

## PERSPECTIVE

# Hierarchical temporal processing deficit model of reality distortion and psychoses

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**We posit in this article that hierarchical temporal processing deficit is the underlying basis of reality distortion and psychoses. Schizophrenia is a prototypical reality distortion disorder in which the patient manifests with auditory hallucinations, delusions, disorganized speech and thinking, cognitive impairment, avolition and social and occupational dysfunction. Reality distortion can be present in many other disorders including bipolar disorder, major depression and even dementia. Conceptually, schizophrenia is a heterogeneous entity likely to be because of numerous causes similar to dementia. Although no single symptom or set of symptoms is pathognomonic, a cardinal feature in all patients with schizophrenia is chronic distortion of reality. The model that we have proposed accounts for the varied manifestations of reality distortion including hallucinations and delusions. In this paper we consider the implications of this model for the underlying biology of psychoses and also for the neurobiology of schizophrenia and suggest potential targets to consider for the etiology and pathophysiology of reality distortion, especially in the context of schizophrenia.**

*Molecular Psychiatry* (2011) 16, 129–144; doi:10.1038/mp.2010.63

**Keywords:** hierarchical; model; schizophrenia; genes; molecular; symptom

## Introduction

Reality distortion can be a feature of many psychiatric disorders such as mood disorders, delirium, dementia and schizophrenia. The prototypical disorder with reality distortion is schizophrenia. Schizophrenia is a disorder in which the patient manifests with auditory hallucinations, delusions, disorganized speech and thinking, cognitive impairment, avolition and social and occupational dysfunction. Conceptually, schizophrenia is a heterogeneous and clinically diverse entity likely to be because of numerous causes similar to dementia. The diagnosis of schizophrenia is made on the basis of a varied set of characteristic signs and symptoms. Oulis *et al.*<sup>1</sup> investigated the lifetime fulfillment of five sub-criteria of the primary diagnostic criterion in inpatients with a definite diagnosis of *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition schizophrenic disorder. Among the five diagnostic features captured by criterion A, only delusions were found to be almost universal, whereas of the remaining four, only hallucinations and negative symptoms occurred in

more than half of all the cases. Although no single symptom or set of symptoms is pathognomonic, a cardinal feature in all patients is chronic distortion of reality. While reality distortion can also be found in other psychiatric states such as mania, depression, dementia and delirium, the ongoing presence of severe reality distortion over time without an accompanying mood disorder is most generally associated with the diagnosis of schizophrenia.

There are many hypotheses regarding the potential causes of schizophrenia, including genetic,<sup>2</sup> viral,<sup>3</sup> neurotransmitters such as dopamine<sup>4</sup> or interactions between neurotransmitters<sup>5</sup> or brain structural anomalies.<sup>6</sup> Most of these hypotheses do not account for how or why these presumed causes lead to the manifestations of reality distortion in schizophrenia. They are also unidimensional and limited. We recently posited that schizophrenia is the result of impairment of hierarchical temporal processing by the brain.<sup>7</sup> The model that we have proposed accounts, in particular, for reality distortion. The hierarchical temporal deficit is a fundamental trait that may be a better target for the study of etiology and pathophysiology than any one of the clinical syndromes with which reality distortion is associated. In this paper, we extend our discussion to consider the implications of this model for the underlying biology of reality distortion and psychoses and by extension for the neurobiology of schizophrenia and suggest potential targets to consider for the etiology of this

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Received 29 June 2009; revised 14 March 2010; accepted 8 April 2010

illness. A key to begin to make sense of psychoses and reality distortion is to understand perception and memory prediction.

### Perception

The classical notion of perception is to conceptualize it as similar to recording of the world as it is. But perception is not unidirectional. Vision is not the same as a movie recording. It is not a bottom-up reconstruction of sensory input. Information in the visual world cannot be mapped unambiguously back onto real-world sources. Similar perceptual processes exist in the other sensory modalities. Perceptual processes therefore involve systems of inferring by matching multisensory input to a construct that serves as a working model of the world.<sup>8</sup> Helmholtz proposed that the raw 'sensations' generated by the physiological infrastructure of the eye and the input stages of the visual brain are interpreted by information derived from experience. Helmholtz described this process as making 'unconscious inferences' about reality. More recently, Purves proposed that percepts are simply subjective sensations that link stimuli to the empirical significance of their sources according to the success or failure of prior stimuli-guided behavior.<sup>9</sup> 'The conceptual basis of this alternative approach is that the percept elicited by any particular stimulus parameter corresponds not to a statistically determined value of the relevant qualities in the physical world but rather to the relative frequency of occurrence of that particular stimulus parameter in relation to all other instances of that parameter experienced in the past.'<sup>9</sup> An approach similar in principle to that used to rationalize the percepts elicited by visual stimuli can be used to explain why we hear the tones the way we do. In either case the key element is recognition and learning; percepts are generated by the interaction of bottom-up sensory input and top-down expectation of the meaning of the input. Hawkins suggested that this is best explained as a hierarchical process and suggests that this is the general operating principle of the brain.<sup>10</sup>

### Framework

The framework for understanding processing that we have outlined is an integration of what Hawkins has proposed with an additional axiom that humans are born with a certain set of neural structures and functions that help us navigate the world. These structures and functions form the basic principle on which the model is built.<sup>7</sup> The framework can be summarized as follows:

1. Sensory inputs are matched in a hierarchy of recognition that also generates predictions of the next event.
2. At each level there is recognition, learning and forwarding of signals, both to the next level up and to the level below.
3. At initial input levels neurons are fast changing and spatially specific; at higher levels they are slow and spatially invariant.

4. Each hierarchy level remembers frequently observed temporal sequences of input patterns and generates labels (assigns meaning) or constructs for these sequences.
5. Each hierarchy level is capable of storing frequently observed sequences of patterns and developing invariant representations.
6. When an input sequence matches a preexisting sequence at a given layer of the hierarchy, a construct is propagated up the hierarchy—thus eliminating details at higher levels and enabling them to learn higher-order inferences. But when there is no match between input and preexisting sequences, a more complete representation propagates upward.
7. Higher levels predict future input by matching partial sequences and projecting their future expectations to the lower levels.
8. Higher levels of the cortical hierarchy predict the future on a longer time scale, and over a wider range of sensory input. Lower levels interpret limited domains.
9. Connections from the higher level states predispose selected transitions in the lower-level state.
10. The model of the external world that is built consists of the sum of a person's invariant constructs/memories and the preexistent evolutionary configuration. This model is updated to accommodate new experiences within the framework of its preexisting structure.
11. As we interpret the world, the higher cortical areas are constantly comparing current circumstances to invariant memory stores to form predictions about the next moment of experience (memory prediction) or more likely as posited by Purves<sup>9</sup> about the likelihood of the successful behavior or response. These predictions set the stage for perception by the priming levels likely to be activated by the bottom-up sensory signals. The overall model posits that the nature of the output from a given area of cortex depends on coincidence with the patterns of the bottom-up input it is receiving at any given time. When a person is in a new situation and is experiencing 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; that is, the signals are passed on to the next highest layer and this pattern extends till a match is achieved. In this way, 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 higher-level patterns.

### Brain structure and organization as it relates to model

#### *Neocortex*

The primary activity of the brain is to relate the organism with its environment. It collects stimuli by the means of sensory receptors. The input information is transferred into the brain and compared with

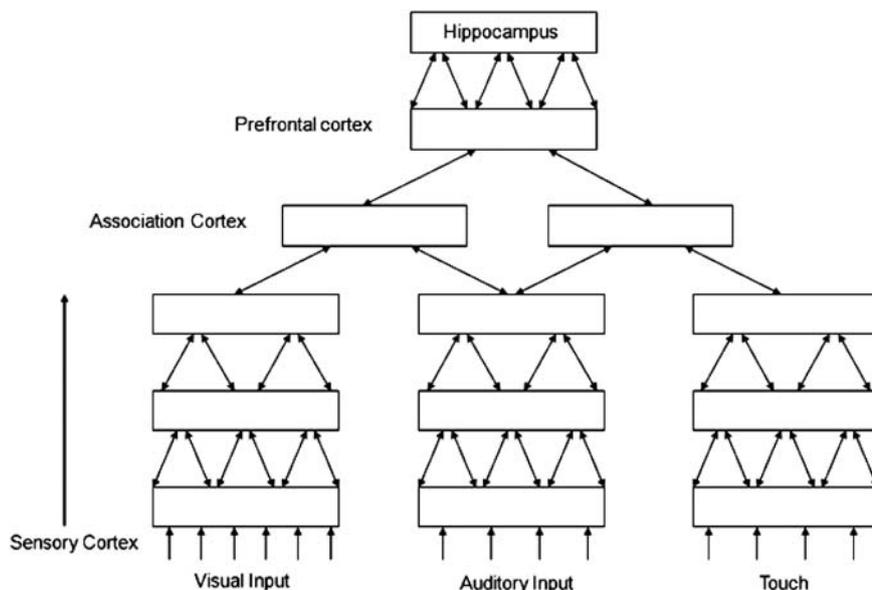
the preexisting stored information to produce the right outputs and to create/update stored information. Activity can also occur internally to the brain, with the output directed at the external world and/or at other parts of the brain. Sensory information input to the brain is first processed in the sensory cortices. It is here that the early and simple stages of recognition take place. Then the information flows to the unimodal association areas in which additional recognition of the presumed sensory signal of the particular sense takes place. The information further flows to the multimodal association regions, which puts the information in perspective for the recognition of other sensory inputs. At the same time at each level the signals generate prediction of future events. The cortical organization into columns at each area—primary, unimodal and multimodal—is completely in line with the functional hierarchical organization proposed by Hawkins<sup>10</sup> (Figure 1).

The neocortex is arranged into vertical column-like arrays of cell bodies orthogonal to the laminae.<sup>11</sup> These columns are morphological correlates of the functionality of the cortex. A column can be seen as the cortex's physical representation of a hierarchical state: all the layers in a single column participate as one element in a single hierarchical level. Each neuron in the column receives several thousand inputs. The neocortex is composed of six layers, with interneurons in all the layers, pyramidal cells in layers 2–6 (L2–6) and spiny stellate cells in L4 of the primary sensory cortex. The pyramidal cells are excitatory glutamatergic neurons. Connections from the lower-level regions project to just a few regions higher in the processing hierarchy, and these feed-forward projections tend to terminate in the superficial layers of the cortex. In contrast, projections that originate in higher-level regions tend to target many

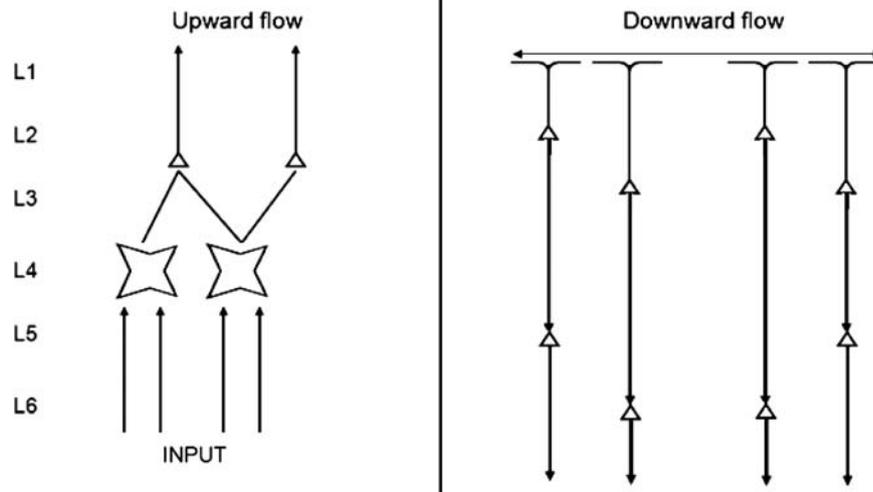
regions in the processing hierarchy, have wider connection patterns within these regions and terminate in the deep cortical layers.<sup>11</sup>

Thalamic input enters primarily into L4 targeting neurons and dendrites of neurons that pass through L4 (see Figure 1). L4 cells form a recurrent microcircuit within L4 and also project to pyramidal neurons in L3. L3 pyramidal cells are interconnected with each other to form a strong recurrent microcircuit. They also project to pyramidal cells in L2 and both L2 and L3 receive input and provide output to associational brain regions. L2/3 cells project to L5 pyramidal cells. The axon of each pyramidal neuron branches profusely, making many excitatory glutamatergic synaptic contacts. Inhibitory neurons are interspersed and are  $\gamma$ -aminobutyric acid (GABA)-ergic. Pyramidal neurons are covered with thousands of dendritic spines that constitute the postsynaptic sites for most glutamatergic synapses. The number of spines represents an estimate of the number of synaptic inputs onto a neuron. Distinct populations of GABAergic interneurons target specific cellular domains on the pyramidal neuron. Detailed neuronal circuits are yet to be fully elucidated.

Most of L5 and L6 pyramidal cells connect outside their layer of origin. In the superficial layers, the pyramidal cells make extensive connections within the same layers, monosynaptic recurrent connections between L2 and L3 pyramidal cells predominate more than in any other layer. In general, pyramidal neurons in the superficial L2 and L3 seems to be the key neurons that have a role in recognition by matching. Top-down activation from other columns in the cortex arrives at L2 and L3 through L1. This is the layer that distributes activation across columns. L2 and L3 compare bottom-up and top-down information, and generate matches when sufficient concordance is



**Figure 1** Graphical representation of hierarchical temporal processing (modified from Hawkins).



**Figure 2** Bottom-up and top-down processing. Flow of information in cortical units by layer (L) (modified from Hawkins).

achieved, or the more variable signals that occur when this fails. These signals are propagated up the hierarchy (through L4) and also down the hierarchy (through L1). The pyramidal cells of L5 drive sub-cortical structures involved in action (e.g., basal ganglia) and their activity constitutes the output of the cortical column. The same L5 pyramidal cells influence the ongoing input by their connection to L4 pyramidal cells that connect to the thalamic input layers. There is significant variation in this structure (Figure 2). For a detailed discussion see.<sup>12</sup>

Hawkins places particular emphasis on the role of the interconnections between the columns, and the activation of the columns as a whole. The hypothesis is that nerve cells in the middle layers of the cortex, in which thalamic afferents terminate, are joined by connections to cells in layers lying superficial and deep to them, so that all cells in the column are excited by incoming stimuli with only small latency differences. The columns form a series of repeating units across the horizontal extent of the cortex. Interneurons have smooth or sparsely spiny dendrites and locally projecting axons, and modulate cortical output and plasticity. Cortical interneurons are involved in the developmental processes, such as regulation of neuronal proliferation and migration and development of cortical circuitry. Cortical interneurons accomplish specific functions through subtypes, defined by their morphological, physiological and molecular characteristics. In addition to the cortex, Hawkins suggests that the thalamus and hippocampus are also involved.<sup>10</sup>

#### *Thalamus*

The thalamus have a role in temporal sequencing.<sup>10</sup> This operates in conjunction with the higher-level identification of the sequence. L5 cells send a branch

to the nonspecific cells of the thalamus. The nonspecific cells of the thalamus project to L1 of the neo-cortex in many adjacent columns. There are two inputs to L1: one from the higher regions of cortex and the other from the nonspecific cells of the thalamus. Thus, the output of a column generates L1 activity, which will coincide with the input to a column that is temporally subsequent within a sequence, thus providing the basis for Hebbian learning of sequences. The thalamus is also active as a sensory intermediate.

#### *Hippocampus*

The hippocampus is the key location for long-term memory.<sup>13</sup> Therefore, the hippocampus is thought as the top level of the cortical hierarchy, specialized to retain memories of events that propagate all the way to the top.<sup>10</sup>

#### *Circuit processing*

In the single neuron, information is coded in spike sequence, and is transferred to the other neurons by synapses.<sup>14,15</sup> The coded stimulus that is passed along the chain from one neuron to the other, is not represented in all the neurons as a copy of the same sequence of spikes.<sup>14</sup> Each neuron receives inputs from many neurons and its output is the result of the complex processes of integration. A pyramidal neuron often requires the simultaneous activation of several dendritic synaptic contacts to reach the threshold for spike generation. This posits that the information carried by a single neuron is insufficient to activate the postsynaptic neuron if it is not 'in coincidence' with other neurons (coincidence detection). The resulting spikes represent integration of information carried by all the stimulating neurons.<sup>16,17</sup> Synaptic transmission can be visualized as a mechanism of conversion of presynaptic spikes, to a

graded variation of the postsynaptic membrane potential. Pyramidal neurons therefore are thought to operate as coincidence detectors. The successive integrations along the pathways make decoding the spike sequence of a single neuron almost impossible.

The inhibitory circuits also have a key role in modulating temporal processing. Inhibition has been divided into two different types: feed-forward and feedback inhibition. Feed-forward inhibition simultaneously activates both pyramidal cells and inhibitory interneurons.<sup>18</sup> Feed-forward inhibition shortens the duration of excitatory postsynaptic potentials. Spikes triggered by these occur in a narrow time window, increasing the temporal precision of pyramidal output. Feedback inhibition is triggered by collaterals of the pyramidal cells, which activate interneurons when an output spike is generated.<sup>18</sup> Feed-forward and feedback inhibition provides complementary controls of excitability: In each column, when there is coincidence, signals are sent to the next level up and to the thalamus nonspecific neurons, but when there is no coincidence the signal is not passed on. Mumford<sup>19</sup> proposed a top-down/bottom-up model with the build-up of processing that takes into account information based on priors in its top-down/bottom-up loops that complement what we have proposed. This model posits that processing builds up in increasing complexity and systems carry both the information that has been successfully predicted by higher-level regions and the residual that needs to be explained. A recent computational model shows a physiologically plausible mechanism describing how synchronized activity may govern top-down/bottom-up integration, and how this interaction can facilitate cortical processing.<sup>20</sup>

Glutamatergic excitatory synapses have at least two types of colocalized receptors besides metabotropic receptors: the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and the *N*-methyl-D-aspartate (NMDA) receptors.<sup>21</sup> GABAergic synapses have GABA-binding receptors. The postsynaptic receptor composition is one of the most important factors of regulation of information passed by synaptic transmission. Neurotransmitters, such as dopamine, serotonin, noradrenalin and acetylcholine, modulate pyramidal-neuron function. They change various features of pyramidal-neuron function by targeting channels that are gated by voltage. This, in turn, can affect various cellular functions, such as synaptic strength, firing rates, firing modes and dendritic excitability.

At each level Hebbian learning is conceptualized as part of the framework. Hebbian theory suggests a basic mechanism of synaptic plasticity wherein change in synaptic connectivity arises from the presynaptic cell's repeated influence of the postsynaptic cell. Distal synapses on a pyramidal neuron cooperate with proximal synaptic inputs to contribute to action-potential initiation. The Hebbian theory is often simplistically summarized as 'cells that fire

together, wire together'. Hebbian plasticity involves at least two mechanisms: long-term potentiation and long-term depression.<sup>22,23</sup> Long-term potentiation is the increase of synapse sensitivity on account of a prolonged stimulation by the presynaptic neuron of the postsynaptic neuron. If the postsynaptic cell does not become sufficiently depolarized long-term potentiation does not occur. Long-term depression works in the same way; however, it focuses on the lack of depolarization. These changes are specific to each synapse. A neuron can have multiple different synapses all modulated through the same mechanisms. A mechanism for plasticity involves dendritic spines. Spines are highly plastic. These spines undergo changes in shape and size and neuronal activity regulates spine turnover and these changes alter the function of neuronal circuits. The long-term effect of these structural changes is an alteration in neuronal connectivity.<sup>23</sup> AMPA receptors stabilize spines, suggesting a role for glutamate receptors in promoting structural plasticity.<sup>24</sup>

Long-term potentiation requires a cascade of signaling events that include glutamate receptors, protein kinases and transcription factors, which lead to changes in gene transcription. Regulation of chromatin structure also serves as an additional level of control by histone acetylation. Protein phosphorylation takes longer and lasts longer, providing an additional mechanism for long-lasting memory storage. For a detailed discussion see reference 25.

#### *Dopamine and its role*

Dopamine (DA) is an important regulator of neuronal excitability and glutamate-dependent plasticity in the prefrontal cortex (PFC). D1 receptors are predominantly localized in pyramidal-like cells and parvalbumin positive cells. Studies have shown that DA receptors regulate AMPA receptor trafficking in the PFC and other regions.<sup>26,27</sup> D(1) dopamine receptors potentiate *N*-methyl-D-aspartate-mediated excitability increase in L5 prefrontal cortical pyramidal neurons. A number of other studies have also reported inhibitory effects of D2 family receptors on NMDA receptor currents in PFC pyramidal neurons. One mechanism underlying this effect may be the activation of GABA interneurons leading to pyramidal cell inhibition.<sup>28</sup> The mesocortical DA system is thus believed to optimize the characteristics of glutamatergic and GABAergic transmission in the cortex to communicate temporally precise information and to modulate network activity patterns on prolonged timescales. Clearly, there is a tremendous need to understand the dynamics of dopamine regulation of the cortical microcircuits.

### **Cortical development as it pertains to model**

#### *Development of projection neurons*

Initial brain development is accomplished in human embryos during the first 3–4 months of

**Table 1** Genes and transcription factors that have a role in cortex development and phenotypes of human mutations

<i>Gene or transcription factor</i>	<i>Human mutation phenotype</i>	<i>References</i>
<i>Foxg1</i> FORKHEAD BOX G1	Microcephaly, mental retardation (RETTS)	59
<i>Emx2</i> EMPTY SPIRACLES, DROSOPHILA, 2	Schizencephaly	61
<i>Pax6</i> PAIRED BOX GENE 6	Autism mental retardation	62
<i>Tbr2</i> T-BOX, BRAIN, 2	Microcephaly	140
<i>Ngn2</i> NEUROGENIN 2	—	
<i>Cux1</i>	—	
<i>Cux2</i>	—	
<i>Fezf2</i>	—	
<i>Ctip2</i>	—	
<i>Sox5</i> SRY-BOX 5	—	
<i>Reelin</i>	Lissencephaly schizophrenia	141
<i>PAFAH1b1</i> PLATELET-ACTIVATING FACTOR ACETYLHYDROLASE, ISOFORM 1B(lis1)	Lissencephaly	142,143
<i>BRN1</i>	—	
<i>BRN2</i>	—	
14-3-3epsilon ( <i>YWHAE</i> )	Schizophrenia	144
(CNTN)-associated protein-2 ( <i>CNTNAP2</i> )	Autism, schizophrenia	145,146

embryogenesis. This critical period of gestation is sensitive to interference from environmental, pathogenic and genetic factors.<sup>29,30</sup> The mammalian cortex consists of six layers of neurons, which are generated in an orderly manner during development. Neural progenitors in the ventricular zone give rise to distinct neural cell types in a characteristic temporal order, which then migrate in the developing cortex to populate different cortical layers. Peak migratory activity occurs between the third and fifth months of gestation, and migration is completed during the third trimester.<sup>31</sup> By the seventh month the cortex is clearly divided into six layers. The Cajal–Retzius cells are among the first postmitotic neurons to exit the ventricular zone.<sup>32</sup> They reside in L1 of the cortex and secrete an extracellular matrix protein, reelin, which provides a critical signal for the migration of later-born neurons in the cortical laminae. The cohorts of projection neurons that follow migrate along the radial glial cells to form the five other cortical layers in an inside-out fashion. First-born neurons migrate short distances and form the deep layers of cortex, whereas late-born neurons migrate longer distances and populate the superficial layers. The fate of a cortical neuron is thus determined by its birth date.<sup>33–41</sup> Early progenitors that produce deep-layer neurons, are multipotent and can produce upper-layer neurons when transplanted into an older brain environment.<sup>42,43</sup> The converse, however, is not true. Late-born progenitors are unable to generate deep-layer neurons.<sup>44</sup> The molecular mechanisms underlying the control of neuronal identity in the developing cerebral cortex involves sequential patterns of gene expression. Several genes have been involved in this process.<sup>45–52</sup> Mutations or loss of these genes can cause severe development and cognitive brain disorders in humans<sup>53</sup> (see Table 1).

Reelin is expressed mostly in the most superficial layer of the neocortex during corticogenesis and it regulates the development of the cortical plate.<sup>54</sup> Homozygous mutations in the *reelin* gene result in a severe disruption of cellular layer formation in the cerebral cortex, hippocampus and cerebellum<sup>55</sup> and cause lissencephaly.<sup>56</sup> It is of interest to note that reelin variants have also been associated with schizophrenia.<sup>57</sup>

The transcription factor, *Foxg1*, is known to affect neural fate in early phases of cortical development. *Foxg1* suppresses the generation of Cajal–Retzius cells,<sup>58</sup> and thus facilitates the transition from Cajal–Retzius cells to deep-layer neurons. Two different truncation mutants of *Foxg1* have been identified in two girls with Rett syndrome.<sup>59</sup> Both had microcephaly and mental retardation. Three other transcription factors, LIM homeobox 2,<sup>60</sup> paired box 6<sup>46,50</sup> and empty spiracles homolo 2<sup>61</sup> also restrict the generation of Cajal–Retzius cells to a narrow developmental window. In a 13-year-old boy deletion of *Pax 6* was linked to aniridia, autism and mental retardation,<sup>62</sup> whereas *Emx2* gene mutations have been associated with schizencephaly.<sup>61</sup>

Deep-layer neurons (L5–L6) are generated by early-born progenitor cells in the ventricular zone. These progenitors express a number of transcription factors such as *Fezf2*, *Sox2* and *Emx2*, which regulate the fate of their progeny. For example, the zinc-finger transcription factor *Fezf2* regulates a fate switch in cortical development. In its absence, many L5 and L6 neurons acquire the fate of callosal projection neurons (neurons that project their axon to the corpus callosum), whereas the ectopic expression of *Fezf2* in deep-layer neurons redirects the axons of callosal neurons to sub-cortical targets.<sup>63</sup> L5 and L6 neurons express a second zinc-finger transcription factor,

**Table 2** Genes that have a role in the interneural development

<i>Gene</i>	<i>Human phenotype</i>	<i>Cortical interneuron phenotype mouse</i>
<i>Dlx1</i> (DISTAL-LESS HOMEBOX 1)	Autism spectrum <sup>147</sup>	Cell subtype-specific reduction of somatostatin-positive and calretinin-positive cortical and hippocampal interneuron <sup>148</sup>
<i>Dlx2</i> (DISTAL-LESS HOMEBOX 2)	Autism spectrum	Altered differentiation of interneurons in the olfactory bulb <sup>149</sup>
<i>Nkx2.1</i> (NK2 HOMEBOX 1)	Choreoathetosis, congenital hypothyroidism. <sup>71</sup>	Defects were found in the ventral region of the forebrain <sup>150</sup>
<i>Shh</i> (sonic hedgehog)	Autosomal dominant holoprosencephaly-3, cleft lip and/or palate, microcephaly	Decreased interneurons <sup>151</sup>
<i>Six 3</i> (homologs of the <i>Drosophila</i> 'sine oculis')	Holoprosencephaly <sup>152</sup>	Decreased interneurons <sup>153</sup>
<i>Mash1</i> (MAMMALIAN ACHAETE-SCUTE HOMOLOG 1) (ARISTALESS-RELATED HOMEBOX, X-LINKED;) <i>ARX</i>	Central hypoventilation syndrome <sup>154</sup> Early-onset epileptic encephalopathy. <sup>70</sup>	Dysgenesis of striatum <sup>155</sup> Abnormal interneurons <sup>156</sup>
<i>Tailless</i>	—	Maintains adult neural stem cells in an undifferentiated proliferative state decreased rhinencephalon <sup>157</sup>

*Ctip2*, which functions downstream of *Fezf2*, in regulating the fate of subcortically projecting L5 neurons and corticothalamic projection neurons in L6.<sup>63</sup> Upstream of the *Fezf2-Ctip2* pathway, *Sox5* has been implicated in regulating the timing of deep layer differentiation of subcortical projection neurons.<sup>64</sup> Callosal projection neurons, which are predominantly found in upper cortical layers, require the chromatin remodeling protein, *Satb2*, for the formation of their normal projections, and in the absence of *Satb2*, these cells extend axons toward subcortical targets.<sup>54</sup>

Upper-layer neurons arise from progenitor cells in the sub-ventricular zone. Here again, sub-ventricular zone precursors cells exhibit patterns of gene expression, which match those in upper-layer neurons. Sub-ventricular zone neuron precursors express the transcription factors T-BOX Brain 2,<sup>50</sup> neurogenin 2,<sup>65</sup> cut-like homeobox 1 and cut-like homeobox 2.<sup>52</sup> The progressive attenuation of *Pax6* expression and the initiation of *Tbr2* expression characterize the transition to intermediate progenitors. Deletion of *Trb2* in mice resulted in microcephaly. In *Trb2*<sup>-/-</sup> homozygous mutants, the number of subventricular zone progenitor cells was reduced and differentiation of upper cortical layer neurons was disturbed.

#### *Interneuron development*

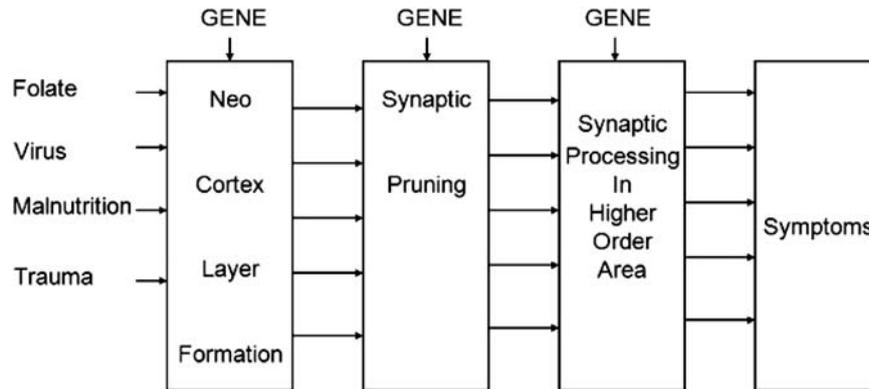
In contrast to the excitatory cortical projection neurons, which derive from the dorsal telencephalon and migrate radially to the cortical plate, GABAergic neurons originate from the ventral telencephalon and migrate tangentially into the developing cortex.<sup>67,68</sup> Several transcription factors, including *Arx*, *Nkx2.1*,

*Dlx1/2* and *Mash1*, have been shown to genetically specify GABAergic phenotypic features.<sup>49,69</sup> Dysfunction of these genes causes abnormal interneuron development and brain disorders (Table 2). For example, a mutation of *Arx*, which seems to be regulated by *Dlx1* and *Dlx2*, results in the abnormal development of interneurons in mice and severe infantile seizures in humans.<sup>70</sup> Humans with single-copy mutations in *Nkx2.1* develop a moderate movement disorder that was associated in one study with a reduction in the number of striatal interneurons, although seizures have not been reported.<sup>71</sup>

GABA-mediated signaling is involved in neuronal proliferation, migration and differentiation in the developing nervous system.<sup>72</sup> One remarkable feature of GABA is that it functions as an excitatory neurotransmitter during early brain development.<sup>73</sup> GABA becomes inhibitory soon after birth upon expression of the potassium/chloride exchanger *KCC2*, which controls the reversal potential of chloride ions.<sup>74</sup> GABA stimulates the motility and migration of embryonic interneurons<sup>75</sup> and can promote directed migration (chemotaxis) of cortical neurons.<sup>76–78</sup> A recent report indicates that *KCC2* expression and transition of GABA from an excitatory to inhibitory neurotransmitter promotes the termination of interneuron migration during cortical development.<sup>75</sup> Surprisingly, however, mice with null mutations in genes of the GABA pathway have few developmental abnormalities in the central nervous system.<sup>79</sup>

#### *Adolescent cortical development*

In humans, the initial genesis of neurons is followed by the loss of up to 50% of cortical neurons later in



**Figure 3** Multiple stages and factors that can impair cortical development and processing in schizophrenia.

gestation.<sup>80</sup> In early postnatal brain development, there is a marked increase in synaptic density<sup>81</sup> which is then pruned during childhood and adolescence. Giedd *et al.*<sup>82</sup> showed that the gray matter increases during childhood and adolescence and then decreases but the white matter myelination process seems to continue into adulthood. Cortical gray maturation progresses in a 'back-to-front' manner.<sup>83</sup> Analyses using cortical thickness show that both childhood onset schizophrenia probands and healthy siblings with glutamic acid decarboxylase risk allele, a modulator enzyme that converts glutamate to GABA,<sup>84</sup> have steeper slopes of cortical gray matter loss in prefrontal cortex. This is accordance with our previous discussion on GABA that it exerts morphogenetic functions during development.

### What happens in psychoses?

We propose that in psychoses and reality distortion there is a problem in communication between different layers of the cortex in the column such that memory-based prediction of perception is impaired. In reversible psychoses, as in mania and depression and potentially in those patients diagnosed with schizophrenia who remit or recover, there may be a similar impairment; however, it is likely to be functional and probably not structural as in chronic schizophrenia. The clinical presentation of schizophrenia is not a true phenotype, as it comprises varied symptoms that derive from diverse systems, occurs in nonoverlapping patterns and does not breed true. We would posit that the true endophenotype of schizophrenia is a defect in hierarchical temporal processing (memory-prediction deficit), which is the meta-process that underlies diverse impairments in cognition and the complex and varied signs and symptoms of schizophrenia. This way of thinking about psychoses is very similar to the way in which we think about cancer, which is also a disease with diverse clinical presentations because of a more fundamental process, misregulation of cell proliferation. For psychoses and reality distortion, it is impaired hierarchical temporal processing. In the

early stages of the disease process, 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. Thus, information needs to be sent repeatedly to higher hierarchical levels for interpretation. This reduction in the correct identification of percepts, combined with real-world information processing demands, affords the opportunity for arbitrary internally generated interpretations of reality to intrude on perception and thought. A repeated inability to perceive correctly may lead to an accumulation of inaccurate but internally meaningful perceptions that could then build on one another into incorrect beliefs. This failed process may be at the core of the development of a tendency for 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 hallucinations and delusions. We suggest that this could be the result of various factors acting at different times (see Figure 3).

Impairment of the memory-prediction function in schizophrenic patients represents a unifying deficit underlying the defined cognitive deficits associated with the disease. Prediction based on earlier experience serves to speed perception, thought and action by priming cortical columns that are expected to be driven by the bottom-up input. In addition, prediction serves to direct attention to sensory features of expected importance, or to stimuli that violate predictions. As elements of the sensory world are less contextually integrated in schizophrenia, the predictive signal that cascades from higher to lower cortical regions is incomplete. More of the sensory world is unpredictable for someone with psychoses or schizophrenia, the salience of items is developed more randomly, sensations compete for limited attentional resources and the formation of long-term memories is inadequate. Impairments of memory-prediction function thus impair performance on

a broad range of tasks that depend on key cognitive abilities such as processing speed, long-term memory and attention.

### What is the evidence for this hypothesis?

There are at least three major lines of evidence in support of our premise in the context of the prototypical disorder schizophrenia. They include morphological and structural deficits in schizophrenia, the cognitive features of the disorder and the putative genetic risk factors.

#### *Brain structural deficits in schizophrenia as it relates to model*

Multiple structural deficits in the multimodal association areas, hippocampus and thalamus have been shown in schizophrenia and are in accordance with our hypothesis that higher hierarchical levels are impaired.<sup>84</sup> One component of these circuits, pyramidal cells in deep L3 of the auditory association cortex (area 42), has reduced mean somal volume in patients with schizophrenia.<sup>85</sup> This pattern of abnormalities is consistent with impairments of auditory feed-forward projection neurons and is consistent with our hypothesis.<sup>85</sup> Lower dendrite density in deep L3 of Brodmann Area 41 and 42 of patients with schizophrenia reflects concurrent reductions in excitatory afferent input.<sup>86</sup> This may also contribute to impairments in the auditory sensory processing that are present in patients with schizophrenia. In addition, similar changes are seen in the visual system. Top-down facilitation is triggered by magnocellular information projected to the orbitofrontal cortex.<sup>87</sup> Schizophrenia is associated with the impairment of the magnocellular visual pathway, which is in accordance with our hypothesis as shown by functional imaging and by diffusion tensor imaging.<sup>88</sup> In addition, there are changes in the primary visual cortex.<sup>89</sup>

Critically, there are similar changes in the prefrontal cortex, that is, deep L3 of PFC area.<sup>89</sup> Pyramidal neurons in L3 were significantly decreased. In addition, GABAergic neurons are reduced substantially in the middle layers of the PFC<sup>90</sup> and there is a reduction in dendritic spines.<sup>91</sup> As noted earlier, these neurons are of particular interest in schizophrenia because they (1) receive direct synaptic input from dopamine axons, (2) exert powerful inhibitory control over the excitatory output of L3 pyramidal neurons and (3) undergo substantial developmental changes during late adolescence, the typical age of onset of schizophrenia. Other evidence although not as well developed involves the hippocampus and anterior cingulate. Numerous studies have shown anomalies in the structure and function of these areas of the brain in schizophrenia. Neuropathological studies have shown deficits of GABAergic interneurons in the hippocampus in schizophrenia, although other changes are controversial. Similar postmortem findings are indicated for the anterior cingulate in which imaging-related changes are accompanied by

reductions in neuronal, synaptic and dendritic density, and increased afferent input. We would predict that in other forms of psychoses and reality distortion there would be functional deficits and in those disease entities in which there is persistent psychoses, structural and cellular deficits will be seen.

#### *Perceptual and cognitive deficits in schizophrenia as it relates to model*

One of the key elements predicted by the model will be that the pathways involved in top-down facilitation are affected in schizophrenia. Although classic models of cognition and perception have assumed that perception is mediated by bottom-up processes, the current model allows for a top-down memory-based prediction of perception. Therefore, a recent emphasis on perception deficits in schizophrenia<sup>92</sup> is not inconsistent with the hierarchical temporal processing deficit model of schizophrenia presented here. Consistent with the structural changes, there is evidence of visual dysfunction.<sup>88,93,94</sup> Deficits in the functioning of the magnocellular pathway have been shown by psychophysical tasks in nonmedicated schizophrenia patients.<sup>93–95</sup> Schizophrenia patients have trouble with processing and recognizing incomplete sensory information. Schizophrenia patients require more complete visual stimuli than healthy controls to identify images.<sup>96,97</sup> This suggests that patients have higher-order top-down processing difficulty. However, they perform better when asked to draw the fragmented stimuli from memory as accurately as possible even though they cannot recognize the objects.<sup>98</sup> Again, this is consistent with intact bottom-up processing but impaired top-down processing. The same pattern is seen with processing faces. Schizophrenia patients have trouble in recognizing a briefly flashed, degraded face, even if they can recognize faces that are vertically flipped. This suggests that the impairment is not because of generalized visual processing deficits<sup>99</sup> but that top-down processes exert less guidance. This, in turn, may underlie their impaired processing of emotional components of facial expressions.<sup>99,100</sup> One of the more robust physiological findings in schizophrenic patients is reduced mismatch negativity to auditory odd-ball stimuli.<sup>101</sup> This is elicited in controls when a regular series of tones is interrupted by a tone that deviates. The mismatch negativity results reflect a process of predicting sensory input based on expectations formed by previous experience.<sup>102</sup> The decreased mismatch negativity seen in individuals with schizophrenia suggests a deficit in these processes and is consistent with the model proposed here.

Schizophrenic patients, unlike controls, do not exhibit a decrease in the N400 peaks to semantically primed words compared with unprimed words,<sup>103</sup> suggesting a hypoactivation of concept representations semantically related to the prime. This again reflects a defect in top-down processing. The deficit in automatic retrieval of semantically related words seen in schizophrenia leads not only to impaired

verbal comprehension, but also to disordered speech production. The brain is believed to organize and coordinates information through synchronized oscillatory activity between neuronal assemblies. The  $\theta$  (4–7 Hz) and  $\gamma$  (30–100 Hz) activities seem to be universal properties of circuits that are gated by feed-forward inhibition.<sup>104</sup> A functional role of  $\gamma$ -band oscillations for information processing in cortical networks has been obtained in studies investigating the relations between stimulus-induced synchronization of  $\gamma$  oscillations and feature binding in cat primary visual cortex (V1) by Gray and Singer. A series of studies has examined  $\gamma$ -band activity in patients with schizophrenia, providing consistent evidence for the presence of abnormal  $\gamma$ -band oscillations. However, this is on a scale larger than a single neocortex unit and the evidence is supportive, but it cannot be taken as definitive. We would similarly posit that in other forms of psychoses similar perceptual deficits will be seen during psychotic time periods.

#### *Susceptibility genes for schizophrenia and associated neurodevelopment disorders*

The subtle structural abnormalities in the brains of people with schizophrenia and the early onset of disease (adolescence) are consistent with the emerging view that schizophrenia is a disorder of neurodevelopment.<sup>105</sup> These subtle changes could be in the form of neuronal migration and/or synaptic deficits of both pyramidal neurons and interneurons. However, patterning of the neocortex is essentially completed before birth, implying that embryonic neurodevelopmental defects would manifest themselves as clinical symptoms (psychosis) much later in life. Although the main architecture of the cortex is established before birth, it is clear that substantial refinement of cortical circuits occurs later in life. For example, there is massive pruning of cortical synapses and increased myelination during adolescence,<sup>106</sup> at a time that coincides with the enhancement of cognitive abilities and functional maturation of the PFC. One view stipulates that a prenatal neurodevelopment defect remains clinically silent until it interacts with maturational and/or environmental events later in life to cause disease.<sup>107</sup> Such events could include altered synaptic pruning during adolescence or hormonal changes during puberty. Alternatively, schizophrenia could result from defects in neurodevelopment events that occur later in life and coincide with the onset of disease, such as abnormal synaptic pruning, decrease number of a specific class of interneurons, or altered neurogenesis in the adult. Environmental factors, both prenatal perinatal and postnatal, are also likely to be important etiological factors. Serious viral central nervous system infections during both fetal life and childhood seem to be associated with the development of schizophrenia and nonaffective psychoses.<sup>108</sup> Schizophrenia and other nonaffective psychoses are strongly associated with hypoxic-ischemia-related fetal/neonatal compli-

cations of disordered growth and development. Early gestational exposure to the Dutch Hunger Winter of 1944–1945 and to a severe famine in China are each associated with an increased risk of schizophrenia in offspring.<sup>109–111</sup>

Among the various neurodevelopmental events that shape the final architecture and connectivity of the cortex, defects in neuronal migration and synaptic functions have often been associated with schizophrenia. In the context of our hypothesis, subtle alterations in neuronal migration and/or synapse function could lead to misconnectivity of different cortical layers in a column such that external sensory inputs generate inappropriate cognitive responses and accurate memory-based prediction of perception is impaired. In this section, we review recent evidence that points to a role of susceptibility genes for schizophrenia on cortical migration, neuronal circuit assembly and synaptic functions (Tables 1 and 2).

The main evidence for neuronal migration defects in schizophrenia is based on the observation that many candidate susceptibility genes for schizophrenia regulate neuronal migration during corticogenesis (Tables 1 and 2). Disease-associated mutations, truncations or deletions of these genes often cause abnormalities in neuronal migration and cortex development in animal models (see below) suggesting that defects in neuronal migration might represent one etiological cause of schizophrenia.

Disrupted-in-schizophrenia-1 (*DISC1*) was initially identified as a gene disrupted by a balanced chromosomal translocation on chromosome 1q42 that cosegregates with schizophrenia and other psychiatric disorders in a large Scottish family.<sup>112</sup> The translocation breakpoint is located in one exon of *DISC1*, resulting in a C-terminal truncated form of the gene product. *DISC1* has since been implicated in schizophrenia in other ethnic groups, based on linkage and single-nucleotide polymorphism association studies. Several reports point to a role of *DISC1* in neuronal morphogenesis and migration early on during brain development. In utero electroporation of short-hairpin RNAs against *DISC1* or expression of a disease-associated truncated mutant of *DISC1* (*mutDISC1*) in mouse embryos leads to impaired neuron migration to the cortical plate.<sup>113</sup> Silencing of *DISC1* or overexpressing *mutDISC1* result in misoriented dendrites in the developing cortex.<sup>113</sup> In addition, the expression of *mutDISC1* also impairs neurite outgrowth *in vitro*.<sup>114</sup> *DISC-1* seems to regulate neuronal migration and outgrowth through interaction with the dynein motor complex, which associates with the centrosome. The centrosome functions as the main microtubule organizing center in the mammalian cells and has been proposed to regulate nucleokinesis, the process by which the nucleus is pulled toward the leading edge of a migrating neuron.

Interestingly, *DISC1* is part of a protein complex that includes several important regulators of neuronal migration including NUDEL, LIS1, reelin and double cortin (DCX). Mutations of these genes cause Lissen-

cephaly. *DISC1* directly interacts with NUDEL, which bridges *DISC1* to other components of the complex.<sup>115</sup> The disease-truncated mutant of *DISC1* is unable to bind to NUDEL and is released from the dynein motor complex, suggesting that *DISC1* is part of the machinery that regulates microtubule dynamics during cortical migration. Defects in neuronal migration resulting from the expression of disease-associated mut*DISC1* (i.e. retarded radial migration) are subtle compared with those caused by the efficient knockdown of *DISC1* using short-hairpin RNAs,<sup>113</sup> suggesting that only partial impairment of *DISC1* may occur in the brain of these Scottish patients because of one disrupted allele of *DISC1* on chromosomal translocation (haploinsufficiency) and/or mild dominant-negative effect of mut*DISC1*. Partial impairment of *DISC1* function results in a minor migration phenotype, which could progressively evolve into altered cortical connectivity and contribute to disease. Interestingly, point mutations in *reelin* have been genetically linked to schizophrenia,<sup>57</sup> whereas loss-of-function mutations cause Lissencephaly.<sup>56</sup> These data support the notion that partial impairment (as opposed to complete inactivation) of genes regulating neuronal migration causes a subtle and progressive deviation from the normal developmental trajectory that could result in schizophrenia.

Recent evidence indicates that *DISC1* may also control later neurodevelopmental stages in the adult. A recent report shows that *DISC1* regulates the integration of newly generated neurons in the adult dentate gyrus.<sup>116</sup> Although *DISC1* is broadly expressed in the developing brain, its expression profile is restricted in the adult to dentate granule cells of the hippocampus, suggesting a role of *DISC1* in adult neurogenesis. Using an oncoretrovirus approach to specifically deliver short-hairpin RNAs against *DISC1* in dividing progenitor cells of the adult dentate gyrus,<sup>117</sup> Xin Duan *et al.*, have found that down-regulation of *DISC1* leads to accelerated neuronal integration, characterized by aberrant dendritic morphogenesis and mispositioning of new dentate granule cells because of overextended migration.<sup>116</sup> Interestingly, knockdown of *DISC1* led to the unusual appearance of basal dendrites in these adult-born neurons, a phenotype that was reported earlier in some schizophrenic patients.<sup>118</sup> In addition, the neurons of the newborns with reduced levels of *DISC1* exhibit enhanced excitability and accelerated synapse formation. *DISC1* cooperates with *NUDEL* to control neuronal integration, suggesting that *DISC1* regulates neurogenesis at least in part through its role on microtubule dynamics. These results point to a negative modulatory role of *DISC1* in all steps of neuronal integration in the adult dentate gyrus, a notion that is in apparent contradiction with the role of *DISC1* in the developing cortex.

The role of *DISC1* in neuronal integration in the dentate gyrus is particularly interesting with regard to the importance of the mossy fiber synapse in hippocampal functions and psychiatric disorders.<sup>119</sup>

The axons of the granules cells in the dentate gyrus, the mossy fibers, synapse onto CA3 pyramidal neurons in the tri-synaptic circuit of the hippocampus. Mossy fiber synapses are characterized by an unusual form of short-term presynaptic plasticity, termed frequency facilitation, which functions as a high-pass filter to mediate selective activation of postsynaptic CA3 neurons during high-frequency stimulation. Frequency facilitation of the mossy fiber synapse is established during postnatal development and is thought to have a central role in information processing and storage in the hippocampus. Recently, the dentate gyrus was shown to discriminate between new representations (memories), and related representations that already exist in the network, a process termed pattern separation,<sup>120</sup> which is impaired in schizophrenics. Two other schizophrenia susceptibility genes have been linked to neurogenesis in the dentate gyrus and mossy fiber synaptic functions. The transcription factor, *NPAS3* (neuronal PAS domain 3), is disrupted by a chromosomal translocation (14q13) in a family with schizophrenia.<sup>121</sup> Genetic deletion of *NPAS* in mice causes reduced neurogenesis in the adult dentate gyrus and hyperactivity.<sup>122</sup> The *DTNBP1* gene, a promising candidate susceptibility gene for schizophrenia, shows reduced expression in mossy fibers synaptic terminals in schizophrenia brains. *DTNBP1* has been proposed to regulate glutamate release in presynaptic terminals, and mice lacking *dysbindin-1*, the mouse ortholog of *DTNBP1*, show impaired working memory. Taken together, these results suggest a model wherein aberrant integration of adult-born neurons in the dentate gyrus, in conjunction with reduced neurogenesis and abnormal release of glutamate at the mossy fiber terminals, impairs higher-order top-down processing of sensory inputs in the hippocampus of schizophrenia patients.

Neuregulin-1 (*NRG1*) is a leading gene in schizophrenia, with strong genetic evidence for a direct contribution to the disease.<sup>123</sup> More than 20 single-nucleotide polymorphisms in the *NRG1* locus have been repeatedly associated with schizophrenia in diverse populations.<sup>123</sup> *NRG1* is a member of the neuregulins, a family of trophic factors that signal through ErbB receptors. The wealth of data accumulated over the last 15 years has established key roles of *NRG1* in a broad range of neurodevelopmental processes, including neural fate determination, migration of interneurons, myelination and synaptic plasticity.<sup>124,125</sup> *NRG1* impinges on neural migration in two distinct ways. First, *NRG1* regulates the differentiation of radial glia. Blockage of *NRG1* signaling results in shorter radial glia fibers and thus impairs neuronal motility and radial migration of cortical projection neurons. Second, *NRG1* controls the migration of GABAergic interneurons in the developing cortex. Interneurons destined to the neocortex migrate tangentially from the ventral telencephalon. Tangential migration of GABAergic neurons is achieved through a series of attractive and repulsive guidance events, and *NRG1* is one important chemoattractant cue that

regulates this process. In support of a role of neuregulin signaling in schizophrenia, the *ERBB4* gene, which encodes a type I transmembrane tyrosine kinase receptor for neuregulins, is disrupted by a 399-kb deletion in one case of the childhood onset of schizophrenia<sup>126</sup> and has been recently identified as a strong common variant associated with schizophrenia in a recent large-scale genome-wide association study.<sup>127</sup>

Importantly, schizophrenia patients show a pronounced deficiency in a sub-class of interneurons called the Chandelier cells,<sup>4,128</sup> which synapse on the initial segment of L3 pyramidal cells in the cortex. L3 pyramidal neurons and chandelier cells share common afferent inputs from the thalamus, resulting in a feed-forward disinaptic circuit that synchronizes the firing activity of the local populations of pyramidal neurons. Synapse formation between Chandelier cells and pyramidal neurons markedly increases during puberty and declines during adolescence.<sup>4</sup> As Chandelier cells are powerful modulators of pyramidal neuron outputs, a decrease in the inhibitory synapses of Chandelier cells may contribute to disturbances in the cognitive functions (i.e. working memory) observed in schizophrenia patients.

In a series of three large-scale genome-wide association studies, polygenic variations at the major histocompatibility complex locus have been implicated in schizophrenia and bipolar disorders.<sup>127,129,130</sup> Members of major histocompatibility complex class I family of proteins are central in the adaptive immune system, in which they present self and nonself peptides for immune surveillance, raising the interesting possibility that there is a link between schizophrenia and infection or autoimmunity. Recent evidence indicates that major histocompatibility complex class I molecules regulate neuronal development and synaptic plasticity in healthy, uninfected neurons,<sup>131</sup> suggesting that genetic alteration of major histocompatibility complex class I may modify neuronal connectivity and contribute to the development of schizophrenia.

Intriguingly, some of the candidate genes for schizophrenia have also been implicated in autism, suggesting that these two psychiatric disorders share pathogenic mechanisms in neurodevelopment and synapse function. Copy number variations in several different chromosomal regions (22q11.2, 1q21.1, 15q11.2, 15q13.3) predispose for both autism and schizophrenia.<sup>132</sup> Single genes have now been implicated in both schizophrenia and autism and include *DISC1*,<sup>133</sup> *reelin*,<sup>134</sup> and contactin-associated protein 2.<sup>132</sup> These data support the idea that susceptibility for schizophrenia and autism may have common genetic fingerprints. This may extend to other forms of psychoses in which there could be risk genes that cut across current nosological schemes.

### What do we predict?

The basic consequence of the model is that we can make a series of predictions about the heterogeneous entity, schizophrenia and about psychoses.

The first and key prediction is that the primary deficit in all psychoses and schizophrenia will be in hierarchical temporal processing expressed as memory-prediction errors. Therefore, a key prediction will be that during psychosis there should be a deficit in this process. This way of thinking about psychoses and/or schizophrenia is very similar to the way in which we think about cancer, a disease with diverse clinical presentations that are due to a fundamental process, namely dysregulation of cell proliferation. This fundamental memory-prediction deficit becomes the underlying structural basis of all the commonly described core features of psychoses and schizophrenia, such as reality distortion delusions, hallucinations and cognitive impairment. We would similarly posit that in other forms of psychoses similar memory prediction and perceptual deficits will be seen during the psychotic time periods. Four such tests are described below; for a more detailed discussion, see reference.<sup>135</sup>

#### *Binocular depth inversion*

Binocular depth inversion frequently occurs when viewing 'hollow' versions of common objects created by switching the images typically viewed by each eye and is especially prevalent when viewing hollow faces.<sup>136</sup> This illusory perception reflects top-down 'hypotheses' overriding bottom-up sensory information of unlikely stimuli. When viewing hollow presentations of common visual objects, patients with schizophrenia more frequently report perceiving the veridical convex stimuli than do control participants.<sup>137</sup>

#### *Perceptual closure*

Objects in the environment are often partially obscured by other overlapping stimuli, but the human visual system still shows a remarkable ability to identify objects from these fragmented sensory inputs.<sup>96,97</sup> When presented with fragmented line drawings of common objects in a stepwise fashion (whereby each successive presentation of a given stimulus is more complete), individuals with schizophrenia require more complete stimuli before they are able to recognize the figures. The visual closure task offers a direct measure of the process by which invariant representations affect current perception; it may be especially sensitive to changes that occur early in the conversion to psychosis.

#### *Spurious messages from noise*

When presented with multispeaker babble consisting of 12 independent streams of speech and given the task of repeating any words or phrases that they perceive, patients with early-phase psychosis report longer word strings than healthy controls or more chronic schizophrenia patients.<sup>138</sup> Deficits in memory-prediction function reduce the automaticity with which the world is perceived and understood, thereby weighting internally generated interpretations of reality that color perception. As memory-prediction

function is hypothesized to be impaired before the onset of psychosis, this task may identify at-risk patients. In fact, pilot data suggest that at-risk patients who later convert to schizophrenia spectrum disorders report longer word strings in contrast to participants who fail to convert, suggesting a greater propensity to increase the salience of illusory auditory information perceived from background noise.

#### Reality distortion

Another task by Sorkin *et al.*<sup>139</sup> evaluated the ability of patients with schizophrenia to assess incoherence in the environment. They used a head-mounted display-delivered virtual reality. Apart from the deliberately planted incoherencies the virtual environment resembled the real world. Whenever the path of the participant traversed an incoherent event the participant had to detect the incoherency. Schizophrenia patients performed very poorly and could be differentiated from the normal population. A falsifying hypothesis for our theory is that all patients with schizophrenia will have an abnormal profile on one or more of these tasks. These deficits will provide greater power for the prediction of psychosis than currently existing cognitive measures. But it does not mean that everyone with this deficit will have psychosis.

The second prediction (falsifying hypotheses) is that this memory-prediction deficit as tested by the tasks described above when present in individuals will presage conversion to schizophrenia and maybe other forms of psychoses. Adolescents and young adults who manifest 'high-risk' symptoms such as social withdrawal, unusual thinking, and disorganization will be more likely to show memory-prediction impairments. Young people with the most impaired performance on memory-prediction tasks will be at the greatest risk for schizophrenia.

The third series of predictions logically flows from the above that most of the causes in schizophrenia will be developmental and will include genes that affect development of the cortex, myelination and those affecting formation and maintenance of synapses, especially those that involve the pyramidal and GABAergic neurons. Many of the potential pathways have been highlighted earlier and we would posit that these should be the pathways of high interest for showing anomalies. It points out a number of risk pathways and biological approaches that can be undertaken. As we noted, the processes that underlie disruption of hierarchical recognition and learning are likely to be because of many factors, many of which could be environmental (see Figure 3). The evidence that is accumulating with regard to hypoxia/ischemia and infections during development in early childhood and the effects of nutrition, would be of major relevance.

Another key and explicit implication is that schizophrenia, as we describe it, is a syndrome that is constituted by many distinct diseases, some albeit rare due to a single cause and many due to multitude

of factors both genetic and environmental. This also means that traditional genetic studies are unlikely to be greatly informative because they measure a multitude of phenotypes. This approach may extend to other forms of psychoses in which there could be risk genes and other pathway changes both functional and structural that cut across current nosological schemes. Future studies using the revised notions that we have described will lead to a better understanding of diseases such as psychoses and schizophrenia and may be more specific and targeted treatment.

#### Conflict of interest

The authors declare no conflict of interest.

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