved by synchronization of gamma-frequency oscillations in recurrent thalamocortical networks, and that hallucinations that occur in schizophrenia, for example, result from underconstrained activation in this circuitry. As the authors note, the idea that gamma activity in thalamocortical networks subserves perception has been suggested previously by Llinas and colleagues (Llinas et al. 1994), and that dysfunction in thalamic nuclei may result in hallucinations has also been proposed (e.g., Gruzelier 1999). However, although resting heavily on prior work, the stated aim of the authors is to provide a "unified pathophysiological framework for hallucinations in neurological and psychiatric conditions" (target article, Abstract), and in that they have succeeded admirably.

B&Y argue that hallucinations differ from "normal" perceptions only in the degree to which they are constrained by sensory input. They argue that this constraint is mediated by inhibition of specific thalamic nuclei by the reticular thalamic nucleus (and modulation of gamma activity). Hallucinations arise when the constraint is compromised, by dysfunction of the reticular nucleus, or indeed compromised sensory input to specific thalamic nuclei. The authors support their proposal with an impressive array of suggestions as to how arousal and attentional mechanisms modulate thalamocortical gamma activity, and how clinical findings regarding hallucinations may be explained by their model.

The potential future utility of B&Y's proposed framework remains to be seen, however. There is apparently, as yet, a lack of anatomical evidence (either gross or micro) that would support the presence of a dysfunction in the reticular thalamus in those prone to hallucinations, and, as the authors themselves note, functional imaging studies showing, for example, coactivation of auditory thalamus and auditory cortex during both speech perception and verbal hallucinations are required.

Nevertheless, B&Y's proposals deserve to be more fully explored in the variety of conditions they mention, and indeed, their general framework may also be applied to other populations as well. For example, it has been proposed that language- and reading-impaired individuals (such as those with dyslexia) have fundamental difficulties with temporal processing (Hautus et al. 2003; Lovegrove et al. 1990; Stein 1994; Tallal et al. 1996; Wright et al. 1997). With auditory processing at least, this is usually attributed to an abnormality in the magnocellular system. An analogous abnormality is usually assumed for deficits in temporal processing in the visual domain as well (Habib 2000). As B&Y note, however, the reticular nucleus participates in time-dependent analysis of auditory input, and thus a dysfunction of this nucleus might also be hypothesized. Magnetoencephalographic investigation of gamma activity during temporal processing tasks (paradigmatically similar to investigations of the auditory P50 discussed by the authors) has indeed shown clear differences between good and poor readers (Nagarajan et al. 1999). Of interest here, as well, is that it has been proposed that dyslexia and schizophrenia may be considered to be representatives of a related spectrum of disorders (Stein 1994). Although the degree of atypical magnocellular development and atypical cerebral asymmetry was proposed to determine the manifestations and severity of these disorders, abnormal reticular thalamus function might also be proposed as a common factor. Of course, the rather different extents to which dyslexics and schizophrenics are prone to hallucinations would have to be explained by other factors.

Finally, and more generally, it might be argued that, although necessary for conscious perception, gamma activity in thalamocortical networks may not be sufficient for a full contextual integration of perceptual information. Certainly, Llinas et al. (e.g., 1994) and Crick & Koch (1990) suggest that gamma frequency oscillation may be the fundamental feature responsible for conscious experience. However, it has also been suggested that different frequencies of oscillation may be required for different scales of cortical integration (von Stein & Sarthein 2000). In this view, gamma frequency oscillation may be required for integration in relatively local networks (or local cell assembly formation), whereas slower oscillation, in the theta range, for example (4–7 Hz), might underlie longer-range integration, or indeed the formation of global cell assemblies. It is conceivable that the content of perception is represented in local assemblies formed by gamma activity, whereas integration of this information into a context may require interaction within a global assembly maintained by lower-frequency oscillations. Lisman and Idiart (1995), for example, have suggested how gamma oscillations "nested" in theta oscillations might subserve mnemonic processing in hippocampus. Thus, gamma might simultaneously occur in local nodes of a global network, but integration is maintained by simultaneous theta-rhythmic activity across the global network. It is possible that global integration is required for the "substantiality, richness, and clarity" (sect. 2, para. 4) of perceptual (or indeed hallucinatory) experience. In this regard, it has recently been shown that theta-rhythmic EEG increases over left superior temporal cortex during hallucinations in a schizophrenic (Ishii et al. 2000).

It has been recently proposed that theta performs a role in integrating activity in hippocampal, thalamic, and cortical sites during mnemonic processing (Kirk & MacKay 2003). Critical thalamic nuclei appear to be the anterior thalamic complex and mediodorsal thalamus (see also Aggleton & Brown 1999). It is interesting that volume reductions in the medial dorsal thalamus are commonly reported in schizophrenia (e.g., Danos et al. 2003). Thus, perhaps, abnormalities in nuclei in addition to the reticular thalamus should be examined when considering manifestations of schizophrenic symptoms such as hallucinations.

Probing cortico-cortical interactions that underlie the multiple sensory, cognitive, and everyday functional deficits in schizophrenia

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Abstract: Schizophrenia patients exhibit impairments across multiple clinical, cognitive, and functional domains. A fundamental abnormality of the timing and/or efficiency of neural processes across disparate brain regions (i.e., cortico-cortical communications) may underlie many of the deficits in schizophrenia. Because gamma synchrony is temporally correlated with many cognitive processes, probing patterns of gamma activation may shed light on the functional integrity of neural circuits in schizophrenia and related disorders.

Patients with schizophrenia exhibit widespread deficits in many domains that range from abnormalities in basic sensory registration and processing (e.g., Adler et al. 1982; Braff 1989; Braff et al. 1978; Ford et al. 2004; Shelley et al. 1991) to impairments in higher cognitive operations such as sustained attention, processing speed, working memory, verbal memory, and executive functioning (e.g., Green 1998). These widespread deficits have resulted in the conceptualization of schizophrenia as a neural circuit disorder by Behrendt & Young (B&Y) in their target article, as well as by a number of other investigators (e.g., Andreasen 1999; Braff 1999; Green & Nuechterlein 1999; Kwon et al. 1999; Swerdlow & Koob1987). A disruption in the fluid coordination of functions across disparate brain regions that subserve complex cognitive functions could result in the deficits that are frequently observed across several cognitive domains (e.g., attention, memory). In this context, Andreasen (1999) proposed that the heterogeneous "group of schizophrenias" share a common underlying defect in a fundamental "timing or sequencing component of mental activity" across multiple brain regions to account for the heterogeneous constellation of clinical and cognitive deficits.

Recent advances in cognitive neuroscience have begun to illuminate the time-linked mechanisms by which anatomically distinct brain regions communicate in order to integrate and coordinate basic functions that are critical for perception, information processing, learning, and memory. In particular, synchronous neural oscillations in the 24–50 Hz range (centered near 40 Hz and referred to as the "gamma band") occur in the cortex of many species and appear to reflect a fundamental CNS resonance frequency that is critical for communication across multiple brain regions (Traub et al. 1996). The temporal synchronization of gamma band oscillations has been proposed as a candidate mechanism for dynamically "binding" distributed sets of neurons to form coherent functional assemblies (Joliot et al. 1994; Miltner et al. 1999; Traub et al. 1996). Transient synchronous gamma band oscillations are generated across a wide range of cognitive operations such as sensory discrimination, learning, and memory – all domains in which many schizophrenia patients have deficits (for reviews, see Lee et al. 2003; Phillips & Silverstein 2003). Thus, the study of high-frequency cortical oscillations in the scalp-recorded electroencephalogram (EEG) may shed light on the functional integrity of neural circuits in schizophrenia with high temporal resolution (e.g., Lee et al. 2003; Spencer et al. 2003).

Rather than examine transient gamma band oscillations that are endogenously generated during a cognitive task, Kwon and colleagues (1999) directly evaluated the driving or "entrainment" of the EEG to steady-state stimulation at varying frequencies, including the gamma range (40 Hz), to test whether neural circuits in schizophrenia patients can support normal gamma synchronization. When receiving periodic stimulation, neural networks behave like a tuned oscillator, with the EEG synchronizing to the frequency of stimulation. Kwon et al. observed that schizophrenia patients have selectively reduced EEG synchrony to 40-Hz stimulation, but normal synchrony to 20- and 30-Hz stimulation. They speculated that a dysregulation of the circuits producing the gamma rhythm might interfere with transmission of high-frequency information and contribute to many of the cognitive deficits that require rapid temporal integration.

Because transient gamma range oscillations are temporally correlated with many cognitive processes (Lee et al. 2003; Phillips & Silverstein 2003), abnormal patterns of gamma activity may provide a neurophysiological reflection of disturbances in integrative functioning in schizophrenia. Thus, it is possible that a variety of cognitive deficits in schizophrenia can be distilled into a small number of core abnormalities in the timing, synchronization, and efficiency of neural processes across different brain regions (Green & Nuechterlein 1999). In this context, we have shown that visual masking deficits in schizophrenia patients are also associated with abnormal transient cortical gamma band oscillations (Green et al. 2003).

Are deficits in the ability to support gamma range oscillations associated with other abnormalities in sensory, cognitive, or everyday functioning? Schizophrenia patients often have large-effect size deficits in the routine processing of simple sensory stimuli using multiple paradigms. These deficits are seen in gamma band entrainment, as described earlier (Kwon et al. 1999), and in conceptually related measures of early-stage sensory processing, such as Mismatch Negativity (MMN), which also reflect neural circuit-based information processing (e.g., Javitt 2000; Light & Braff 2005; Michie 2001; Salisbury et al. 2002; Umbricht et al. 2003). Mismatch Negativity (MMN) is an auditory event-related-potential (ERP) component that is elicited when a sequence of repetitive standard sounds is interrupted infrequently by deviant, "oddball" stimuli (e.g., infrequent stimuli that differ in duration or pitch from the more frequently presented stimuli). MMN occurs rapidly; following "deviant" stimuli the response onset can be as early as 50 msec, peaking after an additional 100–150 msec. Physiologically, MMN is the first measurable brain response component that differentiates between frequent and deviant auditory stimuli and reflects the properties of an automatic, memory-based comparison process (Naatanen et al. 1989). Deficits in MMN represent a remarkably robust finding in schizophrenia research, and we have demonstrated that MMN deficits are highly associated ($r = -0.65$) with impairments in "real-world" everyday functioning (Light & Braff 2005). Thus, MMN may be a better predictor of functional status than many traditional neuropsychological tests ($r = 0.30$ to 0.40; e.g., Green 1996; Green et al. 2000; Palmer et al. 2002).

Studies of normal subjects have identified a role of transient gamma-band oscillations observed during MMN recordings (Haenschel et al. 2000; Karakas et al. 2000). Specifically, non-phase-locked gamma oscillations (termed *induced*) are not apparent in average waveforms, but temporally coincide with MMN latency in normal subjects (e.g., Haenschel et al. 2000; Karakas et al. 2000). The extent to which a failure to support gamma-range oscillations is associated with other abnormal sensory-processing and functional deficits, however, is unknown. Thus, B&Y's target article raises many questions in an important, developing field of psychiatric neuroscience. Clearly, additional studies are needed to determine if a reduced capacity to support high-frequency oscillations in the gamma range is associated with deficits across the multiple sensory, cognitive, clinical, and functional domains frequently observed in schizophrenia patients. To do this, B&Y's ideas must be translated into falsifiable hypotheses that will advance our understanding of cortical coordination dynamics in schizophrenia.

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Thalamus, a theory of everything?

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Abstract: Hallucinations do not originate in a single region of the brain, the thalamus, and cannot be traced back to a single pathological mechanism. They emerge from the complex interaction of several brain regions, and are not necessarily the result of sensory impairment or the effect of a defective filter. In the case of schizophrenia, hallucinations are accessory symptoms, in Bleuler's sense, and are thus not central to this disorder.

In the target article, Behrendt & Young (B&Y) give a detailed survey of the thalamocortical system in its relation to hallucinations in neurological and psychiatric conditions. The thalamus as an "entrance door" to virtually all the sensory channels has always attracted the attention of schizophrenia researchers. This region of the brain alone – so the assumption goes – could be the cause of many distortions in perception and of hallucinations, because if it were damaged it would not be able to fulfill its function of gating or filtering incoming information. Defects in sensory "gating" or filtering of stimuli could therefore lead to "input overload" (McGhie & Chapman 1961), and thus to the difficulty of distinguishing between "self" and "nonself."

This model is based on a false notion, namely, the notion that perception is a passive process. Ever since Gibson's (1966) studies, it has become increasingly clear that perception is generated by means of motor processes (star-nosed mole, Catania 1999; bat, Kuc 1994; and saccades in humans, Ballard et al. 1997). Finally, it has recently been shown that visual pattern recognition is a pattern formation in the cerebral cortex (Kenet et al. 2003).

In the brain, perception arises from the interaction of many regions. For the visual system, for example, Felleman and Van Essen (1991) found a hierarchy of extremely complex and varied connections. Studies on so-called blindsight – where the thalamus remains intact – have shown us that only a few cortical regions of this complex system (e.g., V1) provide conscious perception (Weiskrantz et al. 1995).

Hallucinations are no more passive than perception is. Obviously, pathological activity is generated starting from the visual cortex and is detached from sensory input. This can be clearly seen from the Charles Bonnet Syndrome (CBS). The first person to describe CBS, de Morsier (1936), pointed out in his studies that the presence of an eye disease was not the most important etiological factor in these hallucinations; he thus excluded the theory of visual impairment. Ffytche and Howard (1999) saw a relationship between CBS and eye disease, however they clearly located the disorder in the cerebral cortex. They were able to classify important types of hallucination and to prove, using fMRI, that increases in activity within the specialized visual cortex are the cause of certain types of visual hallucinations. In their view, various factors result in such increases in activity, but the thalamus is of little importance in this context.

Schizophrenics also experience visual hallucinations in the form described by Ffytche and Howard (1999). They experience these distortions not only in hallucinatory but also in perceptual form. The essential difference to CBS is illustrated by the fact that a particular facial contortion, for example, is interpreted by CBS patients as not being real, whereas schizophrenics interpret it as real. The model of visual impairment and underconstrained perception lacks the ability to explain this complexity of hallucinatory events.

Also, the verbal hallucinations frequently observed in schizophrenia indicate the interaction of various regions of the brain. During the second half of the nineteenth century, psychiatrists (Cramer 1889; Séglas 1892) recognized on the basis of clinical observations that verbal hallucinations are closely linked with the process of language production. And Bleuler (1911/1950) argued against Kraepelin that hallucinations could not be only "perceptual" (cf. Kraepelin 1919/1971), for the simple reason that they clearly had intentional contents.

Thus, clinical experience supports the idea that hallucinations in general are not purely "sensory," but instead are motor disorders. It has been possible to show that in most cases, patients developed activities of the speech muscles in hallucinations they claimed to hear (subvocal speech, Bick & Kinsbourne 1987; Gould 1948).

The emergence of imaging procedures has made it possible to show in numerous studies that activations of the motor language region are in fact involved in hallucinations (e.g., McGuire et al. 1993).

B&Y believe that their understanding of the mechanism of hallucination holds the key to understanding schizophrenia. Bleuler (1911/1950) described the hallucinations and abnormal perceptual experiences in schizophrenia as being "accessory" symptoms, whereas he considered the fundamental features of the disorder to be disorganized thinking, affective disturbances, autism, and ambivalence. He emphasized that this illness is distinguished by the simultaneous existence of normal and bizarre behavior and of simultaneous hallucinatory and normal perception. In this case, the nervous system should be overconstrained rather than underconstrained.

B&Y automatically run into difficulties when they try to ascribe the variety of disorders in schizophrenia to a hallucinatory predisposition. Schizophrenia affects such a variety of mental processes, and so many regions of the brain have been described using imaging processes whereby their functions are shown to deviate from those of normal subjects, that to attribute all these changes to the thalamus would mean attributing the entirety of all mental processes to the thalamus.

All in all, the disease seems to be characterized primarily by motor disorders, which are independent of acts of perception in every respect. These include, among others, motivational disorders, which Kraepelin (1919/1971) compared with the frontal lobe syndrome, as well as numerous other motor disorders scarcely discussed in the literature, with perhaps the exception of the impressive catatonic states. In this context, it seems important that the sensory apparatus remains completely intact during these catatonic states, as the minutely detailed descriptions given after such states show.

It does not appear to make much sense to grant one system – the thalamocortical system – a privileged position among the many other systems in the brain. It makes more sense when searching for the origin of perception and hallucination to identify the region in which these perceptions and hallucinations become conscious. Even if it should be the case that the thalamocortical system has a massive influence on the state of the brain, the individual contents of consciousness are generated by very precisely determinable regions in the cerebral cortex.

Deregulation of the balance between data and conceptually driven processing: A shift toward the conceptual

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Abstract: Behrendt & Young (B&Y) propose that a dysfunction in the reticular thalamic nucleus contributes to disinhibition of specific thalamic nuclei, allowing cortical attention mechanisms to engage thalamic relay neurons, causing underconstrained activation of the cortex and hallucinations. The following hypothesis challenges the notion of impaired sensory gating by providing the alternative view that hypofrontality reduces the power of incoming stimuli, causing internal drives to override consciousness, resulting in hallucinations.

I suggest that a dysfunction in the reticular thalamic nucleus does not explain all the findings in the schizophrenia literature. I propose that a mechanism, which I refer to as "dynamic modulating equilibrium" and which mediates the balance between afferent stimulation and intrinsic activation, is faulty. This dysfunction leads to a shift in the locus of attention toward the conceptual (intrinsic) side of the interaction. This view is consistent with the target article in regard to the basic equality between the waking (data-driven) and dreaming (conceptual) state, except that this position does not view the imbalance as a result of overactivation of thalamic relay cells. Instead, as a consequence of reduced prefrontal activity (Niznikiewicz et al. 2003), modulation or amplification of external input is decreased. This reduced impact of external sensory information shifts the locus of attention on the continuum between the balance of these two states internally. (To elaborate: When daydreaming, attention is focused inward, therefore reducing the impact of the external world on cortical networks. On the other side of the continuum would be, for example, intense focus during batting at a baseball game. During this time, very little inward thought would occur compared to daydreaming.)

According to the target article, intrinsic activation is present and underlying, and external input only constrains the underlying excitation; therefore, any reduction of afferent stimuli should lead to an increase in weighting of internally driven thoughts and stimulus patterns. This shift in weighting causes disproportionate amplification of internally driven thoughts and perceptions, thereby bringing them into awareness as hallucinations. This is consistent with the phenomenology of "thoughts becoming audible" (Alpert & Angrist 2003).

Instead of a deficit in gating resulting in sensory flooding and overactivation of the cortex (Adler et al. 1982), I suggest the opposite – namely, that there is less resolution of afferent stimuli from diminished amplification. The following outlines are evidence for this approach.

The reduced N400 wave to incongruent words at the end of a sentence, found in schizophrenic populations, is interpreted as an overly broad lexical search (Mathalon et al. 2002). These findings lend support for the proposed hypothesis and reflect the signal-to-noise and time-dependent manner of activation in cortical networks. In indirect priming paradigms, priming is facilitated at short Stimulus Onset Asynchrony (SOA) and is reduced at longer intervals for schizophrenic subjects. In contrast, normal subjects' results show that priming is facilitated at longer SOAs and is reduced at shorter SOAs. This has been interpreted as diffuse activation in the semantic maps (semantic loosening), which returns to baseline levels in a shorter time frame in schizophrenics compared with controls (Mathalon et al. 2002; Spitzer 1997).

Because increased constriction of a semantic concept will increase the time the concept stays activated, the same should hold true for lower-level functioning related to external input. Compatible with this viewpoint, and an alternative interpretation of the reduced P50 ratio found in schizophrenia patients, is that it reflects a loss of short-term sensory memory. I posit that, as a result of the reduced amplification shifting the locus of attention inward, the excitation caused by the first click does not reach a critical activation threshold to sustain its activation pattern across the temporal gap. When the second click is introduced, the reduced P50 ratio reflects the decay of activation and "forgetting" of the previous stimuli, and therefore no inhibition is necessary. The difference found between schizophrenics and normal subjects has been eliminated in two different task manipulations, compared to the standard 500-msec interval approach. The first one varied the time interval and found that at 75 msec (Nagamoto et al. 1989), 750 msec, and 1000 msec (Dolu et al. 2001) no differences were found. For the 75-msec condition, gating occurred, and for the 750-msec and 1000-msec intervals, gating did not occur for patients or controls. In the 75-msec task, the latency was short enough for the stimulus to remain active, whereas for the 750-msec and 1000-msec tasks, the activation of both the controls and patients had already dissipated. The second study found no difference in gating when the click presentation was of 10 msec duration (Guterman & Josiassen 1994), suggesting that the stimulus intensity reached a threshold to remain active for the schizophrenia patients.

The lower amplitude of the P50 wave in schizophrenia patients, compared to first-degree relatives and controls (Freedman et al. 1983), can be interpreted within this hypothesis as being reduced amplification. Studies have shown that the P50's amplitude can be manipulated by stimulus intensity. Ninomiya et al. (2000) report that an increase in decibels (up to 85 db) increases the amplitude, whereas another study found increased amplitude to the human voice from multiple band frequencies to recruit more of the cortex (Chen et al. 1997). These findings reflect the variability related to stimulus intensity and time. Caution should be used when interpreting the reduced P50 ratio in schizophrenia patients as being solely a deficit in gating. Further studies that vary intensity and time intervals are needed to elucidate this variability.

Finally, because a diminished P50 ratio is found in both patients and their first-degree relatives, as well as the relatives who do not have the reduced P50 amplitude (Clementz et al. 1998), this finding can be inferred to indicate a greater shift toward the internal on the continuum of attentional locus during active psychosis, reflecting the vulnerability of the relatives.

Deficits in visual backward-masking (VBM) tasks found in schizophrenia patients are thought to result from an interruption of the first mask because of an overactive transient channel (Butler et al. 2002). Consistent with the target article's view that the first mask failed to engage gamma oscillations is the finding that reduced amplification of the first stimulus results in a more rapidly decaying activation pattern that is more easily interrupted by the mask. Because the effects of VBM can be manipulated by intensity, luminance, and time (Butler et al. 2002), just like the amplitude of the P50, the assumptions that the findings infer gating deficits in schizophrenia have to be questioned.

This novel theory would predict a global reduction in high-frequency gamma waves induced by stimuli. Evidence for this deficit is outlined in Phillips and Silverstein's (2003) theory on impairment in cognitive coordination, which results from NMDA-receptor hypofunctioning reducing gamma-wave synchronization. The main effect of reduced synchronization is contextual ambiguity and thought disorganization.

The target article offers an integrative approach to psychosis and hallucinations, combining findings from psychophysical and behavioral measures. Because the brain works as an integrative system, it seems that psychosis can emerge from a dysfunction of gating, the balance between excitation and inhibition, or structures that play central roles in modulating and integrating information.

Getting real about experience

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Abstract: The idea that experience is essentially subjective rather than of the real world is paradoxical and deeply flawed. The external world is, much more than a mere constraint, essential to meaningfully describe experience and neural activity. This is illustrated by an analysis of the phenomenology of veridical perception and by the study of experience in psychopathology by the Experience Sampling Method (ESM).

Behrendt & Young (B&Y) must be complemented for the well-documented development of their case. It is unfortunate, however, that the philosophical framework that holds together their effort is deeply problematic, even fatally flawed. The idea that experience

is fundamentally subjective, and merely *constrained* by external reality should be seen as a can of worms rather than as a promising starting point for empirical and theoretical scientific research. Perhaps, most fundamentally, its truth would paradoxically imply that it could not be stated: How would we know about the constraining role of external reality if all of experience were subjective? More concretely, how could subjective experiences be externalized in "virtual space" if there were nothing either external or spatial – that is, if the concepts of externality and space really referred to nothing at all? Similarly, what would experience be of, if it were "merely subjective"? What are these "subjective items" that constitute subjectivity? The authors assume that the experienced world emerges from autonomous neural activity, without providing any explanation for how autonomous neural activity could ever give rise to the experience of a real world in all its infinite variety.

The infelicitous implications of their philosophical foundations manifest themselves throughout the article. An example can be found in the discussion of how to account for the (presumed) phenomenology of hallucinatory experiences. Cognitive theories are criticized for explaining this in terms of a misattribution to external reality. According to the authors, this move is insufficient because it is doubtful that just a misattribution to external origin could transform thoughts or mental images into perceptual experiences. Whatever the merits of cognitivism, it seems in any case to have an explanatory advantage over B&Y's theory. While cognitivism has at least *some* explanation for the phenomenology of hallucinations, the authors have none. They simply propose to put hallucinations in the same bag as veridical perceptions, and take both as a kind of primitive. Someone who has no explanation for A & B is simply not in a position to criticize someone else for not having an explanation for B. This is not to say that we think the cognitivist explanation should be endorsed. On the contrary, we think it suffers, though in a milder way, from the same deficiency as the target article: the overemphasis of factors purely "in the head" of subjects, whereas a more fruitful strategy would be to look for how subjects interact with the environment out there.

Experiential phenomenology can only be accounted for in terms of a description of person/environment interaction. The specifics of the external context as it is interacted with, are necessary ingredients in any attempt to make sense of the mental, as well as the neurophysiological. This can be illustrated with respect to the phenomenology of veridical experience. Veridical experience has the phenomenology of being confronted with a real world because it is a specific kind of interaction with that environment. Two crucial aspects necessary to account for this feeling of "presence" are what have been called "bodiliness" and "grabbiness" (Myin & O'Regan 2002; O'Regan & Noë 2001; O'Regan et al., in press). "Bodiliness" refers to the fact that, in perception, every change in bodily position gives rise to perceptual changes, whereas "grabbiness" refers to the complementary aspect – that is, in the prototypical perceptual situation, every change in what's being perceived will attract the perceiver's attention. Bodiliness and grabbiness thus define the uniquely perceptual condition in which a perceiver and the perceived environment are so closely knit together that any change in the one has immediate effects on the other. Thus, the notions of bodiliness and grabbiness provide for an explanation where the authors have none; yet, unlike the rather shallow cognitivist explanation, this explanation crucially involves the specific ways in which the perceiver interacts with the environment.

Now, to get a real grip on hallucination, on how precisely it is similar to and differs from veridical perception: hallucinations should likewise be taken seriously as contextually situated in and constitutively articulated (rather than merely *constrained*!) by that context. In an ongoing research effort, one of us (I. M.-G.), is showing how fruitful the contextually situated study of subjective experience in psychopathology can be. The Experience Sampling Method (ESM), a structured diary technique to assess thoughts, mood, and context in daily life, is being used to study the interaction between context and psychopathology (Myin-Germeys et al. 2001b). It has been demonstrated that small daily stresses in everyday life have a direct effect on psychosis intensity (both hallucinations and delusions) in subjects at increased risk for onset (first-degree relatives) and relapse (patients in a clinical state of remission) of psychosis (Myin-Germeys et al., submitted). In a study of hallucinations and delusions in currently ill patients with psychosis, it was found that the intensity of both delusions and hallucinations changes from moment to moment (Delespaul et al. 2002). These changes were directly related to contextual features. For hallucinations, it was clear that the specifics of the context modified hallucination intensity. Social withdrawal resulted in a decrease of hallucinatory intensity, whereas social engagement slightly raised intensity levels. Not being involved in an activity at all or doing work-related activities led to decreases in intensity over time, whereas passive leisure activities such as watching TV resulted in increases in intensity levels of hallucinations. For delusions, again several very specific contexts were found that were involved in the onset of a delusional moment (Myin-Germeys et al. 2001a). The presence of family or acquaintances decreased the risk of subsequently experiencing a delusional moment, whereas withdrawal from activities increased the risk of experiencing a delusional moment. These results suggest that psychopathology is deeply contextual, and, rather than unexplainedly arising from strictly neural dynamics, is a function of the sense or meaning of the situation a person finds herself faced with.

In other words, we claim that only a contextually sensitive method such as ESM is able to provide a grip on the phenomenology in all its variability and real complexity. The context of experience is richly *articulate*d – indeed it has the richness of the world, as it *is* the world – and it is richly *articulating*, as testified by the ESM results on the impact of the nature of the task involved and the identity of the persons present on delusions. Reducing the environmental influence to that of a "mere constraint" seems unhelpful and of breathtaking simplicity.

Finally, it should be noted that studying experience in its worldly context provides the framework without which it is impossible to understand neurophysiological data. Purely neuroscientific description can only be meaningfully interpreted and seen as relevant to the study of psychopathology in terms of the role neurally described events play in specifics of the person/environment interaction. Psychopathology is primarily a problem that we care about because it affects a person's abilities to deal with his or her environment, rather than because it is some way in which neural processes go astray. We should not exclusively try to understand the personal in terms of the neural, but often, rather, the other way around (Myin 2004).

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Belief in the primacy of fantasy is misleading and unnecessary

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Abstract: We can live in fantasy only if we survive in reality. Visual experience that carries information about the real world – that is, normal perception – serves that goal. Normal perception is not merely constrained hallucination, and it can usually be distinguished from internally generated images, with which it is rarely confused. Modulatory processes, such as attention, do indeed affect most levels of perceptual processing, but they do so without invalidating the transmission of the signals that they modulate.

The only hallucination of which I have much personal knowledge is dream imagery. Upon waking, it does sometimes seem to me

that the dream had all the richness of normal perception, but I do not then mistake the clouds that I see out of the window for dreams or any other form of imagery. I see the rich, evanescent, and unpredictable forms that they appear to take, and know that I did not and could not imagine them. Why do I have such confidence, when I have never had any independent validation of the reality of perceived cloud forms? It is because, in cases where the things perceived are more accessible, the senses are constantly providing information about things that could not have been predicted and which (i.e., the information) is then confirmed by further action. Behrendt & Young (B&Y) say that normal perception ensues only if the pattern of sensory input matches the pattern of pre-activation provided by prefrontal attentional mechanisms. I do not see how they can look at the clouds and justify that view. Of course, my conscious experience is not of water droplets, and even less is it of the counterintuitive entities of subatomic physics, but that in no way implies that I can predict the images that clouds help form on my retina.

I am as sceptical of the richness of my own dream imagery as I am of the claims of others to have such richly detailed images. This is in part because for several years I studied visual imagery using a simple change detection paradigm that directly compared sensory storage (SS) with a basic form of imagery, that is, short-term visual memory (STVM; Phillips 1974; 1983). Many studies using many subjects showed unequivocally that the amount that can be voluntarily held in mind, even for only a few seconds, is many orders of magnitude less than that which vision delivers and which survives briefly in SS. Studies of change blindness (Rensink 2002; Simons & Levin 1997) show that these severe capacity limitations on internal representations apply also to natural scenes. A host of neurobiological and psychophysical studies confirms the everyday impression that our visual systems are designed to convey an enormous amount of information about the world. The huge channel capacity required is costly, both anatomically and energetically, and this cost is borne because it greatly enhances our adaptation to the real world. Imagination can do so too, but I do not see the need for it to operate at such a detailed level, nor do I know of any unequivocal evidence that it does. My working assumption is therefore that I can imagine something as having detail, without imagining the detail that it has.

What then of the descending pathways, which in channel capacity clearly rival the feed-forward pathways? Evidence that B&Y review, and plenty more, shows modulatory interactions to be widespread, but what kind of interaction are they and what do they do? One common view is that they increase the salience of relevant signals. This view can be made formally precise (e.g., Kay et al. 1998; Smyth et al. 1996), and can be related in detail to both neurophysiology (Phillips & Singer 1997) and psychopathology (Phillips & Silverstein 2003). This view of modulation requires the prior existence of signals to be modulated, however. B&Y seem to have a different conception in that they present modulation as something that can itself create images. Prima facie this seems highly counterproductive. For example, if attentional processes themselves generate images, then things searched for will be seen everywhere, and never found. It would therefore be helpful if the authors clarified their concept of modulation. Is it essentially the same as ours or not? If it is, then perhaps they emphasize noise because that might provide the prior signals on which modulatory processes operate. Such an argument does not require a belief in the primacy of fantasy, however. Indeed, it implies that the normal function of modulation is not to generate hallucinations but to increase the salience of signals that transmit information about the environment and which are relevant to the context within which they occur.

How then can I explain my richly detailed dream experiences and reports of such experiences by others? One possibility is that the reports are valid. We might then try to explain them as occurring when episodic and semantic memory are used to create vague, schematic scenes, which somehow are then filled-in with a rich array of details by selective enhancement of noise in lower-level corticothalamic pathways. Though this seems to me to be a defensible view, I do not see how it is in any way necessary. Another possibility seems to me more likely: that reports of highly detailed images are invalid. I thought that psychology learned long ago that although introspective reports may provide data worth explaining, they cannot be taken at face value as valid descriptions of internal mental processes (Dennett 1991; O'Regan & Noe 2001). Years of studying imagery using students have indicated to me that ratings of detail and vividness are highly unreliable, easily changed, and little related to objective performance measures. They are likely to be even less reliable in reports of hallucinations, which may differ in some fundamental ways from normal percepts, even though these differences are not a prominent part of the experience. Belief in the essential equivalence of hallucinations and valid perceptions may therefore be misleading, in that it could discourage therapies that aim to enhance their discrimination. Throughout their article B&Y seem to assume that reports of internally generated images can be taken at face value, and require no further validation or test. I do not see how this naive introspectionism can be justified.

It might be thought that no validation of internal imagery is possible, so we must either accept naive introspectionism or ignore the data altogether. Not so. We cannot argue that we must accept the truth of an introspective report simply because we have no way of testing it! Methods for objectively studying imagery are therefore needed. Showing that some aspect of reported content correlates with brain activity or behaviour will not do. I do not doubt that images have content. What I doubt is that they have such a richness of detail that it makes them essentially equivalent to normal percepts. Though they were not studies of hallucination, my studies of STVM are among many showing that the richness of detail in images can be tested. The paradigm I used could be applied to at least some of the hallucinatory experience to which B&Y refer. Included in the hallucinatory phenomenology described by Santhouse et al. (2000) is visual perseveration, where patients report continuing to see veridical objects or patterns after looking away. If even only one such patient is shown to have the ability to detect changes comparable to those reflecting the high capacity for sensory storage that we all have, but lasting much longer and after having looked at other things, I will recant in amazement.

Underconstrained thalamic activation + underconstrained top-down modulation of cortical input processing = underconstrained perceptions

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Abstract: Behrendt & Young's (B&Y's) theory offers a potentially important perspective on the neurobiology of schizophrenia, but it remains incomplete. In addition to bottom-up contributions, such as those associated with disturbances in sensory constraints on cognitive processes, a comprehensive model requires the integration of the consequences of abnormal top-down modulation of input processing for the evolution of "underconstrained" perceptions. Dysfunctional cholinergic modulation of input functions represents a necessary mechanism for the generation of false perceptions.

Behrendt & Young's (B&Y's) theory requires expansion to include integration of abnormal top-down effects on cortical input processing. The contribution of an abnormally reactive cortical cholinergic input system in schizophrenia to the defective augmentation and filtering of thalamic inputs is arguably a necessary component of a neurocognitive hypothesis of the positive symptoms of schizophrenia.

The proposed loss of sensory-driven, bottom-up constraints on cortical/cognitive processing is intriguing, and is consistent with classical findings on the effects of severe sensory deprivation (Zubek 1969). The functional role of gamma frequency rhythms in cognition is far from settled, however, and the literature concerning gamma-frequency rhythms in schizophrenics is far more complex than the authors suggest (e.g., Lee et al. 2003). Nevertheless, the proposed defect in sensory constraints over cognitive processes is worthy of consideration. But a comprehensive model of schizophrenic symptomatology necessitates an additional class of top-down processes.

A central, and indeed signature, feature of schizophrenia is a fundamental disturbance in attentional processes. The available evidence, based on experiments assessing the effects of selective cortical cholinergic deafferentation and performance-associated cortical acetylcholine (ACh) release, conclusively indicates that the cortical cholinergic input system is necessary for the mediation of a wide range of attentional abilities (Arnold et al. 2002; Chiba et al. 1995; Everitt & Robbins 1997; McGaughy et al. 1996; Passetti et al. 2000; Sarter & Bruno 1997; 2000; Sarter et al. 2001; Turchi & Sarter 1997; 2000). In the cortex, ACh amplifies the processing of thalamic inputs and also suppresses cortico-cortical (or associational) throughput (Donoghue & Carroll 1987; Dykes 1997; Edeline 2003; Hars et al. 1993; Hasselmo & Bower 1992; Hasselmo & McGaughy 2004; Hsieh et al. 2000; Metherate & Ashe 1993; Metherate & Weinberger 1990; Murphy & Sillito 1991; Tremblay et al. 1990a; 1990b; Webster et al. 1991; Weinberger 2003). Presumably, these cholinergic mechanisms underlie behavioral findings such as the selectively disruptive effects of the loss of cortical cholinergic inputs on performance in signal trials in attention tasks (McGaughy et al. 1996).

The basal forebrain corticopetal cholinergic system (of which the nucleus basalis of Meynert represents only one of several regions that form this ascending projection system) mediates both bottom-up (Berntson et al. 1998; 2003a; 2003b; 2003c) and top-down (Sarter et al. 2001) modulation of input processing in attentional contexts. Top-down effects, reflecting the cognitive modulation of input processing, are mediated in part via cholinergic inputs to the prefrontal cortex, which in turn influence basal forebrain neurons (Sarter & Bruno 2002) and, via multisynaptic cortico-cortical innervation of cholinergic terminals, cortical cholinergic activity as well (Nelson et al., in press). Thus, abnormal regulation of the basal forebrain corticopetal cholinergic system has enormous consequences for the attentional modulation of input processing.

Although the current evidence indicating an abnormal regulation of cortical cholinergic inputs in schizophrenia is still limited, a reduction in muscarinic receptor densities has been reported in several post mortem studies (Crook et al. 2000; 2001; Mancama et al. 2003) and by single photon emission computed tomography (SPECT) in medication-free patients (Raedler et al. 2003). The latter study also reported a significant correlation between muscarinic receptor availability and positive symptoms. The interpretation of these data is not straightforward, but these findings correspond with other evidence and conceptualizations that collectively point to an abnormally reactive cortical cholinergic input system in schizophrenia (Hyde & Crook 2001; Sarter 1994; Sarter et al. 1999; 2005; Tandon et al. 1999). For example, chronic (accidental) cholinesterase inhibition yields psychotic symptoms (Bowers et al. 1964; Gershon & Shaw 1961). Furthermore, repeated exposure to amphetamine models the mesolimbic hyperdopaminergic transmission that is a hallmark of psychosis (Laruelle & Abi-Dargham 1999) and remains one of the more productive animal models of schizophrenia (Robinson & Becker 1986). Relevant to the current thesis, repeated amphetamine exposure has also been shown to sensitize cortical ACh release (Nelson et al. 2000). Abnormal increases in cortical ACh efflux are normalized by systemic or intra-accumbens administration of antipsychotic drugs (Moore et al. 1999). These and other data supported the general hypothesis that abnormal activity of cortical cholinergic inputs is a necessary correlate of abnormal mesolimbic dopaminergic transmission (see also Gerber et al. 2001) and that antipsychotic drug treatments act, at least in part, by normalizing the activity of cortical cholinergic transmission (Sarter 1994; Sarter et al. 1999; 2005).

An abnormal reactivity of basal forebrain cholinergic efferents (which may include the projections to the reticular thalamus) impacts the bottom-up and top-down modulation of stimulus processing in attention contexts. Theoretically, the exaggerated processing of normally filtered stimuli may constitute the primary effect of a dysregulated cortical cholinergic input system. Indeed, manipulations that disinhibit this neuronal system resulted in impairments in the performance of animals in non-signal trials of an operant sustained attention task (Deller & Sarter 1998; Holley et al. 1995; Turchi & Sarter 2001), likely reflecting an elaborated processing of non-signal information.

In interaction with an underconstrained thalamocortical input system, as proposed by B&Y, the contributions of an abnormally regulated cortical cholinergic input system to the formation of "false perceptions" could be even more fundamental. If cortical input processing is characterized by limited sensory information, top-down mechanisms would be expected to become more influential (see also Yu & Dayan 2002). Thus, abnormally strong, cholinergically mediated top-down effects may increasingly dominate the perceptual process. However, as the impairments in executive capacities escalate in schizophrenic patients, top-down mechanisms become increasingly dysregulated, eventually yielding a functional disconnection between prefrontal activity and the cholinergic modulation of input functions elsewhere in the cortex. Such a disconnection may be critical for the development of source monitoring problems (Frith & Dolan 1996; Johnson 1997) and thus for the emergence of false perceptions.

Forty years ago, Venables classified schizophrenia as an input dysfunction (Venables 1964). The disruption of thalamocortical information processing and the top-down modulation of cortical input processing appear to represent two necessary mechanisms yielding input dysfunctions. For insufficient sensory information to evolve into an underconstrained perception, abnormal augmentation and defective filtering are necessary mechanisms, and they are likely mediated, at least in part, via a dysregulated cortical cholinergic input system.

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Schizophrenia: A disorder of affective consciousness

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Abstract: Behrendt & Young (B&Y) propose an explanation for schizophrenia in terms of a *cortical* default in the interaction between consciousness and cognition. However, schizophrenia more likely involves miscommunication between subcortical and cortical affective circuits in the brain, a default in the interaction between consciousness and emotion. The typical "affective" nature of hallucinations in schizophrenia provides compelling evidence for *subcortical* involvement.

According to neurocognitive interpretations, hallucinations in schizophrenia result from cortical attentional mechanisms producing conscious experiences unconstrained by actual sensory input (B&Y). It has been argued that functional abnormalities in gating information streams in the brain result in a low signal-to-noise ratio that causes conscious experiences to be derailed (Taylor et al. 2002). Crucially, on the phenomenological level, hallucinations

are characterized by affective content; therefore, a cognitive framework of hallucinations does not come up to the mark. The tendency to link consciousness to cognition has led to definitions of consciousness that leave out any reference to meaning, emotion, and qualia. In these theoretical accounts, the neural correlate of consciousness (NCC) is suggested to involve widely distributed thalamo-cortico-cortical networks preferably resonating at gamma frequency rhythms. Gamma frequency oscillations and synchronization occur in the visual cortex after the detection of scenes, such as randomly moving dots. But is the detection of these meaningless scenes not a misadaptation supervening on the incapability of the visual-attentional system to shut down when nothing of interest is happening? Consciousness cannot be equated with such epiphenomenal forms of detection, but probably defensibly evolved to provide for more flexibility in social-emotional contexts, which are packed with meaning and stuffed with raw feelings – that is, qualia and emotions (Buck 1999; Ressler 2004; Schutter & Van Honk 2004a). This is exactly why hallucinations in schizophrenia carry their typical affective tone, as described by B&Y. The authors nevertheless discuss schizophrenia as a disorder of consciousness and cognition, and not primarily as a mood disorder. This is somewhat surprising, because schizophrenics have hallucinations with a strong negative affective content, and it is precisely this content which constitutes the essence of their suffering, because it makes them anxious, depressive, and suicidal (Meltzer & Fatemi 1995). B&Y, on the other hand, suggest that schizophrenia is often preceded by social anxiety and that schizophrenic hallucinations (not unexpectedly) often relate to social fear. Although the comorbidity between schizophrenia and social anxiety has been established (Pallanti et al. 2004), it does not fit with B&Y's reasoning that mood or emotion disturbances are only secondary to schizophrenia. Perhaps more on the right track, Lane (2003) recently argued that the core feature of schizophrenia is a deficit in affective function. In agreement, neuroimaging findings have provided evidence for the notion that the complex nature of affective abnormalities in schizophrenia is indeed associated with processing difficulties in subcortical emotion circuits (Paradiso et al. 2003).

In sum, the traditional cognitive-oriented explanations of consciousness and hallucinations emphasize thalamocortical architectures, whereas the affective-oriented interpretations stress the involvement of subcortical brain regions (Damasio 1999; Panksepp 1998). The subcortical structures generate the primary motivational and emotional drives and the cortical mantle is argued to internally represent and control the afferent subcortical information streams (Phillips et al. 2003; Schutter & Van Honk 2004b). Schizophrenia arguably finds its source on the subcortical level and, in particular, subcortical dysfunction that overrides cortical regulation might be the core brain deficit (Grossberg 2000). It is only on the cortical level that emotion and cognition interact; therefore it is not the affective, but the cognitive, deficit that is secondary to schizophrenia. The morphological brain abnormalities in schizophrenia that have been demonstrated in subcortical affective circuits (e.g., Sanfilipo et al. 2000) add further evidence to the notion that schizophrenia is primarily a disorder of emotion. In particular, positive symptoms in schizophrenia, which include hallucinations and delusions with negative affective content, can be explained in terms of defective cortical–subcortical interaction. The often affect-laden content of hallucinations and delusions arguably points at a cortical malfunction in the effective modulation of subcortical affective output. Moreover, this notion fits with findings of cortical hypoactivity and limbic hyperactivity in schizophrenia (Davis et al. 1991). Furthermore, recent findings by Epstein et al. (1999) suggest that positive symptoms are associated with increased mesotemporal and striatal activity in the context of decreased prefrontal activity. In particular, the amygdalar formation located in the mesotemporal region is argued to contribute to the affective nature of psychoses (Taylor et al. 2002).

According to B&Y, consciousness arguably involves constraining and fusing sensory input through prefrontal modulations. The lack of cortical control over the affective subcortical circuits may consequently manifest itself in a maelstrom of interoceptive and exteroceptive information left unbounded by prefrontal regulation. The inability to fit the perceptual input with the necessary internal schemata is suggested to lead to the positive symptomatology in schizophrenia (Kaprinis et al. 2002). From the functional neuroanatomical perspective, schizophrenia has also been described as a "misconnection" syndrome (Andreasen 1999), which refers to defective functional connectivity in the brain (Paradiso et al. 2003). Loss of executive frontal function might result in a derailment of cognitive processes, termed "cognitive dysmetria" (Andreasen 1999), but we mean to argue that perhaps it is better to use the term "affective dysmetria." Although consciousness and cognition are argued to stem from the higher cortical brain areas, they are both built on primordial motivational and emotional drives seated in the limbic system (Panksepp 1998). The hierarchical brain architecture implies an important role for affect in relation to consciousness, cognition, and psychopathology (Maclean 1990). Therefore, B&Y's cognitive explanation of consciousness and hallucinations in schizophrenia can in no way account for the emotional abnormalities observed in schizophrenia. Emotion is not merely the coloring of cognitive information processing or part of cognition, but rather is the essence of our processing system that controls consciousness and cognition (Damasio 1994).

We conclude that schizophrenia is a disorder of affective consciousness involving subcortically driven dysfunctional cortico–limbic interaction and accompanied by secondary cortical abnormalities in conscious aspects of cognition.

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Distinguishing schizophrenia from the mechanisms underlying hallucinations

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Abstract: This commentary challenges the argument that the diathesis for hallucinations is equivalent to that for schizophrenia. Evidence against this comes from data on the prevalence of hallucinations in schizophrenia, their nonspecificity, and their relationships with moderating variables. We also highlight, however, the manner in which the Behrendt & Young (B&Y) hypothesis extends recent neuroscientific theories of schizophrenia, and its potential treatment applications.

Behrendt & Young (B&Y) propose a theory of hallucinations that departs greatly from traditional views of this symptom, especially as applied to mental illness. On the other hand, some of its basic assumptions are consistent with current neuroscientific theories of schizophrenia. There are also several areas where the theory is either incomplete or unable to account for existing data. In this commentary, we will consider three issues: (1) the consistency of the authors' argument with our recently proposed view of cognitive coordination failures in schizophrenia; (2) general strengths of the article, especially in terms of applications to schizophrenia treatment; and (3) weaknesses of the theory for understanding schizophrenia.

B&Y's focus on abnormalities involving gamma-oscillations in schizophrenia is consistent with our recently proposed theory (Phillips & Silverstein 2003), which focuses on NMDA receptor hypofunction as the basis for reduced context-based cognitive coordination, and therefore as the basis of multiple forms of disorga-

nization in schizophrenia (e.g., in perception, language, motor activity). The authors' concentration on hallucinations and consciousness goes beyond our focus on multiple manifestations of disorganization, and demonstrates the power of applying a model involving disturbed gamma-phase oscillations to other aspects of the illness. Similarly, their concentration on thalamic involvement in gamma-phase synchrony goes beyond our focus on local corticocortical circuitry found throughout the cortex. We suggested that other parts of the brain were likely to be involved and that the thalamus could provide the precise timing signals necessary for the binding of network activity, but this target article more clearly describes a role for subcortical structures. In addition, the authors' focus on the relationship between arousal and the onset of processing disturbances that could lead to hallucinations, and the roles of noradrenaline and acetylcholine in this process, demonstrates how disturbances in coordination can result from a cascade of events involving neurotransmitters other than dopamine and glutamate.

A general strength of the target article is that it emphasizes mechanisms hypothesized to be common to both "normal" perception and hallucinations, as well as specifying what factors lead to the emergence of the latter. This is similar to work being done regarding delusions, which views them as extreme forms of normal beliefs, as opposed to being discontinuous with normal experience, which has been the traditional view of positive symptoms for many years (Jaspers 1916/1963). The reconceptualization of the nature of delusions has formed the basis for successful cognitive-behavioral therapies, involving cognitive reframing techniques, for delusions, paranoid ideation, and distress secondary to hearing hallucinated voices (Chadwick et al. 1996; Kingdon & Turkington 1994). B&Y's thesis, if supported by future research, could provide a normalizing rationale for hallucinations that could greatly assist in psycho-educational and cognitive-behavioral treatment of this symptom. Another strength of the article is the recognition (in sect. 2) that hallucinations are unlikely to be simply thoughts or inner speech that are misattributed to an external origin. In suggesting that the key mechanism involves a deficient balance between the processing of external and internal stimuli rather than simply faulty self-monitoring, B&Y are laying the groundwork for a paradigm shift in how hallucinations are understood and studied. We believe this is important because it is unlikely that all phenomena in schizophrenia can be accounted for simply in terms of executive/frontal lobe dysfunction (Phillips & Silverstein 2003), which is thought to underlie self-monitoring (Turken et al. 2003).

Despite these strengths, B&Y's thesis suffers from at least three weaknesses. First, a central problem with this article is its reliance for its theory of schizophrenia on a theory of hallucinations. This is a problem because only approximately 60% of schizophrenia patients ever have auditory hallucinations, and only approximately 30% ever have visual hallucinations (Slade & Bentall 1988). Other types of hallucinations are rare in schizophrenia. If all schizophrenia patients had some form of hallucination at some point, but not at others (i.e., during the stable phase), then this theory could still hold because it could be argued that the diathesis for hallucinations is always there but that hallucinations only emerge under extreme stress or some other state factor. But, when up to one-third of patients do not have the symptom at all, ever, it seems strained to equate the diathesis for the symptom with the basis of the illness (as in sect. 2.1). Moreover, high rates of hallucinations can be found in other psychiatric disorders. In addition to the well-known findings of hallucinations in bipolar disorder and psychotic depression, high rates of hallucinations have been found in people with histories of child sexual abuse and post-traumatic stress disorder (Morrison et al. 2003; Read & Argyle 1999). Moreover, one study found a high rate (84%) of having had auditory hallucinations among mental health nurses (Milham & Easton 1998). These findings cast doubt on the hypothesis that the essence of schizophrenia is equivalent to the predisposition to develop hallucinations. Interestingly, they also support Bleuler's (1911/1950) seminal view that hallucinations should be considered an "accessory" (as opposed to "fundamental") symptom of schizophrenia.

Second, the argument that verbal hallucinations are more likely to occur in people with mental illness resulting from a combination of a predisposition to develop hallucinations and enduring social anxiety and interpersonal difficulties is problematic in several respects. First, positive symptoms, including hallucinations, are more likely to occur in schizophrenia patients with histories of good premorbid social functioning, whereas other features are characteristic of patients with poor premorbid social functioning (Ross et al. 1994). In addition, the idea that people with mental illness who develop hallucinations are more likely to develop auditory hallucinations is not supported by the evidence from substance abusers, where the prevalence of visual hallucinations is often greater than the prevalence of auditory hallucinations, even though the drugs used are thought to act on the same neurotransmitter systems that are involved in schizophrenia (e.g., amphetamines – dopamine, PCP/ketamine – glutamate; LSD – serotonin). Finally, the issue of moderating variables, exemplified by findings such as the greater incidence of hallucinations in female schizophrenia patients (Sharma et al. 1999), and the decrease in hallucinations as schizophrenia patients age (Schultz et al. 1997) are not addressed by B&Y's theory.

Third, the hypothesis (in sect. 2) that other symptoms of acute psychosis (e.g., thought disturbance, self-experience disturbance) are secondary to hallucinations is not supported by evidence. In contrast, disturbances of self-experience often precede the initial psychotic episode (Klosterkotter 1992), and can also be found in schizoid personality disorder, in which hallucinations are rare (Sass 1992).

In short, although B&Y have put forward an interesting theory of hallucinations, and one that may prove to be of value in understanding schizophrenia, this is not the same as proposing a theory of schizophrenia. In our view, it is unlikely that a single dysfunction can adequately account for all cases of schizophrenia. We also consider it unlikely that, if such a core deficit is found, it will be linked to only one symptom. We and others (e.g., Cohen & Servan-Schreiber 1992; Gray et al. 1991) have proposed views in which disturbances of circuitry can account for multiple phenomena in schizophrenia. However, even in these cases, both theory and data link these disturbances to specific symptom clusters (Barch et al. 2003; Phillips & Silverstein 2003) and do not try to account for all cases. Moreover, neuropsychological and imaging studies indicate that even the most robust deficits in schizophrenia research are rarely found in more than one-third of patients (Heinrichs 2001). Because hallucinations are found in a majority of patients, however, and because schizophrenia treatment involves reducing symptoms (as opposed to being curative), it is imperative that we move forward in our understanding of how these symptoms arise and how they can be reduced. B&Y have provided an important step in this direction.

Brainstem-thalamic neurons implicated in hallucinations

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Abstract: I propose that hyperactivity (or increased numbers) of neurons in the brainstem reticular core promote hallucinations by excessive excitation, coupled with disinhibition, of target thalamocortical neurons. This idea stems from animal experiments using kainate-induced overexcitation of midbrain reticular neurons leading to hallucinatory-type behavior during wakefulness, as well as from data in schizophrenic patients showing an increased number of neurons in mesopontine cholinergic neurons.

The article by Behrendt & Young (B&Y) has the merit of discussing neuronal operations in the circuitry of thalamocortical systems to explain the signs of a major psychiatric disturbance. Such

an attempt is in line with other recent studies that challenged some obsolete beliefs that avoided considering the brain as somehow implicated in the psyche and its disorders.

I would only briefly comment on some points in the opening discussion of the target article, namely, the dilemma of whether hallucinations essentially differ from or, on the contrary, are equivalent with, normal perceptions, which relates to the idea that dreaming mentation in rapid-eye-movement (REM) sleep is fundamentally similar to conscious processes in wakefulness. The latter hypothesis was based on some characteristics of brain electrical activity in both of these brain-activated states. However, when we transcend this apparent commonality and use intracellular recordings from cortical neurons in behaving animals, a clear-cut distinction between waking and REM sleep becomes obvious, emphasizing the differences between these two polar states of vigilance on both physiological and psychological grounds. Thus, periods of inhibition in cortical neurons, which are present during the adaptive state of wakefulness when incoming signals should be tuned and discriminated, are overwhelmed by strong excitatory inputs from subcortical structures during REM sleep. As well, ocular saccades associated with forebrain events during REM sleep, "the stuff that dreams are made of," are associated with peculiar changes in membrane properties and synaptic potentials of cortical neurons, which are not detectable during waking (Steriade et al. 2001; Timofeev et al. 2001). Lastly, a series of monoamine-containing neurons are active during waking but virtually silent during REM sleep, which might account for the bizarre content of mentation during dreaming.

This commentary addresses the role played by brainstem-thalamic neurons in generating hallucinatory behavior. Our experimental data flesh out the authors' hypothesis of thalamocortical neurons' "up-regulation by cholinergic mechanisms." To begin with, despite the focus on brainstem cholinergic systems, in an attempt to identify chemically coded systems within a structure previously regarded as nonspecific, the brainstem reticular core has many more glutamatergic than cholinergic neurons, and the action of glutamate via metabotropic receptors of thalamocortical neurons is quite similar to that of acetylcholine – namely, the blockade of a given potassium current – thereby leading to excitation of target neurons (Steriade et al. 1997). Then, excessive neuronal excitation was found in behaving cats who had a powerful glutamate analog infused into the upper midbrain reticular formation, at which level there are virtually no cholinergic cells but mainly glutamatergic neurons; this led to pupillary dilatation, piloerection, an EEG pattern of extreme arousal, and a hallucinatory-type behavior that began in the first hour following the injection (Kitsikis & Steriade 1981). The animals vocalized in an attacking attitude, moved forward as if stalking a prey or moved back as if defending from an imaginary enemy. The interesting point about this hallucinatory-type behavior is that it appeared during the waking state and that it resembled the oneiric, hallucinatory behavior observed during REM sleep in animals after bilateral lesion of the peri-locus coeruleus region, which abolishes muscular atonia during this sleep state (Jouvet & Delorme 1965). Of course the glutamatergic neuronal excitation in the brainstem reticular core could have been extended to mesopontine cholinergic neurons, which generate ponto-geniculo-occipital waves, a corollary of dreaming mentation, through neuronal interactions at this brainstem level (Steriade et al. 1990b).

A related cause of hallucinations may be the presence of highly increased numbers of neurons in schizophrenic patients, compared to control subjects, in mesopontine cholinergic nuclei (Garcia-Rill et al. 1995). Neurons in these cholinergic nuclei project to all thalamic nuclei of cats and primates – that is, sensory, motor, association, intralaminar, and reticular nuclei (Paré et al. 1988; Steriade et al. 1988). Since brainstem cholinergic neurons projecting to the thalamus increase the rates of spontaneous discharges during brain arousal (Steriade et al. 1990a) and produce depolarization and increased excitability of thalamocortical neurons (Curró Dossi et al. 1991), the increased number of brainstem cholinergic neurons in schizophrenia may lead to an increased reactivity to sensory stimuli reaching thalamic neurons. This increased excitability is unrestrained by inhibitory processes. Actually, brainstem cholinergic neurons hyperpolarize (inhibit) thalamic reticular inhibitory neurons that release GABA as neurotransmitter (Hu et al. 1989) and, thus, disinhibit thalamocortical neurons, thereby further exciting them. The discrepant data between Garcia-Rill et al. (1995) and other studies (German et al. 1999) may result from the fact that Garcia-Rill used only brains from schizophrenics who died after 30 years of disease – that is, the worst of the worst cases.

Finally, the idea that fast (beta and gamma) oscillations are related to normal perceptions in waking or hallucinations in REM sleep should be enlarged, taking into consideration that such fast rhythms are also present during slow-wave sleep. Indeed, these oscillations are voltage-dependent and they are superimposed over the depolarizing (excitatory) phase of the slow oscillation in both animals (Steriade et al. 1996) and humans (Mölle et al. 2002). And, congruently, dreaming is not exclusively occurring during REM sleep but is also present during late stages of slow-wave sleep (Hobson & Pace-Schott 2002; Hobson et al. 2000).

Gamma rhythms as liminal operators in sensory processing

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Abstract: Gamma rhythms are associated with external and internal sensory processing. Within the conceptual framework of "top-down" and "bottom-up" processing, this suggests that gamma represents a format common to both camps. As these oscillations facilitate communication in the temporal domain, they may represent a mechanism by which top-down and bottom-up processing can interact. A breakdown in this interaction may lead to hallucinations.

Gamma frequency oscillations are a nearly ubiquitous feature of the brain's electrical response during sensory tasks. In addition, they are seen in the sleeping brain wherein they have been associated with internally generated sensory events such as the dream state (Llinas & Ribary 1993). These associations, and the relative ease of recording gamma oscillations non-invasively in humans has led to a large corpus of literature implicating specific aspects of gamma frequency rhythmogenesis in a number of conceptual frameworks within cognitive psychology. In particular, seminal work from the laboratory of Singer (e.g., Gray et al. 1992) demonstrated a role for gamma frequency rhythms in the active binding of specific features of a sensory object into a perceived whole. However, more recently the lability of gamma band responses in different subjects and under different external sensory paradigms has led to the suggestion that these rhythms may also form part of the brain's internal "cognitive map," or at least be influenced by it (see Karakas et al. 2001). This collision of external (bottom-up) sensory sequelae and internal (top-down) processing provides a current framework within which gamma rhythms are thought to operate. Behrendt & Young (B&Y) argue that an imbalance in these two facets of cognitive processing, favouring top-down events, may underlie the phenomenon of hallucinations.

From a cellular perspective, gamma oscillations are generated by heterogeneous networks of neurons in response to stimulation. Of particular importance are interneurons in cortical structures. This subclass of neuron have synaptic and intrinsic properties, when functioning as a local network, which are ideally suited to the generation of gamma frequency oscillations in principal, projection neurons (Whittington et al. 1995). The lability of interneuronal firing patterns in response to both local and distal synaptic input makes interneuron-mediated rhythms, such as

gamma and beta, ideal for establishing synchrony and stable phase relationships between anatomically disparate brain regions (Traub et al. 1996). Thus, it appears that during these forms of rhythmogenesis it is the relative timing of outputs from multiple brain regions that is critical for interareal communication (Rodriguez et al. 1999). B&Y argue that such interareal communication underlies a "constraining" influence of externally generated (ascending thalamocortical) sensory input on internally generated percepts (cortico-thalamocortical). They state that removal, or disruption, of these external inputs, in an otherwise normal awake state, may provide a model of hallucinosis. Circumstantial evidence for this hypothesis is particularly strong in cases of protracted loss or disruption of input in specific sensory modalities, as the target article shows. However, the situation is less clear in the case of schizophrenia.

In schizophrenia there is some evidence for disrupted thalamocortical function (Popken et al. 2000; Sharp et al. 2001), but the two brain regions where associated pathology is marked (prefrontal and medial temporal cortices) are heavily involved in higher order (presumably top-down) cognitive processing. Loss or change of function in specific subtypes of interneuron in these areas (Volk et al. 2002; Zhang & Reynolds 2002) suggests possible deficits in gamma frequency rhythmogenesis. Medial temporal processing, particularly involving the hippocampus, has been proposed to mediate context versus content computations (Buzsaki 1996). The frontal cortex is preferentially activated with sensory paradigms associated with top-down processing (Kaiser & Lutzenberger 2003) and may be involved in working memory. Persistent gamma oscillations can be seen in both these regions in the absence of external sensory input. Gamma and related oscillations in other cortical areas are also seen in the absence of discrete external sensory input, where they have been implicated in a continuous rehearsal process for expected (compared to actual) subsequent sensory input (Tallon-Baudry et al. 1998). Such attention-related phenomena have been shown to have a marked effect on external sensory-generated gamma rhythms (Tiitinen et al. 1993).

So it appears that interactions between top-down and bottom-up processing can occur in both directions, using gamma rhythms as a common denominator. Evidence for both a failure of external sensory stimuli to generate gamma oscillations in primary sensory cortex, and disruptions in cortico-cortical temporal processing at gamma frequencies have been reported in schizophrenics (Spencer et al. 2003). Thus, although the case for "underconstrained" top-down sensory processing constitutes an attractive hypothesis for hallucinations in primary sensory impairment, in schizophrenia account must be taken of direct disruption of cortico-cortical interactions, as well. In other words, in schizophrenia, any theory involving changes in the interaction between external sensory input and the internal "perceptual world map" must also consider the possibility that this perceptual world map may itself be faulty.

Author's Response

Psychopathology of psychosis: Towards integration from an idealist perspective

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Abstract: The commentators provide a wealth of additional neurobiological data that ought to be integrated in a comprehensive model. This response article, however, focuses on clarification of conceptual queries, thereby outlining the proposed theory of hallucinations more sharply, discussing its relationship with schizophrenia, and explaining why underconstrained thalamocortical activation may well be a candidate mechanism responsible for acute schizophrenic symptoms other than hallucinations.

R1. Subjective experience and objective reality

According to idealism, objects and events that we perceive are creations of the mind and conform to rules of the mind. However, idealism does *not* necessarily imply that an objective physical reality does not exist. To clarify this point, it may be useful to distinguish between two questions: (a) whether an objective physical reality *exists*, and (b) whether the things that we see, feel, or hear around us *are part of* the physical world (Table 1). The philosophical position that acknowledges the existence of a physical reality but nevertheless denies that what we perceive is part of the physical world can be called *transcendental idealism,* adopting Kant's term. Kant did not deny the existence of a physical world but pointed out that human beings have no possibility of knowing what the real world is like. In contrast to solipsism (also called absolute idealism), transcendental idealism acknowledges that *there is a real world out there.* However, the things that we see, hear, or feel are not copies of things in the real world and do not conform to rules of the real world (Kant, as reviewed in Cutting 1997). According to transcendental idealism, it is not the world we see around us but the material constraints beyond it that represent the physical world. In this sense – it could be replied to **Foss** – Kant's transcendental idealism occupies a specific position among the "species" of idealism.

Transcendental idealism must not be confused with solipsism, as **Myin-Germeys & Myin** seem to do. Although everything that we perceive around us is a mental creation, *the mind is not all that there is* (which would be a solipsist or absolute idealist position). There has to be a physical world that is independent of our mind (rather than there being "nothing either external or spatial" **–** Myin-Germeys & Myin) because the perceived world changes consistently across situations and in agreement with learned behaviour. However, it is important to emphasize again that the world, as we perceive it, is principally different from external physical reality and not just a *transformation* of it, as **Foss** suggests. Disagreeing with Foss, "nothing external [is] being seen," indeed. Objects that surround us in the perceived world do not exist in material reality, as they do not exist without us being consciously aware of them. Perceived objects in-

Table R1. *Relationship between conscious experience and a physical world*[a]

Relationship between mind and the physical world	Nature of the world we perceive: The world that we see around us is an objective physical world	Nature of the world we perceive: What we see around us is fundamentally part of the mind
A. There is only a physical world and mental phenomena can ultimately be reduced to it	*Materialism*	
B. Mental phenomena cannot be reduced to the physical world and form a separate realm	*Dualism*	*Transcendental idealism*
C. There is only a realm of the mind and no external physical world		*Solipsism (absolute idealism)*
	Forms of *realism*	Forms of *idealism*

[a]Transcendental idealism can be delineated from other positions on the relationship between conscious experience and physical world by considering two separate questions. First, is the world that we perceive actually the physical world? Second, what is the relationship between the physical world and the mental realm, irrespective of how we answer the first question?

corporate meaning and fundamentally depend on observation – that is, observation of constancy or change over time. The purpose of perception, and the illusion of objective reality that is inherent to it, is to guide behaviour in an external physical world that we cannot "see" itself. The subjectively perceived world only has to be as elaborate and complex as the organism's repertoire of behavioural interactions with the external physical world. Sensory stimulation is crucially important for relating the internally created image of the world to physical reality – to ensure that behavioural interaction with the physical world is adaptive and to avoid that "things searched for will be seen everywhere" (**Phillips**).

It is argued that the nature and phenomenology of hallucinations can be explained more fruitfully within a framework which accepts that both hallucinations and normal perceptions are subjective experiences and products of the mind. Both are projected into a virtual space surrounding oneself; they differ only with respect to the extent to which they are constrained by physical reality. Thus, transcendental idealism shifts the focus from searching for sources of hallucinations and mechanisms of "inner" mental phenomena to considering factors that can lead to a disruption of external constraints normally imposed on perception. There are other implications of transcendental idealism. First, the perceived world is not constructed from sensory information and cannot be reduced to it. Contrary to the realist stance taken by **Phillips**, who regards sensory input as a signal that carries information about the phenomenal world which is modulated but essentially not altered in sensory systems, sensory input should merely be seen as an external factor that influences the internally generated stream of consciousness. Sensory information derived from the external physical world is not even necessary for perceptual experience, as exemplified by the richness and detail of dream imagery. From Phillips's commentary it appears that the realist stance has to be maintained at the expense of doubting the richness of one's own dream imagery.

Second, being generated internally, the world perceived around us is a subjective experience that is fundamentally private to each observer. This implication is "fundamental" (**Foss**) because it is at odds with common sense, and it challenges – at first sight – the notion that we have access to and can communicate about objective physical reality. The implication may be called "paradoxical" but it is not "deeply flawed" (**Myin-Germeys & Myin**). To explain, although everybody lives in a subjective world of his or her own, we share a single world insofar as the individual subjective worlds are constrained by the same imperceptible external physical reality. When two individuals say that they see the same object in front of them, each of them actually sees only a part of his or her mind. Although it could be argued that the objects they externalise into a virtual space around them look very much the same, they do not see the same thing because nobody has access to anybody else's conscious experience. Nevertheless, everyday experience makes us believe that we observe an objective reality that is independent of our presence and observation. Events and objects appear to exist independently of our mind because they can be acted upon and change consistently with behaviour. Moreover, through social interaction the view of the world becomes a subject of inter-individual validation: The world is experienced as being observable to everybody and is therefore believed to be observer-independent. This is how the subjective experience of the perceived world turns into an illusion of objective reality.

To further respond to concerns expressed by **Myin-Ger-**

meyes & Myin, how is it possible to develop scientific knowledge of the external world? Our system of knowledge is of course related to what is out there in physical reality, but when considering facts of knowledge, we never deal with anything that is independent of consciousness. Science may give us an idea about the external physical world, but what it comprises are mental constructs that only exist at the moment we think about them. Concepts about the world can only be derived from the perceived world; there they have to be consistent with objects and events that are already part of subjective experience. By building theories and inventing concepts, we sophisticate the subjective image of the world rather than get a grasp of the material reality behind it. No conceptualisation and understanding get us beyond the mental realm, which according to idealism is the only realm in which we can operate. When discussing neurobiological data we need to be careful not to mistake the reliability of our knowledge for evidence that they represent aspects of physical reality.

The again paradoxical conclusion from these considerations is that even when researchers look at objects of their investigation and consider their seemingly objective data, they exercise introspection. It may be replied to **Phillips** that the inspection of clouds in the sky during wakefulness is not really so different from one's dream imagery while immersed in a dream; and remembering the contents of a lucid dream should not be significantly more challenging than recollecting the details of clouds after a delay that allows for the extinction of sensory memory.

R1.1. Dreaming

Not only is there no need to be sceptical about one's introspection into dream imagery, as **Phillips** is, but such an exercise is actually highly instructive. The phenomenological similarities between dreaming and normal wakeful perception are striking and further support the notion by R. R. Llinas and others (cf. Llinas & Pare 1991; Llinas & Ribary 1993) that these phenomena are in their very nature manifestations of the same process, although, as **Steriade** explains, there are a number of neurophysiological differences. Similarly to wakeful perception, objects and sceneries that we see in dreams surround us. Secondly, they are also substantial and clear in their appearance. The complexity and detail of visual imagery in dreaming suggests that even wakeful perception does not have to derive from sensory information to be as complex as it is, which is the very insight that Phillips knows challenges his understanding. Thirdly, as in wakeful perception, images perceived in dreams are alienated from the dreamer who finds himself interacting with apparently external objects and events. Fourthly, dream images seem to be real to the dreamer, and even gross violations of logic do not provoke questioning of their reality. Only when we wake up and start interacting with the external world do we understand that those sceneries were a fantasy and must have been produced in our mind. We are prevented from gaining this very insight into the subjective nature of the perceived world in the wakeful state as long as the phenomena into which the conscious stream differentiates are compatible with behavioural interaction with the external physical world; and this is precisely why Phillips never challenges the reality of his perceptions of clouds and water droplets.

The relationship between dreaming and strong nocturnal stimuli provides an intuitive model for the relationship between wakeful perception and the external physical world. Strong nocturnal stimuli can influence the flow of dream imagery, but the perception of these stimuli is largely determined by current dream themes and preoccupations of the dreamer, and has little in common with what they turn out to be upon awakening. Similarly, images, smells, and sounds that surround us in the state of wakefulness are not a reflection of what is out there in the physical world and do not represent external physical reality. To use **Foss**'s radar analogy, although a material event would have caused a deflection in the radar detector, what enters the "awareness" of the detector is an image that has almost nothing to do with the causal event and certainly *is* not this event itself. In dreaming, conscious imagery "floats" relatively unrestricted, whereas in the wakeful state the perceived world is "pinned" to an invisible physical reality beyond it. Psychosis is similar to dreaming (a view shared by **Gottesmann**), in the sense that the lack of proper constraints on conscious experience makes it maladaptive for interaction with the physical world (like a malfunctioning radar).

R2. Hallucinations

Transcendental idealism is not only consistent with but also necessary for our functional neuroanatomical model of hallucinations (unless one adopts a position that is similar in its essence, as is done by **Bezzubova & Globus**). To argue with **Foss**, we can uphold the model only for as long as we can insist on the core idea that normal perception is an externally constrained form of dream imagery or hallucination. As demonstrated in **Phillips**'s commentary, it is not possible to maintain the notion of equivalence between hallucinations and normal perception on the basis of a realist position (in the sense of "realism" as defined previously).

If hallucinations and normal perception are equivalent in their nature, their brain mechanisms may not differ significantly: Attentional mechanisms modulate the content of perceptual experience, whether or not this is externally constrained by sensory input. When sensory constraints are disrupted, attentional factors may predominate, giving rise to hallucinations. It has been recognised by clinicians that the content and context of verbal hallucinations are crucially dependent on psychological factors relating to personality, unconscious conflicts, and social concerns (see the target article). At times of increased social stress and anxiety, such patients would pay increased attention to social cues, and it is in the focus of attention where voices talking about or to the patient would emerge. Thus, adopting transcendental idealism, we did arrive at an explanation for the phenomenology of hallucinations (in terms of experiential quality, grammatical form, content, and circumstances of occurrence) – contrary to the assertion by **Myin-Germeys & Myin** that we have "none."

R2.1. Hallucinations and imagery

With respect to their phenomenology, hallucinations are not usually seen as a form of mental imagery, contrary to **Phillips**'s understanding. True hallucinations in particular are thought to be experientially identical to normal perception (Jaspers 1946/1963). Patients in acute psychosis typically have no insight into the unreality of their perceptual experiences; they react to their hallucinations as if

these were normal perceptions and will often deny that they are hearing "voices." There are, however, forms of hallucinations that share certain characteristics with mental imagery; these "pseudohallucinations" (Jaspers 1946/1963) are often accompanied by preserved insight, so that patients typically complain about their "voices." Cutting (1997) agreed that hallucinations characteristically appear "real" to the hallucinator, although, again, the aspect of reality may change along a spectrum. Regarding the phenomenology of hallucinations, Cutting wrote:

> the "world" of the hallucinator is no less real to the participant during a hallucinatory phase than is the "world" of the sane person when awake. To understand the nature of hallucinations it is not sufficient to simply determine the conditions under which non-real mental events (e.g. images, thoughts) somehow become invested with reality. This mistake is made by virtually all investigators of hallucinations in the recent past. . . . It makes no sense to regard a hallucination as a unique and generally pathological instance of subjective-turned-objective phenomenon, and to enquire into the reason for this, if, according to Kant and Schopenhauer, normal perception is achieved in exactly the same way. (Cutting 1997, p. 83)

One may reject the notion that hallucinations are a form of mental imagery and still argue that mental imagery is involved in the mechanism that produces hallucinations. Both phenomena reflect the workings of top-down processes and it would not be surprising to find a tendency to abnormally vivid imagery in patients with a predisposition to hallucinations. However it could be suggested to **Aleman**, **de Haan**, **& Kahn** (**Aleman et al**.) that mental imagery, on the one hand, and normal perception and hallucinations, on the other, involve different attentional stances in terms of the pattern or direction of top-down processes. For want of a better description, in mental imagery one tends to recreate something "inside" that is egosyntonic from the outset, whereas in hallucinations – and normal perception, for that matter – one expects or fears to encounter something "outside." It is perhaps because of this difference that secondary attributional mechanisms have to be postulated in models that explain hallucinations as derivatives of mental imagery. Not only would one have to explain how vivid imagery acquires perceptual qualities, but also the need arises to invoke some cognitive "external misattribution." We can avoid this problem by simply regarding hallucinations as underconstrained perceptions that are generated in the focus of attention, which is externalised from the outset. If social fears and situationally increased arousal were to play a complementary role in the generation of schizophrenic hallucinations, then hallucinations would be more likely to arise in the focus of externalised attention than from vivid mental imagery.

Mental imagery differs from normal perception, hallucinations, and dream imagery in that it is neither substantial nor persistent. If there is a significant overlap between neuronal assemblies underlying these experiences, then, as **Harris** asks, "how does the healthy brain keep the internally generated and external worlds separate?" Experiential substantiality and persistence may depend on the extent and temporal duration of resonant patterns of thalamocortical gamma oscillations. This is normally assisted by consistent sensory input of some minimal duration to specific thalamic nuclei, in agreement with the "time-on" theory proposed by Libet et al. (1991). However, if there is excessive neural noise in thalamic nuclei, thalamocortical assemblies that are induced by attentional mechanisms (but would normally subside quickly in the absence of supporting sensory input) can persist and become more extensive (drawing on regions coding for additional features), thereby facilitating or even necessitating the externalisation of the experience in the form of hallucinations. To respond to Harris's commentary, while neural assemblies underlying mental imagery are uncoupled from sensory input and hence can recruit thalamic relay cells into resonant patterns only briefly (explaining their fleeting and insubstantial character), neuronal assemblies underlying hallucinations can persist and extend because – according to the hypothesis – they recruit relay cells despite being uncoupled from sensory input.

R2.2. Verbal hallucinations and subvocal speech

Thought processes – involving the reciprocal interaction between conative and cognitive aspects – generate subvocal or "inner" speech (McDougall 1924). In inner speech, patterns of perioral, laryngeal, and respiratory muscular activities are produced that are similar to those generated during overt speech but do not result in audible vocalisations. Conative aspects of thought produce changes in perioral muscular and respiratory activity and subsequent reafferentation influences the progression of one cognition on to another, although we are not normally aware of this. In young children, verbal thinking may rely on the conscious execution of subvocal speech more clearly. Gradually, elementary acts of subvocal speech would become automatic and the subject becomes unaware of the involvement of subvocal speech. This may resemble overlearned activities, such as driving a car, where much of the lower-level motor behaviour has become automatic and only higher-order behavioural steps require conscious guidance.

Functional neuroimaging studies of actively hallucinating patients cited in the target article, as well as further work cited by **Hoffman**, **Mathalon**, **Ford**, **& Krystal** (**Hoffman et al**.), show that verbal hallucinations involve activity in cortical areas that are normally concerned with auditory perception and processing of external speech, which is consistent with the notion that verbal hallucinations are perceptions that are merely underconstrained by external sensory input. However, such studies can also show activation in brain areas that are believed to subserve inner speech (Sukhwinder et al. 2000). Bick and Kinsbourne (1987) found that intentional manoeuvres that engaged vocal and oral musculature in another activity, but not control manoeuvres, abolished verbal hallucinations in schizophrenic patients. Gould (1949) described a patient with persistent auditory hallucinations whose amplified subvocal speech production as heard by the investigator closely corresponded to the reported content of hallucinatory voices; the patient was not aware of this correspondence, which suggests that the involvement of subvocal speech is an unconscious mechanism. In response to **Massing**'s proposal that hallucinations are "motor disorders," how can one explain the involvement of inner speech in verbal hallucinations?

It is widely believed that auditory verbal hallucinations arise from a disorder of inner speech, particularly from a disorder of the "monitoring" of inner speech (e.g., David 1994; McGuire et al. 1995). However, a series of auditory

imagery tasks administered to patients prone to auditory verbal hallucinations did not show any abnormality in their inner speech processing (Evans et al. 2000). In any case – as appreciated by many commentators, **Silverstein & Phillips** in particular – it is not clear how one's inner speech misattributed to an external source can suddenly acquire the substantiality and grammatical form of other people's voices. Hallucinations are probably not caused by any abnormality in inner speech mechanisms, and the role of subvocal speech in verbal hallucinations may perhaps be consistent with its role in verbal thought, contributing to the progression of hallucinatory content. If thinking is mediated (not generated) by subvocal speech, it may not be surprising that verbal hallucinations are accompanied by subvocal speech, as well. Similarly to verbal thought, patients who experience verbal hallucinations would usually be unaware of this.

Verbal hallucinations tend to evolve over time. At first, voices are primitive and few in number; with time, new voices are added and utterances become more diverse and complex (Nayani & David 1996). The intimacy of voices increases and hallucinatory dialogues become increasingly detailed (Nayani & David 1996). Patients establish a coherent relationship with their voices, which may serve an adaptive function and contribute to the chronicity of hallucinations (Benjamin 1989). Although, at first, verbal hallucinations may be fearfully expected intrusions into the overly attentive mind, gradually, voices become incorporated into ego-defence mechanisms that alleviate anxiety and counter low self-esteem. This evolution of hallucinatory voices may be in part based on progressive involvement of subvocal speech. Patients unconsciously develop skills of manipulating the content of their "voices" by using subvocal speech, similarly to how a child would learn to use subvocal speech to manipulate his thought process.

Such development cannot be envisaged for visual hallucinations. Moreover – as argued in the target article – it is more difficult *not* to develop insight into the unreality and pathological nature of visual hallucinations. For these reasons, visual hallucinations are less likely to perpetuate mental illness; they do occur however in abundance in drug-induced psychosis, where – in comparison to schizophrenia – they may reflect a more severe but transient hallucinatory disposition, which I hope answers a comment made by **Silverstein & Phillips**.

R3. Psychophysiological markers of underconstrained perception

In patients who are prone to hallucinate, we may expect to find clinical evidence for a relative uncoupling of perceptual experience from sensory input, even in the absence of frank hallucinations. Mere perceptual distortions are likely to predate the development of perceptual deceptions, as can be concluded from the study by Klosterkotter et al. (2001), who showed that disturbances in language perception and visual distortions are among the prodromal symptoms that predict later transition to overt schizophrenia with high probability. (To respond to a criticism by **Silverstein & Phillips**, it is not argued that such distortions, as well as initial disturbances of self-experience, are secondary to hallucinations, but instead, that they are secondary to a predisposition to underconstrained perception.)

There are findings showing that in schizophrenia, sensitivity of perceptual processes to external sensory stimulation is decreased. Patients with schizophrenia are impaired in their ability to distinguish between figure and ground (Liddle 1987; Straube 1975), detect visual targets at the local versus global level (Carter et al. 1996), or detect blurred visual targets (Nuechterlein et al. 1992) – findings that were associated with the presence of hallucinations or psychosis. In the auditory modality, chronic schizophrenia was found to be associated with a deficit in the ability to match two tones separated by a brief delay (Rabinowicz et al. 2000). The discrepancy between external auditory input and the patient's perception becomes even more apparent when attentional factors such as expectation are involved, as shown by the finding that the verbal transformation effect (a word that is repeated over and over turns into a different word) in hallucinators depends on suggestion used by the experimenter (Haddock et al. 1995).

Mismatch negativity is a negative evoked potential component with a peak latency of 50–200 msec. It is elicited whenever infrequent-duration- or pitch-deviant stimuli unexpectedly interrupt a sequence of standard auditory stimuli in an auditory oddball paradigm, regardless of whether the subject actively attends to the sequence. Mismatch negativity is generated in the primary auditory cortex in the superior temporal plane. In patients with schizophrenia, amplitudes of mismatch negativity are reduced, particularly at left temporal recording sites (Hirayasu et al. 1998; Javitt et al. 1993).

Mismatch negativity is commonly regarded as a measure of pre-attentive auditory sensory memory, which registers current auditory input for comparison with subsequent stimuli. However, mismatch negativity should also depend on subjects' ability to discriminate between deviant and standard stimuli – that is, on their auditory perceptual sensitivity. When subjects learn to discriminate between two complex auditory stimuli, then mismatch negativity to deviant stimuli increases (Atienza & Cantero 2001). Similarly, reducing the audibility of standard and deviant speech stimuli by adding a masking noise of varying intensity was shown to result in amplitude reduction and latency increase of mismatch negativity in response to deviant speech stimuli (Müller-Gass et al. 2001). The results obtained by Rabinowicz et al. (2000) indicate that schizophrenic patients have a reduced ability to discriminate between different tones. Reduced sensitivity to variations in auditory stimulation would be likely to manifest in smaller changes in the electrical cortical response to deviant tones, regardless of the integrity of auditory sensory memory.

Javitt et al. (2000) found that, among schizophrenic patients, impairment of mismatch negativity generation to pitch-deviant tones embedded in a series of standard tones was correlated with a reduced ability to match two separate tones, suggesting that a similar physiological mechanism may underlie both deficits. Reduced mismatch negativity and tone-matching deficits were both correlated with negative symptom ratings (Javitt et al. 2000). The deficit in mismatch negativity generation in schizophrenia could be explained, therefore, in terms of reduced perceptual sensitivity. Auditory perception in patients with schizophrenia is simply less sensitive to variations in external sensory stimulation, which appears to be a deficit that is independent of active psychosis and more related to schizophrenic vulnerability. The findings by Müller-Gass et al. (2001) in normal

subjects may provide a clue as to what might be the cause in schizophrenia for such perceptual insensitivity to sensory stimulation. Similarly to the addition of external noise, endogenous "noise" in specific thalamic nuclei may mask sensory input and reduce its impact on intrinsic thalamocortical processes underlying perception.

From this perspective, the data reviewed by **Light** are particularly interesting. It would appear that – like visual backward masking deficits – the reduction in mismatch negativity is related to deficits in the ability to support gamma oscillations while – at the same time – it (that is, the reduction of mismatch negativity) indicates an uncoupling of perception from sensory input. It is no wonder, therefore, that mismatch negativity deficits are associated with impairments in "real-world" functioning, as Light points out. Given that they are such robust findings in schizophrenia, there is an exciting prospect that auditory mismatch negativity reduction may – like visual backward masking deficits – serve one day as an objective marker for *under* constrained perception and therefore reveal a predisposition to hallucinations in the absence of clinically apparent hallucinations (the latter, strictly speaking, being *un* constrained perceptions).

R4. Other symptoms of acute schizophrenia

Silverstein & Phillips are concerned about an apparent restriction of the diathesis for schizophrenia to a diathesis for hallucinations. **Massing** states that the notion of underconstrained perception runs into automatic difficulties when faced with the spectrum of psychotic symptoms. Let us consider the possibilities that other psychotic symptoms of acute schizophrenia are either produced by a mechanism similar to the one suggested for hallucinations or arise secondarily to insufficiently constrained perception or outright hallucinations. The fact that hallucinations, passivity phenomena, catatonic symptoms, disturbances of self-experience, and formal thought disorder tend to co-occur during an acute psychotic episode would support this assumption. It is conceivable that underconstrained perception in the auditory, visual, or kinaesthetic modality will affect the control of voluntary movement or speech production, consistent with the observation by Chapman (1966) that in some patients with schizophrenia, passivity experiences and catatonic symptoms develop on the background of primary disturbances in visual or speech perception.

Alternatively, disturbances in speech or movement in psychosis – passivity phenomena in particular – may result from underconstrained thalamocortical activation in frontal cortical areas, thus involving a *similar* mechanism. **Whittington** reminds us that cognitive functions based on prefrontal areas (such as attention and pursuit of goals over time) depend on gamma synchronization, as well. In contrast to postcentral sensory regions of the cerebral cortex, activity in thalamocortical circuits in prefrontal and premotor regions is not constrained directly by sensory input, but is controlled by input from basal ganglia.

R4.1. Passivity phenomena

Passivity phenomena, such as "made" actions, thoughts, or impulses, were recognised by Schneider (1957) as schizophrenic symptoms of first rank. Patients with passivity phenomena lack a sense of agency ("coming from me") when experiencing their actions or thoughts. This may give rise to delusional elaboration. When experiencing their unintended actions or thoughts, patients come to the conclusion – depending on their cultural and educational background – that they are controlled by machines, television sets, implants, aliens, or religious figures (delusions of alien control).

Hoffman et al. think it to be an advantage of misattribution-based cognitive models of hallucinations that they can be traced to the central monitoring hypothesis, which involves comparison of efference copies or corollary discharge patterns of actions with movement intentions (cf. Frith, as reviewed in Gallagher 2000). This argument can be turned around. Experimental findings cited in support of the hypothesis that central monitoring of actions is deficient in patients with passivity phenomena (Frith & Done 1989; Mlakar et al. 1994) or those cited in support of the hypothesis that schizophrenic patients have difficulties in attributing action to the proper agent (Daprati et al. 1997) can be explained more parsimoniously as evidence for reduced sensitivity or reduced accuracy of kinaesthetic perception – that is, evidence for a lack of reafferent proprioceptive constraints on intrinsic thalamocortical activity underlying movement perception. This would lead to an increased reliance on visual feedback during the control of voluntary action and a reduced likelihood to detect a discrepancy between one's own visually hidden movement and a visually presented movement of the experimenter, as shown in some of these experiments. Although a tendency of misattribution to an external origin as defined by such experiments may be associated with passivity phenomena or hallucinations, this does not necessarily mean that the generation of these symptoms crucially involves misattribution as – in the case of hallucinations – is argued by **Aleman et al**., **Glicksohn**, and Hoffman et al. Let us concentrate here on "made" action in trying to find an alternative explanation for passivity phenomena.

Neuroimaging studies demonstrate that the perception of other people's actions or salient objects in the environment automatically activates premotor and motor areas in the frontal cortex (reviewed in Grezes & Decety 2001; Jeannerod 2001). Movement plans (intentions) appear to be formed automatically in posterior parietal areas as salient stimuli are perceived (Andersen & Buneo 2002), activating motor response dispositions in connected premotor areas. Elsner and Hommel (2001) argued that perception of stimuli reminiscent of environmental effects of previously rewarded behaviour or even anticipatory imagery of such effects automatically activates response tendencies to behaviourally obtain the reward (Elsner & Hommel 2001). Several perceived stimuli or anticipatory images may activate competing response tendencies, and there has to be a mechanism for selecting between them in accordance with the motivational state of the organism. Automatic response tendencies that are incompatible with current drives and strivings for goals have to be suppressed (Elsner & Hommel 2001). Competitive selection among response dispositions is implemented on the level of the dorsal striatum (caudate nucleus and putamen), which functions as a lateral inhibitory network in a "winner-takes-it-all" fashion (Kropotov & Etlinger 1999; Parkinson et al. 2000; Schall 2001). Competitive selection is modulated (as suggested by Miller & Cohen 2001) by inhibitory and excita-

tory biasing signals from prefrontal cortices representing desired behavioural goals. The prefrontal cortex appears to play an important role not only in determining which events are to be perceived, but also which of the corresponding premotor response dispositions is to be selected and actualised in overt behaviour.

Functional binding of motor action components into single representations is likely to involve gamma synchronisation of thalamocortical activity in premotor areas. Electroencephalographic desynchronisation (corresponding to gamma synchronisation and beta rhythm suppression) can be seen over frontal motor and premotor areas in relation to preparation and execution of voluntary action (Pfurtscheller et al. 1994), but it also occurs during perception of salient stimuli and imagination of movement. Brown and Marsden (1998) argued that the basal ganglia play an important role in gamma synchronisation and the binding of distributed cortical activity. Excessive inhibition of the globus pallidus internal segment (linking dorsal striatum with thalamus) by dopamine agonists can lead to excessive facilitation of thalamocortical gamma activity and binding of unrelated elements of motor activity (Brown & Marsden 1998). Brown and Marsden (1998) raised the possibility that gamma synchronisation may be exaggerated in schizophrenia, as well.

If thalamocortical cells are disinhibited excessively, either as a result of reticular thalamic nucleus dysfunction or reduced pallidal input to the thalamus, inappropriate response dispositions would require less excitatory influences to gain actualisation and more inhibitory control to prevent them from actualisation. In other words, the threshold for action generation in premotor/motor regions would be reduced, allowing for response generation regardless of motivational factors. Kropotov and Etlinger (1999) also speculated that schizophrenic symptoms could arise when the threshold for action selection is low, and, as a result, unneeded actions in response to situationally irrelevant stimuli are not inhibited. Specifically, it is suggested here that failure of suppression of motor acts initiated by irrelevant sensory stimuli may represent a mechanism for passivity phenomena in schizophrenia. As a result of the lowering of the threshold for action selection, action selection could become uncoupled from desired goals (which are represented in the prefrontal cortices) and more basic drives (which are implemented in the limbic regions).

Because irrelevant acts would be perceived on execution, and at the same time not be conducive to drives and strivings, they would be experienced as passive. We can appreciate this argument if we again adopt a stance of transcendental idealism. An implication of transcendental idealism is that our awareness of body or limb movement is dependent on the execution of movement in the physical realm. Whatever we are aware of is essentially part of the realm of subjective conscious experience – as opposed to the physical realm – and this has to include our experience of body movement. Thus, motor actions that we are aware of are not *movements* but *perceptions* of movements. Motor actions are conscious not because they are intended and carried out by some agency, but only insofar as they are *perceived.* Already, James (1890) pointed out that our awareness of movement is an afferent – not efferent – phenomenon, being a consequence and not an antecedent to the actual movement in the physical realm.

Because our awareness of movement has to be secondary to the execution of movement, the sense of agency of movement has to be a consequence of action execution, as well. The sense of agency, that is, the experience that voluntary action or thought was seemingly brought about by the self, must not be confused with the sense of volition, which precedes voluntary action. The sense of volition, reflecting a conflict between action tendencies, is neither necessary nor sufficient for voluntary action (Bennett & Hacker 2003). Both sense of volition and sense of agency are aspects of self-experience, however, it is the post-action sense of agency and not the pre-action sense of volition that is disturbed in passivity phenomena. Although voluntary action (that is, its perception) is accompanied by a *sense* of agency, the self is not the agent of voluntary action. This has long been recognised by philosophers such as Spinoza, Kant, Hume, Hegel, and Jaspers. What then, if not the self, is the organising and motivating principle of behaviour? McDougall (1924) argued that we are driven to action by instincts and derived desires on all levels of behaviour. The sense of self – insofar as it is related to the sense of agency – may stem from the reduction in drive or desire that accompanies all voluntary action. According to Jaspers (1946/1963), our awareness of agency ("coming from me") is a spontaneous experience that is linked to "discharges of psychic effects." This – it may be suggested – and not cognitive attribution based on comparison with efference copies, as reviewed by **Hoffman et al**., may provide the sense of self-generation that accompanies perceived movements and other aspects of conscious experience.

It may be interesting to study the relationship between passivity phenomena and striatal function. The nucleus accumbens (ventral striatum) controls activation in parts of the prefrontal thalamocortical system via the ventral pallidum. It receives dense dopaminergic innervation from the ventral tegmental area. O'Donnell and Grace (1999) argued that positive symptoms of schizophrenia result from increased dopaminergic activity in the nucleus accumbens, leading to excessive prefrontal cortex activation. Perhaps, as a result, patients may experience an imposition of emotions and goals ("made" feelings, "made" impulses). A similar mechanism involving the dorsal striatum may lead to activation in premotor areas that is unrelated to drives and goals (manifesting in "made" actions). **Gargiulo & Landa de Gargiulo** support the view that dysfunction of the ventral striatum resulting from corticostriatal glutamatergic dysfunction or hyperactivity of dopaminergic input may be responsible for excessive thalamocortical activity in prefrontal areas and symptom generation in schizophrenia, particularly disorganised behaviour that is not contextualised to the situation or is irrelevant to the emotional/motivational state. Additionally, an increase in dopaminergic functioning in the nucleus accumbens may contribute to symptom formation by suppression of reticular thalamic nucleus function, as suggested by **Gottesmann**, as well as O'Donnell and Grace (1999).

R4.2. Catatonic symptoms

Let us look into **Massing**'s assertion that in catatonic states perception remains "completely intact." Catatonic symptoms are seen characteristically in the acute phase of catatonic and hebephrenic forms of schizophrenia. Catatonia encompasses motor symptoms such as diminished responsiveness, impoverished expressive movements, and a vari-

ety of abnormal *goal-directed* (obstruction, ambitendency), *induced* (negativism, opposition, echopraxia), and *spontaneous* movements (stereotypies, parakinesis), along with certain abnormalities in speech (mutism, echolalia, perseveration). Examining the development of symptoms in the early stages of schizophrenia, Chapman (1966) found that there is an intricate relationship between disturbances in visual perception and catatonic motility. Severe and transient perceptual instability (with visual fragmentation and alterations in size, shape, brightness, and movement of objects) was usually present from the early stages of schizophrenia and – if it did occur – predicted the development into hebephrenic or catatonic schizophrenia (Chapman 1966). Hebephrenic and, especially, catatonic patients appeared to deal with their disturbances in visual perception, particularly a breakdown in visual constancy, by controlling and restricting their movements. Patients reported that as soon as they moved, their perceived environment started to change or turn into "a fast series of pictures" (Chapman 1966).

Apart from being a direct consequence of disturbed visual perception, catatonic symptoms may also result from instabilities in kinaesthetic perception, leading to uncoupling of the perception of one's movements from the execution of motor action in the physical realm. This may explain patients' difficulties in monitoring voluntary movement. Chapman (1966) described how schizophrenic patients had to concentrate on their movements and monitor motor acts that they "used to do without thinking" (Chapman 1966). Instead of executing movements as whole sequences and directing attention towards the overall goal of the behavioural sequence, patients had to pay attention to the execution of each individual step in a sequence. They had to increase conscious control of their movements also for fear of carrying out a "wrong" or unintended movement (Chapman 1966). One can see that in these situations, patients may prefer to restrict their movements or move stereotypically. In a similar manner, mutism and echolalia may be secondary to the patients' difficulties in monitoring their speech (Chapman 1966).

It has to be noted that the majority of schizophrenic patients do not experience catatonic symptoms or marked visual disturbances, their symptomatology is confined more or less to hallucinations and delusions (paranoid schizophrenia). It could be argued that early disturbances in visual perception, which are associated with a poor prognosis in schizophrenia (Chapman 1966), indicate a greater predisposition to underconstrained perception affecting all sensory modalities (including somatosensory) to an equal extent. In patients with paranoid schizophrenia, as opposed to catatonic or hebephrenic forms, the biological predisposition to underconstrained perception may be less severe, thereby explaining the restriction of perceptual deceptions to the auditory modality in which additional personality and interpersonal factors, acting through increased attention to social cues, can play an important complementary role.

R4.3. Formal thought disorder

Finally, underconstrained perception may also provide an explanatory model for some cases of formal thought disorder in schizophrenia. Whereas some types of formal thought disorder (manifesting in speech disorder) may arise from distraction by intermittent hallucinations or thought insertions, or result from high levels of anxiety and hyperarousal, schizophasia (word salad) in particular may perhaps result from underconstrained perception of one's own speech, causing a disruption in the feedback control of language production. The mechanism may be similar to Wernicke's dysphasia, which can phenomenologically resemble schizophasia. Here, too, speech output systems are not affected directly, but language perception is impaired (as a result of temporal lobe damage). Similarly, Chapman (1966) regarded speech disturbances in some schizophrenic patients as a paroxysmal form of dysphasia, resembling the paroxysmal dysphasia that can occur in patients with temporal lobe epilepsy. He noted that patients with schizophrenia intermittently had difficulties controlling their speech, producing unintended words or conveying unintended meanings. Patients had to monitor their speech consciously and deliberately; at the same time they had difficulties comprehending the speech of others (Chapman 1966), indicating that the problem may be primarily one of speech perception. Chapman (1966) concluded that patients with schizophrenia suffer from a breakdown in the normally automatic process of monitoring of one's speech.

Like all motor behaviour, speech becomes conscious only at the point of its perception. If perception of one's own speech is underconstrained by auditory input and therefore uncoupled from externally generated speech, the patient would hear what he expects to hear almost regardless of his speech production; his garbled speech output would have little impact on his underconstrained speech perception, unlike the perception of his speech by others. There is some evidence to support this model. Hotchkiss and Harvey (1990) examined the ability of auditory distraction to interfere with speech production in patients with schizophrenia. Patients with schizophrenia were exposed to alternating blocks of spoken text, random words, white noise, and silence while conversing with an interviewer. The presence of all types of irrelevant distraction, including white noise, led to an increase in the production of reference failures on the part of the patients. By comparison, normal subjects were not affected. Antipsychotic medication reduced the disturbing effect of irrelevant distracting information on speech production (Moskowitz et al. 1991). Hotchkiss and Harvey (1990) proposed that "perceptual overload" stressed the "information processing capacity" of patients with schizophrenia to an extent that their language production suffered. However, Harvey (2000) acknowledged that it is not clear why such reduced information processing capacity should result in formal thought disorder when normal subjects who perform poorly on indices of information processing capacity do not usually demonstrate formal thought disorder. Alternatively, it may be suggested that patients with schizophrenia – whose perception is already insufficiently constrained by sensory input – fail to accurately perceive their own speech as soon as external sensory constraints normally imposed on language perception are further disrupted by the addition of what is effectively external noise.

Patients with schizophrenia show deficits in visual backward masking during both active psychosis and in clinical remission (Green et al. 1999). 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. Compared to normal subjects, patients with schizophrenia require longer interstimulus intervals between the

presentation of target and mask to be able to identify the target stimulus. Green et al. (1999) related visual backward masking deficits in patients with schizophrenia to a failure to establish cortical oscillations in the gamma range. Impaired gamma response synchronisation in the thalamocortical system may in effect amount to an uncoupling of perception from peripheral sensory input, assuming that gamma synchronisation indeed subserves perception. In patients with schizophrenia, poor performance in visual backward masking tasks was correlated with a measure of thought disorder (Perry & Braff 1994), which may be consistent with the hypothesis that underconstrained speech perception is involved in some forms of thought disorder.

There are other points worth mentioning in response to the concerns by **Silverstein & Phillips** that the proposed model relies excessively on a model of hallucinations. First, patients should normally *not* be diagnosed as having schizophrenia unless they have had clear-cut episodes of true psychotic symptoms – most commonly, but not exclusively, hallucinations (recognizing that "schizophrenia" is used more and more as a convenient label for personality disorders that present with factitious psychotic symptoms). Second, patients may hallucinate but present with other symptoms of psychosis and continue to contradict inquiries into hallucinations, depending on their level of insight and the quality of the psychopathological examination. Third, the extent to which perceptual processes are constrained by external sensory input may fluctuate even within a psychotic episode. In some patients, there may be occasional marked disruptions of constraints in conjunction with heightened attention and arousal, manifesting primarily in recurrent hallucinations with content of some psychological significance. In other patients, thalamocortical processes may be *under*constrained continuously during a psychotic episode – not to the point of complete disruption, but merely to the point at which feedback control of speech and motor behaviour become impaired. In any case, it is possible to argue that underconstrained thalamocortical activation is an important mechanism of symptom production in psychosis. On reflection, it is perhaps better to speak of a predisposition to underconstrained perception in general, rather than of a predisposition to hallucinations specifically.

R5. Stress and vulnerability

Silverstein & Phillips point out that hallucinations can be found in other psychiatric disorders, particularly severe mania or depression, thus questioning the notion that a predisposition to hallucinations (or more generally to underconstrained perception) is central to the pathophysiology of schizophrenia. Again, it is important here to remind the reader of the interplay between stress and vulnerability. Slade (1976) emphasised the role of psychological stress in provoking auditory hallucinations in subjects who have a hallucinatory predisposition. Extreme stress can lead to hallucinations even in normal subjects without a predisposition, as illustrated by Siegel's (1984) work on hostage victims. Increased arousal was thought to play a role in the generation of hallucinations in hostage victims (Siegel 1984). Depending on an individual's biological predisposition, the level of psychological stress required to cause hallucinations and psychosis may vary.

We agree with **Meis** that P50 ratio abnormalities may not be indicative of sensory gating deficits. Instead, as discussed in the target article, lack of suppression of the P50 mid-latency evoked response to the second of paired auditory stimuli (S2) may indicate impairment of response synchronisation to sensory stimulation resulting from increased levels of random thalamic activity, which – at the same time – may predispose to underconstrained activation of thalamocortical circuits by attentional mechanisms. Although suppression of S2 P50 is largely insensitive to attentional manipulations, it can be affected in normal subjects by introduction of a brief psychological stressor (White & Yee 1997). Psychological stress is accompanied by cholinergic arousal, but also involves release of noradrenaline; and in normal subjects there is evidence for an association between noradrenergic hyperactivity, as measured by levels of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (pMHPG), and transient lack of suppression of S2 P50 (Waldo et al. 1992).

Franks et al. (1983) demonstrated a reduction in the suppression of S2 P50 in acutely psychotic manic patients, similar to findings in schizophrenia. However, in contrast to patients with schizophrenia, the increase in the P50 S2/S1 amplitude ratio returned to normal with clinical improvement (Franks et al. 1983). Adler et al. (1990) confirmed the transient nature of lack of S2 P50 suppression in manic patients. Importantly, failure to suppress the P50 response to the second of paired stimuli in manic patients was associated with increased noradrenaline metabolism (Adler et al. 1990). A correlation was shown between deficient S2 P50 suppression and increased plasma levels of pMHPG (Baker et al. 1990). Among schizophrenic patients, however, there was no correlation between deficient suppression of S2 P50 and noradrenaline metabolism (Baker et al. 1990). Thus, lack of suppression of P50 to the second stimulus in paired-stimulus paradigms seems to be mediated by noradrenaline only in manic patients (Adler et al. 1990).

Given the universal effectiveness of antipsychotic medication, it may be reasonable to assume that mechanisms for psychosis are universal. Patients with schizophrenia and patients with affective disorders may differ primarily in the extent of their vulnerability to psychosis. Schizophrenia could be construed as a condition of increased vulnerability in which stable predisposing factors afford a permanent lowering of the threshold that variable additional factors have to overcome to produce psychosis (Fig. R1). In schizophrenic patients who show failure of suppression of S2 P50 during remission, only a relatively moderate level of stress may produce levels of thalamic background activity that are compatible with underconstrained thalamocortical activation. This would explain the lack of association with increased noradrenaline metabolism. In patients with mania who appear to have normal baseline levels of thalamic noise, as suggested by normal P50 S2/S1 ratios during remission, excessive stress as reflected in increased noradrenaline metabolism may be necessary to reach critical levels of random background activity in specific thalamic nuclei.

Schizophrenia is a complex condition, the predisposition to underconstrained perception being only one aspect of it. As discussed in the target article and further emphasised by **Glicksohn**, hallucinations are relatively common, but not every individual with a biological vulnerability to hallucinations develops psychosis and schizophrenia. Premorbid limitations in social competence and coping skills (resulting

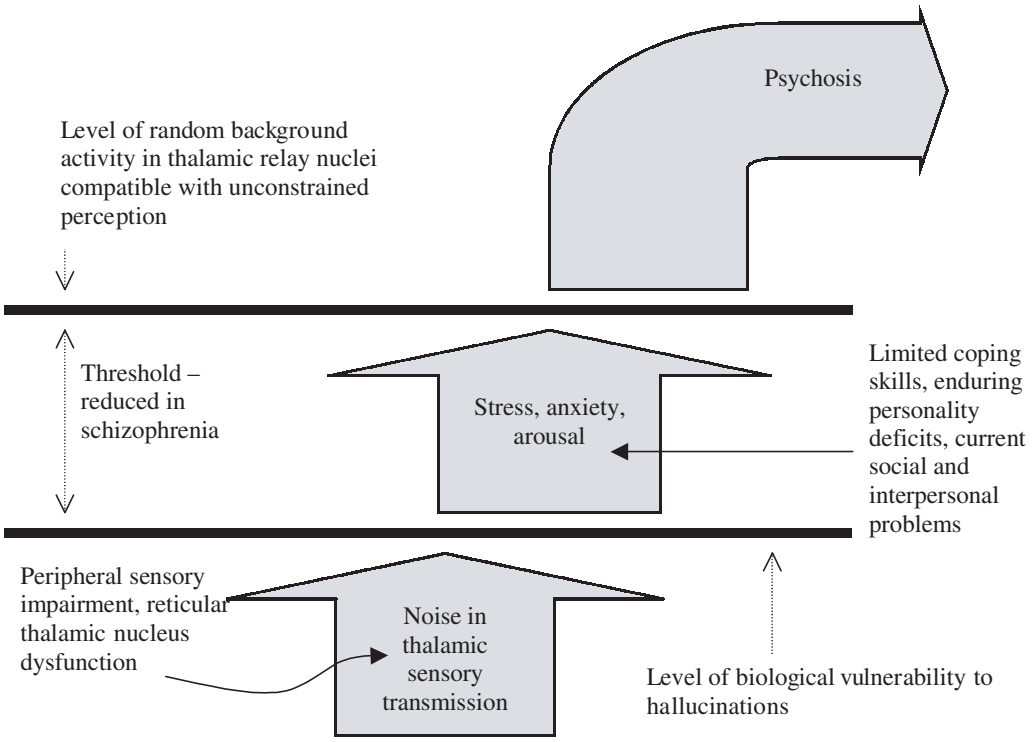

Figure R1. A hypothetical biopsychosocial model. An enduring reduction of the signal-to-noise ratio of activity in specific thalamic nuclei (resulting from biological vulnerability factors) decreases the threshold that additional episode factors (hyperarousal, stress) have to overcome to reach levels of random background activity in specific thalamic nuclei that are compatible with underconstrained thalamocortical activation and hallucinations.

from personality problems or learning difficulties) increase the likelihood of adverse life events and social problems and determine the extent to which the individual's biological vulnerability is stressed. Crucially, lack of insight and adoption of an unconscious defensive role contribute to the perpetuation and development of hallucinations in psychosis. The equation *schizophrenia = predisposition to underconstrained perception + chronic stress secondary to schizoid / schizotypal / paranoid personality disorder* may be an extreme but nevertheless instructive simplification covering some of the more classic cases of schizophrenia. In this equation, the predisposition to underconstrained perception may be severe for constitutional reasons or perhaps is augmented by chronic substance misuse, illustrating that patients with intact premorbid social functioning can develop schizophrenia (the resulting social breakdown perpetuating the disease), to answer another criticism by **Silverstein & Phillips**. While the biological vulnerability to underconstrained perception may be determined in part by constitutionally elevated random activity in specific thalamic nuclei, cholinergic (and noradrenergic) hyperarousal that accompanies psychological stress and social anxiety may mediate between such vulnerability and the development of acute psychosis. Therefore, it is not surprising that physiological abnormalities that can be identified alongside psychotic symptoms in actively symptomatic schizophrenic patients – but not in remitted patients or at-risk populations – (such as electrodermal hyperactivity and excessive beta activity in the electroencephalogram) are related to increased arousal.

According to the proposed model, how does hyperarousal contribute to psychosis? To briefly repeat, cholinergic activation during arousal facilitates the emergence of 40-Hz rhythms in thalamocortical networks and their synchronisation. Reese et al. (1995) considered the possibility that increased activity of the pedunculopontine nucleus in schizophrenia could lead to an increased drive on the thalamus to induce cortical desynchronisation. **Steriade** develops this idea further in his commentary. On the other hand, **Sarter & Berntson** explain that prefrontal attentional mechanisms regulated by basal-forebrain cholinergic input may be dysfunctional and distort thalamocortical activation. As a bottom line, if an increase in thalamocortical activation combines with excessive noise in specific thalamic nuclei (e.g., because of dysfunction of the reticular thalamic nucleus or peripheral sensory disorder), intrinsic thalamocortical processes may become uncoupled from sensory input.

We were not concerned with explaining schizophrenia in all its aspects and variations, but merely with mechanisms of psychosis, hallucinations in particular. Hallucinations in clear consciousness are still the hallmark of psychosis, but psychosis can occur in conditions other than schizophrenia. When regarding schizophrenia as a condition of increased vulnerability to psychosis, then, one can agree with **Silverstein & Phillips** or **Massing** that hallucinations are merely "accessory" symptoms, being confined to episodes of psychosis that afflict patients with schizophrenia more easily than other individuals (including those with major affective disorder). In response to **Schutter & van Honk**, we clearly did not state that emotion is the colouring of cognitive information, that schizophrenia is a cognitive disorder, or that

emotional disturbances are only secondary to schizophrenia. On the contrary, a tendency to emotional difficulties forms part of the schizophrenic background and these difficulties tend to be reflected in hallucinations, as much as emotions and drives generally influence the content of normal perception and dream imagery (in accordance with the notion of fundamental equivalence between normal perception and hallucinations). In response to **Hoffman et al**., "spontaneous gamma resonances in speech processing neurocircuitry are attracted to verbal content that is vulgar or critical and generally emotion-charged" because patterns of gamma resonance are shaped by attentional mechanisms reflecting the patient's psychological problems. It is important to ask what determines the content of hallucinations, but more importantly we need to understand the nature and principle mechanism of hallucinations, and here Schutter & van Honk's notion of schizophrenia being an affective disorder is not helpful.

Externally underconstrained thalamocortical activation may be caused by a combination of factors, including dysregulation of thalamic activity (involving abnormal serotonergic or dopaminergic input to the thalamus or receptor dysfunction in the reticular thalamic nucleus), sensory impairment, and cortical hyperexcitability, along with episodically increased attention and hyperarousal reflecting psychosocial factors, or cholinergic dysfunction. This is precisely the reason our model does not imply an "obvious relation between thalamic pathology and hallucinations" among the various clinical conditions accompanied by hallucinations, contrary to the assertion by **Collerton & Perry**. Although there was greater loss of alpha-7 nicotinic receptors in Lewy body dementia and Alzheimer's disease than in schizophrenia, additional vulnerability factors along with stress-related episode factors are implicated in schizophrenia. In regard to peripheral sensory impairment, we did not assume that this entails a reduction in the amount of sensory input to the thalamus, as implied by Collerton & Perry; the manner in which sensory disorder may contribute to hallucinations is through an increase in the proportion of noise in sensory input, as appreciated by **Disney & Schultz**. Complex visual hallucinations may disappear upon eye closure because this entails a noise reduction in the thalamus. For the same reason, schizophrenic patients may try and keep their voices at bay by wearing earplugs.

R6. Summary

The notion that the world we perceive around us is fundamentally subjective and part of the same realm as some phenomena that we already recognise as "mental" or "inner" may be discarded as idealism, but can provide an interesting avenue to understanding some of the psychopathology that is characteristic of schizophrenia. The core insight is that whatever we perceive – whether the environment or our movements – is an adaptive creation of the mind and not something that is "out there." Physical reality is not part of the world that is accessible to us, although it exists and constrains our experience in the case of normal perception in wakefulness. These views are consistent with various philosophical models as pointed out by **Bezzubova & Globus**, but it is perhaps Kant who can be credited with first recognising idealism as the appropriate philosophical framework for understanding the nature of the perceived world and its phenomena, and at the same time recognising the embeddedness of the phenomenal world in a shared physical world that is beyond subjective experience. In contrast to idealism per se, transcendental idealism allows us to overcome the confusion between subjective experience and objective reality without questioning the existence of the world. In the face of great opposition from philosophical corners, it is a relief to note that our position is shared by Bezzubova & Globus.

Hallucinations are not a manifestation of thalamic disorder, contrary to the interpretation of our model by **Collerton & Perry** and **Massing**. Thalamic mechanisms play a crucial role, however, in balancing the relationship between external sensory input and intrinsically generated functional states of the thalamocortical system (the thalamus not being a gating or filtering device as Massing mistakenly thinks we argue). The cortex is more concerned with determining the *content* of conscious experience rather than linking it to sensory input (the latter being a function of the thalamus) – a distinction that Massing does not appreciate. Thalamocortical activity in postcentral sensory areas is shaped by prefrontal and limbic attentional mechanisms. It is, however, not this modulation itself, but the self-organisation of gamma oscillations (into resonant assemblies) – that which is being modulated – that "create[s] images," to answer **Phillips**'s question. **Gottesman**, **Meis**, **Sarter & Berntson**, and **Whittington** explore how attentional modulation by prefrontal mechanisms itself may be abnormal in schizophrenia. *Sensory* modulation of processes underlying perception crucially depends on the signal-to-noise ratio in thalamic activity – a concept clarified by **Disney & Schultz**. Whereas the impact of sensory input on thalamocortical activity is regulated at the thalamic level, the disposition of thalamic and cortical neurons to resonate in the gamma band (and thus overall perceptual productivity) is regulated at thalamic *and* cortical levels. It is therefore not surprising that a variety of regulatory mechanisms can affect the balance between intrinsic thalamocortical activity and constraining sensory input. In this regard, several commentaries complement the model by highlighting the role of brainstem glutamatergic and cholinergic projections to the thalamus (**Steriade**), basal-forebrain cholinergic input to the cortex (Collerton & Perry; Disney & Schultz; Sarter & Berntson), and serotonergic input to cortex and thalamus (**Goudie & Cole**; Gottesman), the latter being particularly important for understanding antipsychotic drug action, as Goudie & Cole point out. Whittington considers the role of cortical interneurons in the generation of gamma rhythms, whereas **Kirk** discusses the differential contribution of gamma and theta oscillations to conscious experience, showing that our knowledge of the precise neuronal mechanisms of consciousness is in flux.

Regarding implications for treatment, **Bezzubova & Globus** and **Silverstein & Phillips** suggest that the notion of hallucinations as unconstrained perception should stimulate the development of psychotherapies that help patients to normalise their experiences. However, even if this cannot be achieved, **Phillips**'s argument that theories of hallucinations are permissible only if they do not upset psychotherapeutic efforts may not be supportable. Widening the theoretical application of the proposed approach – as Bezzubova & Globus have called for – one can fruitfully consider the psychopathological consequences of an uncoupling of perceived phenomena from sensory constraints

in the domains of speech and voluntary action, as shown here for formal thought disorder and as considered in the commentary by **Kirk** for dyslexia. Taking on board **Goudie & Cole**'s suggestions, we shall become able to integrate clinical and neurobiological findings on drug-induced psychoses. Thus, the work of R. R. Llinas, M. Steriade, and others on intrinsic resonance capabilities of the brain has opened the prospect of a unifying approach to the psychopathology and neurobiology of psychosis – as long as we are willing to embrace the deeper philosophical implications of their work.

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Letters "a" and "r" appearing before authors' initials refer to target article and response respectively.

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