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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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-

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