propose that impairments in this elemental process lead to psychosis in patients with schizophrenia.

The hierarchical model posits that the nature of the output from a given area of cortex depends on temporal coincidence with the patterns of the bottom-up input it receives. If an individual experiences stimuli that do not clearly fit any top-down hypotheses derived from previous experience, a given area of cortex relays the details of the patterns it receives to higher cortical areas; the signals are passed on to the next highest layer and this pattern extends until a match is achieved. As a situation becomes more familiar, the representations of a given level of analysis are shifted to lower cortical areas, freeing higher areas for the detection of high-level patterns. The correct identification of objects, sensations, and processes in the environment is thus based upon probabilistic prediction determined by the accumulation of memories of how the perceptual world is organized and how it operates (Hawkins and Blakeslee, 2004; Purves *et al*, 2001).

We hypothesize that in schizophrenia, the formation and storage of invariant representations at higher hierarchical levels is insufficient. The higher levels do not provide enough input to lower levels for solving the nature of stimuli, and the lower levels do not provide adequate perceptual details to enable a sufficient establishment of perceptual context (Kraus *et al*, 2009). Thus, simple information must be sent repeatedly to higher levels for more effortful interpretation. Reduction in the correct identification of percepts in the context of real-world information-processing demands, affords the opportunity for arbitrary internally generated interpretations of reality to intrude upon perception and thought, leading to an accumulation of inaccurate but internally meaningful perceptions that may build upon one another into incorrect beliefs. This failed process may be at the core of the development of hallucinations and delusions. Context-based perceptions of real objects and real events are reduced in favor of an interpretation of reality that is individually determined and disconnected from the experiences and beliefs shared by others. This, we hypothesize, is the mechanism behind the development of delusions and hallucinations in patients with schizophrenia.

Recent work supports this concept (Javitt, 2009). Patients with schizophrenia have great difficulty in perceiving visual objects among noise and are unable to identify incongruous events in a virtual reality context. Although few studies have addressed whether these cognitive impairments precede the onset of psychosis, there have been some confirming data. Individuals who are soon to develop psychosis experience the perception of more elaborate sequences of verbal stimuli in auditory noise conditions (Hoffman *et al*, 2007). Cognitive paradigms that measure an individual's ability to distinguish percepts from noise based upon context have particular promise for identifying impairments in learning-dependent predictive perception (Koethe *et al*, 2009).

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New Insights into the Mechanisms Underlying the Effects of BDNF on Eating Behavior

Food intake is a complex behavior resulting from interactions between homeostatic and hedonic regulatory mechanisms acting in the energy balance and reward centers of the brain. Alterations in feeding behavior are often pervasive and can lead to obesity and its associated medical complications, including metabolic and cardiovascular disorders and psychological distress. A compelling body of evidence emerged recently, indicating a pivotal role of brain-derived neurotrophic factor (BDNF) in pathological processes leading to abnormal food intake and excessive weight gain. BDNF signals through the TrkB receptor to promote neuronal survival, differentiation, and synaptic plasticity. Perturbing central BDNF signaling in mice results in hyperphagic behavior and obesity (Xu *et al*, 2003; Unger *et al*, 2007). In humans, BDNF haploinsufficiency was linked to elevated food intake and severe weight gain (Han *et al*, 2008). These findings have significant clinical implications, as the *Bdnf*Val66Met allele, which impedes regulated BDNF secretion, is highly prevalent in humans (Shimizu *et al*, 2004).

Previous work indicated that hypothalamic BDNF participates in homeostatic processes that preserve energy levels essential for survival. Recently, we demonstrated an intimate involvement of BDNF in the regulation of hedonic feeding via the positive modulation of the mesolimbic dopamine pathway (Cordeira *et al*, 2010). This neural circuit mediates motivated and reward-seeking behaviors, including consumption of palatable food, and has well-established roles in drug addiction. Mice with selective deletion of *Bdnf* in the ventral tegmental area (VTA), a principal source of mesolimbic BDNF, consumed significantly more palatable high-fat food than control mice, while exhibiting normal intake of standard chow. Furthermore, evoked release of dopamine by mesolimbic fibers in the nucleus accumbens was diminished in mice lacking central BDNF, suggesting decreased VTA dopamine neuron activity and concomitant reductions in neurotransmitter release. It was proposed previously that hypoactivity of the mesolimbic system might result in reward deficiency syndrome and, behaviorally, in compensatory overeating to enhance a deficient dopaminergic system. In support of this model, hyperphagic leptin-deficient mice were also reported to have reduced evoked dopamine release in the nucleus accumbens (Fulton *et al*, 2006). Moreover, we found that administration of a dopamine-1 receptor agonist abrogated overeating in BDNF mutant mice. The results argue strongly that BDNF is a natural modulator of hedonic food intake and that dysregulation of BDNF signaling in the reward circuitry increases the drive to eat in the absence of a homeostatic requirement.

BDNF facilitates synaptic sensitization of VTA dopamine neurons following cocaine withdrawal, which might represent a mechanism mediating cue-associated drug craving and relapse (Pu *et al*, 2006). Many questions remain regarding the effects of BDNF on excitability within the VTA during food reward-related processes. For example, does BDNF facilitate forms of synaptic plasticity in the VTA necessary for food reward learning? Does deficient BDNF signal affect the firing rate of dopamine neurons and impede transitions to burst firing and subsequent dopamine release during food reward-related processes? A better understanding of the cellular and molecular mechanisms underlying the anorexigenic effects of this pleiotropic neurotrophin will facilitate the development of novel therapies for appetitive disorders.

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The Therapeutic Potential of κ-Opioids for Treatment of Pain and Addiction

When the κ-subtype of opioid receptor was first distinguished, there was tremendous interest in developing analgesics that would provide pain-relief without activating the reward pathways stimulated by morphine-like μ-opioids. A nonaddictive opioid has been a holy grail of medicinal chemistry ever since Friedrich Serturner isolated morphine from opium in 1804. Selective κ-agonists were developed, but quickly found to produce different problems including dysphoria, diuresis, and constipation. In addition, their maximal analgesic effects were weaker than μ-opioids in rodents. But interest in κ-opioids as therapeutic tools did not completely die; Shippenberg and colleagues found that κ-agonists reduced the rewarding effects of co-administered addictive drugs; κ-opioid analgesia using pentazocine was seen as an alternative for pain control in people with a risk of drug abuse; and κ-agonists entered clinical trials for the treatment of pain and itch (see Millan, 1990).

Although enthusiasm for agonists waned, interest in κ-antagonists as therapeutic tools got a boost when Carlezon and colleagues showed their activity in the forced swim assay, predictive of antidepressant activity (Mague *et al*, 2003). Following on that study, we reported that κ-antagonism blocked stress-induced potentiation of cocaine reinforcement (McLaughlin *et al*, 2003). Numerous studies have replicated and extended those findings showing the utility of κ-antagonists to block stress-induced reinstatement of extinguished cocaine- and ethanol-seeking, block μ-opioid and cannabinoid withdrawal signs, and block the aversive effects of nicotine. All these effects of κ-antagonists can be attributed to block of the actions of endogenous dynorphins, which are κ-selective opioid peptides released during the stress response (Land *et al*,