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 cortico-cortical 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

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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

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