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

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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-

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