Feature Review

CellPress

Translating the MAM model of psychosis to humans

Gemma Modinos[1*], Paul Allen[1*], Anthony A. Grace[2], and Philip McGuire[1]

[1] Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[2] Departments of Neuroscience, Psychiatry, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA

Elevated dopamine function and alterations in medial temporal lobe (MTL) structure and function are two of the most robust findings in schizophrenia, but how interactions between these abnormalities underlie the onset of psychosis is unclear. The methylazoxymethanol acetate (MAM) rodent model proposes that psychosis develops as a result of a perturbation of MTL function, leading to elevated striatal dopamine dysfunction. Here, we review several recent neuroimaging studies that examine components of the putative model in humans with an ultra high risk (UHR) of the psychosis. While data from these studies are broadly consistent with the MAM model, caution is required when comparing data across animal and human studies.

The neurobiology of psychosis onset

In recent years, several animal models have been developed to advance research into the neurobiological mechanisms that underlie the onset of psychosis (Box 1). The development of these preclinical models has been partly been informed by findings from neuroimaging studies in patients with psychosis, or humans at high risk of developing the disorder. Two of the most robust and replicated clinical findings are that presynaptic dopamine function is elevated in the midbrain and striatum [1–3], and that there are neuroanatomical and physiological alterations in the hippocampus and adjacent MTL structures [4–6]. These two findings have largely been identified through independent bodies of work, and the extent to which the interactions between them contribute to the development of psychosis is still unclear. Dopamine dysfunction has historically been regarded as the primary factor underlying psychosis [7], but recent work in experimental animals, using the methylating agent MAM has highlighted the role of a hippocampal–midbrain–striatal circuit, and introduced the concept that subcortical dopamine function is elevated as a consequence of changes in descending outputs from the MTL [8,9]. The MAM animal model is appealing because it incorporates a disruption of brain development, which is thought to be fundamental to psychotic disorders [10–12]. In this model, neurodevelopment is experimentally perturbed by the administration of methylazoxymethanol acetate to pregnant rats on gestational day 17 [12] (see Box 2 for details). An elaboration of this model can be extended to the psychopathology of psychosis, with the suggestion that the elevation in dopamine function leads to the formation of abnormal associations and that this underlies the generation of symptoms such as delusions [13,14] (Box 3). Ultimately, useful animal models of disease need to provide a framework to generate predictions that can be tested in clinical research. The MAM provides a good example of such a model, because it leads to several neurobiological alterations that can be assessed in humans using neuroimaging methods (Box 4).

Human neuroimaging studies enable the measurement of brain structure, function, and neurochemistry. However, comparing putatively equivalent neurobiological measures across animal and human studies has some limitations. The neuroimaging methods that are used in human studies often only provide indirect or proxy measures of neuronal activity, neurotransmitter function, or inter-regional connectivity. For example, electrophysiological studies in experimental animals can provide a direct measure of neuronal activity, whereas the blood oxygen level-dependent (BOLD) signal that is derived from functional magnetic resonance imaging (fMRI) in humans reflects the vascular response to local neural activity [15]. Microdialysis in freely moving animals permits a dynamic measurement of neurochemistry that is not possible with molecular imaging techniques in humans. Similarly, although magnetic resonance spectroscopy (1H-MRS) can be used to measure neurotransmitter concentrations in humans, it yields an average measure across a relatively large volume that may include white matter, cerebrospinal fluid (CSF), and vascular tissue, as well as gray matter. Moreover, in the case of spectroscopic measures of glutamate, it is difficult to determine whether the signal reflects glutamate in the metabolic or the neurotransmitter pools [16]. By contrast, MRS in animals permits the quantification of glutamate and GABA concentrations that can be verified with *ex vivo* biochemical assays [17]. With these methodological caveats in mind, here we assess the extent to which findings from neuroimaging studies in patients with psychosis and in humans at high risk of the disorder are consistent with what would be predicted from the MAM animal model.

Corresponding author: Modinos, G. (gemma.modinos@kcl.ac.uk).
Keywords: neurobiology; psychosis; neuroimaging; animal research; schizophrenia; prodrome.
*These authors contributed equally to this article.

0166-2236/
 http://dx.doi.org/10.1016/j.tins.2014.12.005

Box 1. Rodent developmental models of psychosis

Prenatal immune activation

Based on the premise that prenatal infection acts as a 'neurodevelopmental disease primer' for several mental illnesses, including schizophrenia, these models use maternal gestational exposure to human influenza virus, the viral mimic polyriboinosinic-polyribocytidilic acid (Poly I:C), the bacterial endotoxin lipopolysaccharide, the locally acting inflammatory agent turpentine, or selected inflammatory cytokines [106,107], resulting in (i) anatomical effects, such as reduced thickness of the neocortex and hippocampus, and decreased myelination and axonal diameters in the hippocampus, but no loss of oligodendrocytes; and (ii) pharmacological effects, such as reductions of cortical reelin immunoreactivity in offspring.

However, more conclusive data on the involvement of reelin in schizophrenia and on the behavioral phenotype of the animal model are required before conclusions about the relevance of this model for schizophrenia can be made.

Neonatal hippocampal lesion

Neonatal hippocampal lesions involve experimental ibotenic acid lesions of the ventral hippocampus in neonatal rats. The lesion affects the ventral hippocampus and subiculum (corresponding to the anterior hippocampus in humans [108]), regions that directly project to the prefrontal cortex. The effects of the lesion are studied when the treated rats become adults, and involve (i) anatomical effects, such as frontal lobe abnormalities, dopamine system dysregulation, molecular changes in the PFC (i.e., decreased NAA levels, GAD67 mRNA, BDNF, and mRNA), shorter basilar dendrites, and reduced spine density; (ii) neurophysiological effects, such as increased mesolimbic/nigrostriatal dopamine transmission; (iii) pharmacological effects, such as amphetamine-induced hyperactivity, apomorphine-induced stereotypies, reduced catalepsy to haloperidol MK-801, and phencyclidine (PCP)-induced hyperactivity; and (iv) behavioral effects, such as sensorimotor gating deficits, deficits in latent inhibition, impaired social behavior, and working memory deficits.

Lesion models demonstrate that neurodevelopmental damage can have selective and delayed adverse consequences after a prolonged period of relative normalcy. However, lesion models have limited construct validity, because there is no evidence that psychotic disorders involve a gross neurodevelopmental 'lesion' in the hippocampal region.

Chronic PCP

These models involve the pharmacological blockade of NMDA receptors in adult animals, based on observations that noncompetitive NMDA antagonists, such as PCP and ketamine, can exacerbate psychotic symptoms in patients with schizophrenia, and have psychotomimetic effects in healthy volunteers [109,110], including: (i) anatomical effects, such as fewer PFC synapses, decreased parvalbumin in hippocampus, and increased astroglia process density without a change in glia number; (ii) neurophysiological effects, such as dysregulation of the firing patterns of mesolimbic and mesocortical dopaminergic neurons; and (iii) behavioral effects, such as sensorimotor gating deficits, reversal learning, extradimensional set-shifting deficits, and impaired social interactions.

Unlike the etiological or neonatal lesion models, the PCP approach does not address the developmental component of schizophrenia.

MAM

MAM administration to pregnant rats disrupts embryonic brain development [8,9,12,111], with the following effects: (i) histological and anatomical effects, such as decreases in cortical thickness and increases in neuronal density (hippocampus, parahippocampal cortex, medial prefrontal cortex) and no differences in neocortical neuron number; decreased parvalbumin expression in ventral hippocampus, medial and orbital prefrontal cortex; (ii) neurophysiological effects, such as abnormalities in corticocortical synaptic transmission, striatal hyperdopaminergia, altered glutamatergic neurotransmission in the hippocampus, and disruption of evoked gamma rhythms; (iii) pharmacology effects, such as increased responsivity to psychostimulants (e.g., amphetamine and phencyclidine) and rapid onset of antipsychotic drug effects on dopaminergic neurons; (iv) behavioral effects, such as cognitive dysfunction, sensorimotor gating deficits, latent inhibition reversal learning deficits, reduced social interaction, and perseverative responding.

Are data from studies in schizophrenia consistent with the MAM model?

Neuroimaging studies in patients who have developed a psychotic disorder have examined several different elements of the MAM model (Box 4 describes testable hypothesis for clinical studies derived from the MAM model).

First, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies have shown that, in schizophrenia, both the synthesis and release of dopamine in the striatum are increased [7,18–24]. Structural MRI studies have demonstrated reductions in MTL volume [4,25–28], while functional and perfusion MRI studies have revealed altered MTL activity at rest [29–33], and altered MTL activation during cognitive tasks involving the processing of salient information in the domains of emotion [34–36], novelty [37], and reward processing [38]. Schizophrenia has also been associated with increased hippocampal glutamate levels [39,40], as assessed using 1H-MRS. However, increased glutamate levels are not specific to the MTL [39,41–43], and both increased [44,45] and decreased glutamate levels have been reported in a variety of cortical and striatal regions [46–48]. These inconsistencies between studies may be related to variations in the age, illness stage, and treatment history of the patients examined [49]. Two spectroscopy studies measured GABA levels in the hippocampus: one reported that these were increased in schizophrenia [50], but the other found no differences relative to healthy controls [48].

Overall, these observations in patients with schizophrenia are broadly consistent with what would be predicted on the basis of the MAM model. However, their interpretation is potentially confounded by the effects of chronic illness and of its treatment with antipsychotic medication [51–54]. The effects of antipsychotics may be particularly important, because these drugs act on central dopamine receptors [2], and are often given for many years, yet a single dose of antipsychotic medication can increase hippocampal perfusion in healthy volunteers [55]. Brain glutamate levels can also be altered by antipsychotic treatment [56]. Moreover, they also appear to change over the course of psychotic disorders, with different findings in patients studied at illness onset compared with patients with a long history of illness [39].

Studies in subjects at UHR for psychosis

The MAM model is particularly relevant to the pathophysiology underlying the onset of psychosis, rather than to that associated with the disorder after it is established. Thus, neuroimaging studies in humans who are experiencing prodromal symptoms and have a very high risk of becoming psychotic in the near future are especially useful in assessing the validity of the MAM model. These UHR

Box 2. The MAM-treated rat as a pathophysiological model of schizophrenia

Adult rats exposed to MAM (22 mg/kg) *in utero* at gestational day 17 show selective histopathology in mediodorsal thalamus, hippocampus, parahippocampal, and prefrontal cortices [12], which may in part be due to a decrease in the density of parvalbumin-positive GABAergic interneurons in these regions [112,113]. Reductions in parvalbumin-positive GABAergic interneurons are a robust finding in patients with schizophrenia [114], and may result in a disinhibition of glutamatergic pyramidal cells [84].

Crucially, MAM-treated rats display elevated striatal dopaminergic activity, which is normalized by inactivating the subiculum, an output region of the MTL that projects to the nucleus accumbens via a polysynaptic pathway involving glutamatergic pyramidal neurons [8]. In healthy rats, electrophysiological stimulation of the subiculum increases subcortical dopamine activity [115]. In MAM-treated rats, overactivity in reciprocal signaling pathways between the MTL and striatum [8], putatively due to a loss of GABAergic inhibition of pyramidal neurons in the MTL, leads to increased glutamate release in the striatum [116]. This stimulates GABAergic neurons that project from the striatum to the ventral pallidum, thereby increasing inhibition of ventral pallidum GABAergic neurons, leading to the disinhibition of midbrain dopaminergic neurons and increased release of dopamine from their terminals in the striatum. Dopaminergic neurons in the midbrain project back to the striatum and hippocampus, producing further disinhibition and forming a positive feedback loop [115]. The projections from the MTL to the striatum mainly terminate in its ventral (limbic) portion [98,117].

Box 3. MAM-model based predictions for human studies and methodological limitations

According to this model, humans at high risk of psychosis, or in the early stages of a psychotic disorder, would be expected to show, relative to healthy controls. (i) Increased resting state perfusion and activation in the MTL. However, while MR and PET perfusion imaging provide an absolute measure of resting cerebral blood flow (rCBF), fMRI provides only a proximal and relative measure of neuronal activation. Thus, predicting the polarity of a given effect is more difficult. (ii) Increased glutamate levels in the MTL and striatum. The MAM model predicts increased glutamate release in the pathways projecting from the ventral hippocampus (subiculum) to the ventral striatum. However, measurement of glutamate concentrations in humans using MRS is difficult at such an anatomically localized level. (iii) Reduced cortical and MTL GABA levels. At present, GABA levels can be measured in cortical areas using 1H-MRS, but reliable measurement of GABA is more difficult in the MTL due to field distortions caused by tissue boundaries. (iv) Increased neuronal activity in the midbrain and increased dopamine release in the ventral striatum. 18-Fluorodopa PET measures presynaptic dopamine synthesis capacity rather than synaptic DA release. However, this may still reflect activity in terminals and, thus, the number of DA neurons that are firing (as observed in MAM rats). (v) Altered associations between glutamate levels in MTL and striatum and dopamine function in the striatum and midbrain. According to the MAM model, there is a causal relation between increased activity in ventral hippocampal pyramidal neurons, increased glutamate release in this region, and increased DA release in the striatum. However, at present, neuroimaging studies in humans typically identify correlational associations between activity and/or neurotransmitter function in different regions, rather than causal relations.

individuals are defined by the presence of a clinical syndrome featuring 'attenuated' psychotic symptoms, and about one third will develop a psychotic disorder within 3 years [57]. A further advantage in studying this group is that many of the factors that potentially confound the interpretation of data from patients with psychosis, such as effects of chronic illness, effects of antipsychotic medication, and between-patient variations in the duration of illness, are minimized: samples of high-risk subjects are at similar stage of the disorder, have no previous history of psychosis, and are usually medication naive. Moreover, longitudinal studies in UHR subjects provide a means of examining the human brain before and after the onset of psychosis in the same individual, an ideal paradigm of investigating factors relevant to the onset of the disorder. Therefore, we particularly focus here on data from this group.

Dopamine dysfunction

PET studies have recently shown that dopamine function is elevated in humans at UHR for psychosis [58,59], particularly in the subgroup that subsequently develops a psychotic disorder [60,61]. This is evident in both the striatum and in the midbrain [60,61], and longitudinal PET data suggest that there is a progressive increase in striatal dopamine function as subjects make the transition from a high-risk to a frankly psychotic state [62].

MTL abnormalities

Several MRI studies using region of interest (ROI) or whole-brain voxel-based morphometric (VBM) methods have reported reduced hippocampal gray matter volume in UHR individuals relative to healthy controls [63–68]. Although not all studies have reported reductions in hippocampal volume (e.g., [69]), a meta-analysis found that, overall, there was a significant bilateral reduction in MTL volume in UHR subjects [70]. There is also evidence that these reductions are greatest in the subgroup of UHR subjects who subsequently develop psychosis [71–73]. Within the MTL, reductions in volume have often been localized to the anterior part of the parahippocampal gyrus [72,73].

MTL function is also altered in humans at high risk of psychosis. In an fMRI study using a verbal memory task, UHR subjects showed reduced activation in the left parahippocampal gyrus during word encoding, and altered hippocampal engagement bilaterally during correct word recognition [74]. Furthermore, in a longitudinal fMRI study, clinical improvement in UHR subjects was associated with a longitudinal normalization of altered activation in the right parahippocampal gyrus during a working memory task [75]. Increased hippocampal activation during a verbal fluency task has also been reported in UHR subjects that developed psychosis relative to those that did not [61]. Increases in activation in MTL regions, particularly in the amygdala, have been reported in UHR subjects when they make abnormal attributions of salience to emotional stimuli [76], and this hyperactivation may predict levels of psychotic symptoms and global functioning [77]. Schobel and colleagues [78] found that resting regional cerebral blood volume (CBV) was increased in the CA1 region of the hippocampus in UHR subjects who subsequently developed psychosis. Follow-up scanning in this sample showed that the subsequent onset of psychosis was associated with a progressive increase in CBV that extended from the CA1 region into the subiculum [78].

Glutamate and GABA dysfunction

MRS in UHR individuals suggests that glutamate levels in the thalamus are lower than in healthy controls [79], and are associated with poor clinical and functional outcomes [80]. Independent work has reported that UHR and first-episode subjects have higher levels of glutamate in the caudate nucleus compared with controls [81], and that the UHR subjects that subsequently developed psychosis had higher striatal glutamate levels than the UHR subjects who did not [82]. Studies that have examined glutamate and glutamine in medial prefrontal and anterior cingulate regions have not found significant differences between UHR subjects and controls [79,80,83].

Currently, there are no published neuroimaging studies reporting GABA concentrations in UHR subjects. However, these are of great interest, because several animal models, including the MAM model, propose that excessive glutamatergic activity in the MTL is secondary to GABA dysfunction [84].

Multimodal imaging studies in UHR subjects

Multimodal neuroimaging studies provide a particularly useful source of data for examining putative interactions within the MAM model between MTL activity, glutamate, and dopamine function, and several studies have used this approach to study UHR subjects (summarized in Table 1).

Glutamate and gray matter volume

Stone and colleagues [79] investigated the relation between regional glutamate levels and gray matter volume by combining ^{1}H-MRS and volumetric MRI. In UHR subjects, the degree to which thalamic glutamate levels were reduced was directly correlated with the magnitude of the reduction in gray matter volume in the MTL and several other cortical regions. No such relation was evident in the controls. This suggests that thalamic glutamatergic dysfunction in UHR individuals is associated with cortical structural abnormalities.

Table 1. Multimodal imaging studies in humans at UHR of psychosis

Refs	Modalities	Findings	HC			UHR		
			N	Age	M/F	*N*	Age (SD)	M/F
Roiser *et al.* [91]	fMRI (salience attribution task) and 18F-DOPA PET	UHR: negative correlation between striatal dopamine synthesis capacity and hippocampal activation to irrelevant stimulus features HC: opposite correlation	18	26.5 (6)	10/8	18	25.7 (4.3)	7/11
Schobel *et al.* [96]	Perfusion MRI and sMRI	UHR: hippocampal hypermetabolism at baseline predicted hippocampal atrophy, which occurred during progression to psychosis	–	–	–	15 NP; 10 P	19.3 (3.9); 20.4 (3.6)	13/2; 9/1
Allen *et al.* [90]	fMRI (episodic memory task) and 18F-DOPA PET	UHR: positive correlation between hippocampal activation during memory task and 18F-DOPA uptake HC: opposite correlation	14	25.7 (4.1)	9/5	20	26.3 (5.1)	10/10
Fusar-Poli *et al.* [94]	fMRI (VF task) and 18F-DOPA PET	UHR: positive correlation between striatal dopamine synthesis capacity and activation in IFC HC: no correlation	14	25.5 (3.6)	10/4	20	26.7 (5)	11/9
Fusar-Poli *et al.* [87]	fMRI (VF task) and 1H-MRS	UHR: positive association between thalamic glutamate levels and activation in hippocampus and temporal cortex; negative association between thalamic glutamate levels and activation in PFC HC: opposite correlation in PFC and temporal cortex and in hippocampus	17	25.5 (3.6)	10/7	24	26.7 (5)	23/1
Valli *et al.* [86]	fMRI (episodic memory task) and 1H-MRS	HC: positive correlation between MTL activation during episodic encoding and MTL glutamate UHR: no correlation	14	25.6 (3.7)	6/8	22	25.72 (4.9)	12/10
Fusar-Poli *et al.* [93]	fMRI (WM task) and 18F-DOPA PET	UHR: negative correlation between striatal dopamine synthesis capacity and prefrontal activation HC: opposite correlation	14	25.5 (3.6)	–	20	26.6 (5)	–
Stone *et al.* [89]	1H-MRS and 18F-DOPA PET	UHR: negative relation between hippocampal glutamate levels and striatal dopamine synthesis capacity HC: no correlation	12	–	–	16	–	–
Stone *et al.* [79]	1H-MRS and sMRI	UHR: level of thalamic glutamate positively correlated with GMV in MTL and insula HC: no correlation	27	25 (4)	14/13	27	25(5)	19/8

Abbreviations: FG, frontal gyrus; Glx, glutamate plus glutamine; GMV, gray matter volume; HC, healthy controls; IFG, inferior frontal gyrus; MMN, mismatch negativity; NP, no psychosis; P; psychosis; R, right; sMRI, structural MRI; VF, verbal fluency; WM, working memory; WMV, white matter volume.

Glutamate MRS and fMRI

Animal studies have shown that hippocampal glutamate is critically involved in memory encoding [85]. By combining fMRI data acquired during memory encoding and ^{1}H-MRS glutamate measures, Valli and colleagues [86] found that, in control subjects, MTL activation was positively correlated with hippocampal glutamate levels, but this relation was not evident in UHR subjects. This suggests that, in UHR subjects, there is a breakdown in the normal relation between MTL glutamate levels and MTL activation. Another fMRI study in UHR subjects examined the relation between thalamic glutamate levels and activation during a verbal fluency task [87]. The relation between thalamic glutamate levels and both MTL and PFC activation was significantly altered in UHR subjects compared with controls. The relation between thalamic glutamate levels and PFC activation was particularly perturbed in UHR subjects who had poor functional outcomes [88].

Glutamate and dopamine

The MAM model proposes that striatal hyperdopaminergia is driven by upstream changes in hippocampal glutamate function. Using ^{1}H-MRS and ^{18}F-DOPA PET data from the same individuals, Stone and colleagues [89] found a negative relation between MTL glutamate and striatal dopaminergic function in UHR subjects, particularly in those UHR subjects who subsequently developed psychosis. This relation was absent in healthy controls.

Dopamine and fMRI

Allen and colleagues [90] used a verbal memory task to examine the relation between MTL activation and striatal dopaminergic function, combining fMRI and ^{18}F-DOPA PET in the same subjects. The relation between striatal dopamine function (in the limbic/ventral subdivision) and MTL activation during both verbal encoding and recognition in UHR subjects was different to that in controls. In controls, there was a negative correlation between activation averaged across the subiculum and hippocampus during correct recognition trials, and dopamine levels in the limbic striatum: this correlation was absent in the UHR group.

Using a salience attribution task, Roiser and colleagues found that UHR subjects attributed inappropriate importance to unrewarded stimuli [91]. These abnormal attributions of salience were associated with activation in the ventral striatum and with an alteration in the relation between hippocampal activation and striatal dopamine function [91]. These findings provide some of the first human evidence to support the model proposed by Kapur and colleagues, which suggests that salience processing is perturbed before the onset of psychosis, and is driven by abnormal striatal dopamine function [92].

Fusar-Poli and colleagues combined fMRI and ^{18}F-DOPA PET to examine the relation between prefrontal cortical activation (during a working memory task) and striatal dopamine function in humans at UHR of psychosis [93]. In UHR subjects, dorsolateral PFC activation was negatively correlated with presynaptic dopamine function in the associative striatum, whereas in controls the correlation was positive. An analogous study using ^{18}F-DOPA PET and fMRI in conjunction with a verbal fluency task found that, in UHR subjects, the ventral PFC response was positively correlated with the level of striatal dopamine function, a relation that was absent in controls [94].

Collectively, these findings suggest that subcortical dopamine dysfunction in UHR subjects is related to alterations in both medial temporal and prefrontal function. This is consistent with the notion that descending inputs from cortical regions may drive elevated dopamine function in psychosis, as proposed by the MAM model [8,9] (Figure 1 displays alterations in the relation between MTL/PFC activation and striatal dopamine function across a range of cognitive tasks). The MTL and PFC both have well-established roles in cognitive processing. For example, projections from the CA1 region of the hippocampus and subiculum to the PFC are critically involved in executive cognitive functions [95]. However, the ways in which dysfunction in the MTL and PFC may interact to disrupt cognitive processing in psychosis are not fully understood.

Longitudinal multimodal studies

Schobel and colleagues [96] reported that UHR subjects showed increased hippocampal perfusion in the CA1 subfield of the hippocampus, and that this was associated with a longitudinal reduction in hippocampal volume during the progression to psychosis, especially in the CA1 field and the subiculum/ventral hippocampus. Although this study did not examine interactions with striatal dopamine levels or *in vivo* measures of glutamate function, in related experiments in mice, the authors found that similar changes in hippocampal perfusion and volume could be induced by ketamine, and were dependent on local glutamate release. Furthermore, these volumetric changes were associated with a local reduction in parvalbumin-positive GABA neurons. Excessive glutamate concentrations around neurons can result in excitotoxicity through the influx of calcium ions [97]. The notion that increased glutamate levels might lead to reduction in gray matter volume is consistent with data from neuroimaging studies that have found that reductions in gray matter volume in first-episode patients and individuals at UHR were correlated with alterations in regional glutamate levels [43,79].

To what extent do human and animal data converge?

The data reviewed above suggest that the findings from neuroimaging studies in patients with schizophrenia, and in UHR subjects are broadly consistent with what would be predicted from the MAM model. A prediction central to the MAM model is that dopamine function is elevated in the striatum. MAM rats show increased dopamine function across the VTA, although the increase in dopaminergic neuron firing is preferentially observed in the lateral VTA, which projects to the rodent homolog of the associative striatum [98]. The MAM model also predicts that there is increased functional activity in the ventral striatum (the target of hippocampal afferents). Neuroimaging data from patients with schizophrenia and humans at UHR of psychosis confirm that striatal dopamine function is elevated, mainly in the associative (dorsal) subdivision [58–60,81]. Animal studies indicate that MTL projections to the ventral striatum can influence dopaminergic activity in the

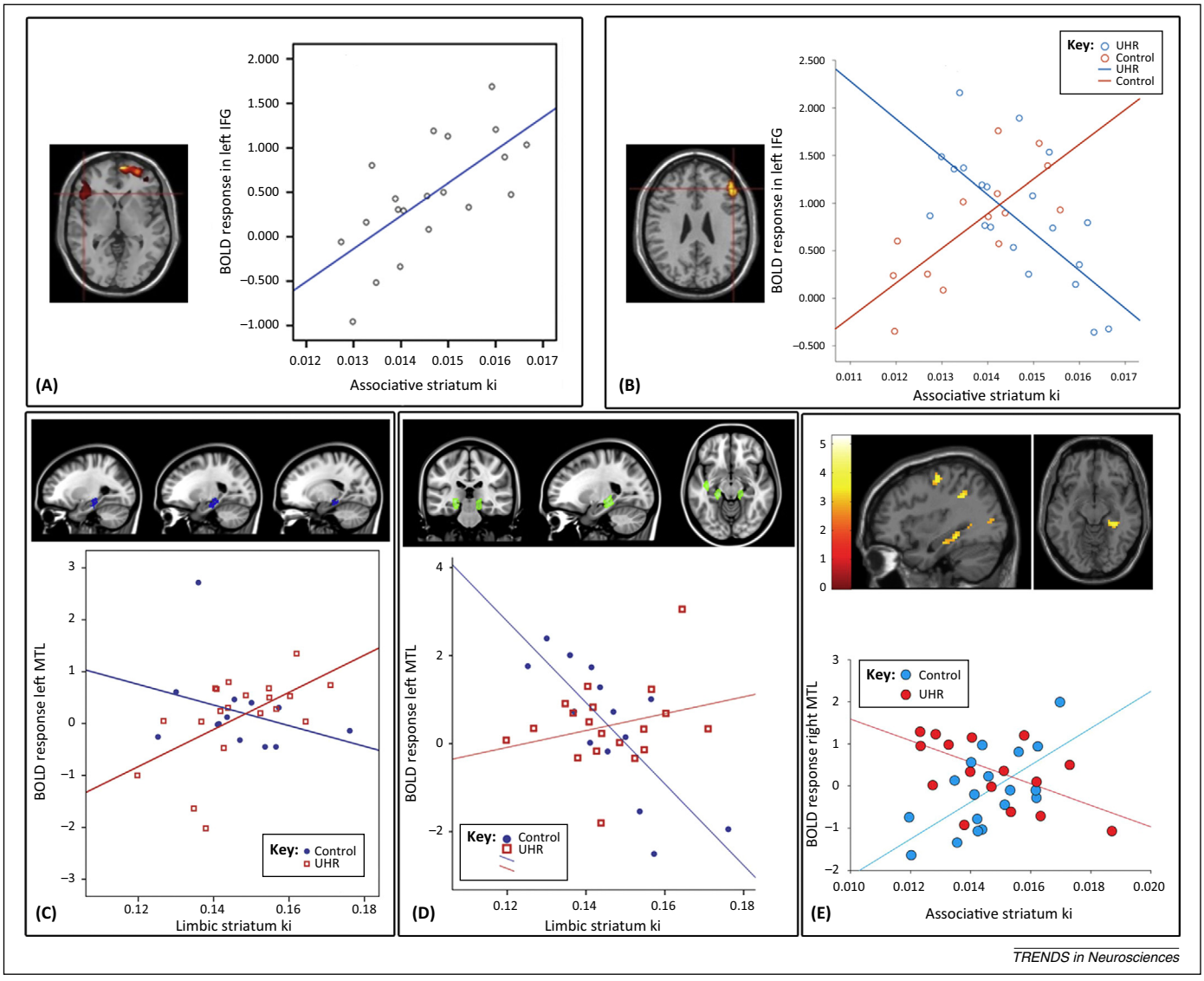

Figure 1. Altered relation between cortical activation and subcortical dopamine function in subjects at ultra high risk (UHR) of psychosis. **(A)** Functional activation in the left inferior frontal gyrus (IFG) during verbal fluency is positively correlated with presynaptic dopaminergic activity in the associative striatum [94]. **(B)** Functional activation in the right IFG during working memory is positively correlated in healthy controls but negatively correlated in UHR subjects [93]. **(C)** Functional activation in the medial temporal lobe (MTL) during verbal encoding is positively correlated with subcortical dopamine levels in UHR subjects but not in healthy controls [90]. **(D)** MTL activation during verbal recognition was negatively correlated with dopamine levels in the healthy control group but not in the UHR group [90]. **(E)** Abnormal interaction between functional activation in right hippocampus and subcortical dopamine function during the processing of reward salience [91]. Abbreviations: BOLD, blood level oxygen-dependent; Ki, ^{18}F-fluorodopa influx constants. Adapted, with permission, from [94] (A), [93] (B), [90] (C,D), and [91] (E).

associative striatum indirectly, via projections to dopamine neurons in the lateral VTA that terminate in the associative striatum [98]. This prediction regarding the localization of functional activity and dopamine dysfunction within the striatum needs to be examined in humans through further research. More specifically, one factor that should be tested is whether there is a correlation between ventral striatal activity and associative striatal dopamine function in human schizophrenia.

One of the most robust findings in relation to glutamate levels in UHR subjects is that these are reduced in the thalamus [79,80]. Although the MAM model does not make specific predictions about glutamate activity in this region, the thalamus is a key component of the circuit that links the MTL and PFC to the striatum and the midbrain [99]. According to the MAM model, cortical glutamate levels are increased due to a reduction in GABAergic inhibition of local pyramidal neurons [14]. MRS studies in patients with schizophrenia have reported both increased and decreased cortical glutamate levels. For example, in chronic, medicated patients, reductions have been described in the medial PFC [39], whereas increases have been reported in the hippocampus [50]. Most studies in unmedicated first-episode patients have found elevated glutamate and glutamine levels in the hippocampus, anterior cingulate, and thalamus [40,42]. These potentially confusing findings may partly reflect a variation in glutamate levels with stage of psychotic illness [39], as well as effects of antipsychotic treatment [56]. Longitudinal MRS studies could help to resolve this issue, but at present there are relatively few of these studies in the literature [43,80].

Another consideration is that the effect of excessive pyramidal activity on local glutamate levels changes over time: this would be consistent with recent longitudinal

data that suggest that thalamic glutamate abnormalities in UHR subjects are more marked at presentation than at follow-up [80]. An interesting prediction arising from the MAM model regarding illness chronology is that the continued presence of hippocampal glutamateric hyperactivity would eventually lead to further hippocampal degeneration. Such a prediction could fit with the structural neuroimaging data showing a smaller hippocampus in established schizophrenia [4], and potentially provide an explanation for the positive symptom burnout observed in chronic schizophrenia possibly due to continued hippocampal damage.

The MAM model predicts that cortical GABA levels are decreased in psychosis due to the loss and dysfunction of inhibitory GABAergic interneurons. Two spectroscopy studies measured GABA levels in the hippocampus in schizophrenia: one reported that these were increased relative to healthy controls [50], whereas the other found no differences [48]. Increased GABA been interpreted as reflecting a compensatory increase in firing by unaffected GABAergic interneurons [100]. As with MRS studies of glutamate, disease stage may influence the nature of the findings: for example, GABA levels in the basal ganglia appear to be reduced in patients in the early stage of psychosis, whereas increased GABA levels in the anterior cingulate cortex and the parieto-occipital cortex have been reported in chronic patients [16]. Antipsychotic medication may also affect MRS measures of GABA [16]. To date, no studies have examined GABAergic function in UHR subjects or medication-naïve patients with psychosis, and how GABA levels relate to glutamate levels in the same individual has yet to be investigated. However, there are preliminary data of reduced GABA levels in the dorsomedial PFC in UHR subjects compared with healthy controls, associated with increased MTL resting-state perfusion [135].

It is important to bear in mind that studies in UHR and psychotic subjects have also identified neurobiological findings in other regions and pathways that are not directly related to the MAM model. Thus, structural and functional alterations in UHR and psychotic subjects are by no means restricted to a circuit involving the MTL, striatum, and midbrain: thus, the onset of psychosis had also been associated with alterations in the structure, function, and connectivity of the prefrontal, anterior cingulate, lateral temporal, and cerebellar cortices [64,72–74,101,102]. Similarly, the MAM model does not postulate a mechanistic role for other risk factors for psychosis, such as genetic abnormalities and neuroinflammation [103,104] (Box 5).

Box 4. Link between pathophysiology and behavior

Lisman and Grace propose that activation of the hippocampal–midbrain loop begins when the hippocampus receives new information that is not already stored in long-term memory [14]. The resulting novelty signal is conveyed through the subiculum, nucleus accumbens, and ventral pallidum to the ventral tegmental area (VTA) where it contributes to novelty-dependent firing of dopaminergic cells. In the ascending arm of the loop, dopamine is released within the hippocampus enhancing long-term potentiation (LTP, a form of synaptic plasticity important for learning [13]).

Functional MRI studies in healthy human subjects suggest that the VTA is activated by salient stimuli that are novel [118] or rewarding [119]. Thus, the human VTA, when activated with the hippocampus, may contribute to an enhancement of learning when stimuli are salient. However, abnormally increased striatal dopamine release may perturb the hippocampal–VTA loop and disrupt the attribution of salience, such that non-novel or unrewarding stimuli become salient. This may lead to the inappropriate associations that are thought to underlie certain psychotic symptoms, particularly delusions [92]. Disruption of dopaminergic signaling between the VTA and hippocampus may also alter PFC function via a glutamatergic hippocampal–prefrontal pathway that originates in the CA1 region of the hippocampus [120], potentially contributing to the cognitive impairments that are seen in patients with schizophrenia [121].

Box 5. Outstanding questions

What does the model not explain about the onset of psychosis?

- The MAM model provides a testable neurobiological framework in which to formulate hypotheses about the development of psychosis in humans. However, there are some factors that are implicated in the development of psychosis that it does not incorporate. Psychosis has a strong genetic component [122], but the role of specific risk genes in the model has yet to be determined.
- A range of environmental factors, including psychosocial stress during development, is known to increase the risk of psychosis, although the neurobiological basis of these effects is unknown. However, stress in experimental animals can influence brain GABA function in the MTL [123–125]. MAM-treated rats are anxious and hyper-responsive to stress [126], and peripubertal administration of benzodiazepines prevents MAM-induced pathology, blocking the elevation in dopamine function normally seen in MAM-treated animals [127]. Stress could also lead to changes in the MTL through its effects on blood cortisol levels. Cortisol levels are altered in UHR subjects [128–130], and are associated with reduced MTL volume in first episode psychosis [131].
- Alterations in the PFC could influence the MAM model circuit in several ways. Research in rodents shows that neurons in the CA1 region of the hippocampus and the subiculum project directly to the PFC [95]. The PFC is also one of the few cortical areas that has direct projections to dopaminergic neurons in the midbrain [132]. It has been suggested that, in the resting state, dopamine levels are regulated by hippocampal–PFC–striatal projections, but that in the presence of salient stimuli, subcortical dopamine function is controlled by a direct connection between the hippocampus and the striatum that bypasses the PFC [133,134].

Concluding remarks

There is a substantial body of evidence from a range of studies in patients with psychosis and individuals at UHR for the disorder that supports the MAM model. Overall, the literature indicates that a hippocampal–midbrain–striatal circuit is abnormal in psychosis, and that this involves alterations in MTL structure and activity, and changes in glutamate and dopamine function. However, caution is needed when comparing various kinds of data across rodent and human studies, because these are not measuring precisely the same neurophysiological and neurochemical processes, and neuroanatomical differences between species should also be considered.

Further work is required to clarify the chronology of these alterations in humans, and their etiology. Longitudinal multimodal studies in high-risk subjects, and studies that integrate neurobiological findings with genetic and environmental risk factors, may address these issues. In addition, the model provides a basis for evaluating the impact of novel experimental and clinical interventions,

such as the administration of compounds that act on GABA or glutamate function in humans at high risk of psychosis [105].

Acknowledgments

This work was supported by a Wellcome Trust Programme Grant (#091667, 2011) and a NARSAD Young Investigator Grant (#21200, G.M., Lieber Investigator).

References

1 Howes, O.D. *et al.* (2012) The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch. Gen. Psychiatry* 69, 776–786
2 Kapur, S. (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am. J. Psychiatry* 160, 13–23
3 Howes, O.D. *et al.* (2009) Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. *Curr. Pharm. Des.* 15, 2550–2559
4 Honea, R. *et al.* (2005) Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am. J. Psychiatry* 162, 2233–2245
5 Arnold, S.E. (1997) The medial temporal lobe in schizophrenia. *J. Neuropsychiatry Clin. Neurosci.* 9, 460–470
6 Tamminga, C.A. *et al.* (2010) The hippocampal formation in schizophrenia. *Am. J. Psychiatry* 167, 1178–1193
7 Howes, O.D. and Kapur, S. (2009) The dopamine hypothesis of schizophrenia: version III–the final common pathway. *Schizophr. Bull.* 35, 549–562
8 Lodge, D.J. and Grace, A.A. (2007) Aberrant hippocampal activity underlies the dopamine dysregulation in an animal model of schizophrenia. *J. Neurosci.* 27, 11424–11430
9 Lodge, D.J. and Grace, A.A. (2011) Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia. *Trends Pharmacol. Sci.* 32, 507–513
10 Flagstad, P. *et al.* (2004) Disruption of neurogenesis on gestational day 17 in the rat causes behavioral changes relevant to positive and negative schizophrenia symptoms and alters amphetamine-induced dopamine release in nucleus accumbens. *Neuropsychopharmacology* 29, 2052–2064
11 Grace, A.A. and Moore, H. (1998) Regulation of information flow in the nucleus accumbens: a model for the pathophysiology of schizophrenia. In *Origins and Development of Schizophrenia: Advances in Experimental Psychopathology* (Lenzenweger, M.F. and Dworkin, R.H., eds), pp. 123–157, American Psychological Association Press
12 Moore, H. *et al.* (2006) A neurobehavioral systems analysis of adult rats exposed to methylazoxymethanol acetate on E17: implications for the neuropathology of schizophrenia. *Biol. Psychiatry* 60, 253–264
13 Lisman, J. *et al.* (2011) A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. *Trends Neurosci.* 34, 536–547
14 Lisman, J.E. and Grace, A.A. (2005) The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron* 46, 703–713
15 Logothetis, N.K. (2002) The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 357, 1003–1037
16 Port, J.D. and Agarwal, N. (2011) MR spectroscopy in schizophrenia. *J. Magn. Reson. Imaging* 34, 1251–1261
17 Waschkies, C.F. *et al.* (2014) Neuropharmacological and neurobiological relevance of in vivo (1)H-MRS of GABA and glutamate for preclinical drug discovery in mental disorders. *Neuropsychopharmacology* 39, 2331–2339
18 Mackay, A.V. *et al.* (1982) Increased brain dopamine and dopamine receptors in schizophrenia. *Arch. Gen. Psychiatry* 39, 991–997
19 Zakzanis, K.K. and Hansen, K.T. (1998) Dopamine D2 densities and the schizophrenic brain. *Schizophr. Res.* 32, 201–206
20 Abi-Dargham, A. (2004) Do we still believe in the dopamine hypothesis? New data bring new evidence. *Int. J. Neuropsychopharmacol.* 7 (Suppl 1), S1–S5
21 Hietala, J. *et al.* (1999) Measurement of striatal D2 dopamine receptor density and affinity with [11C]-raclopride in vivo: a test-retest analysis. *J. Cereb. Blood Flow Metab.* 19, 210–217
22 Lindstrom, L.H. *et al.* (1999) Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. *Biol. Psychiatry* 46, 681–688
23 Laruelle, M. *et al.* (1996) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc. Natl. Acad. Sci. U.S.A.* 93, 9235–9240
24 Davis, K.L. *et al.* (1991) Dopamine in schizophrenia: a review and reconceptualization. *Am. J. Psychiatry* 148, 1474–1486
25 Shenton, M.E. *et al.* (2002) Amygdala-hippocampal shape differences in schizophrenia: the application of 3D shape models to volumetric MR data. *Psychiatry Res.* 115, 15–35
26 Lawrie, S.M. and Abukmeil, S.S. (1998) Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *Br. J. Psychiatry* 172, 110–120
27 Steen, R.G. *et al.* (2006) Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br. J. Psychiatry* 188, 510–518
28 Wright, I.C. *et al.* (2000) Meta-analysis of regional brain volumes in schizophrenia. *Am. J. Psychiatry* 157, 16–25
29 Andreasen, N.C. *et al.* (1997) Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. *Lancet* 349, 1730–1734
30 Malaspina, D. *et al.* (2004) Resting neural activity distinguishes subgroups of schizophrenia patients. *Biol. Psychiatry* 56, 931–937
31 Scheef, L. *et al.* (2010) Resting-state perfusion in nonmedicated schizophrenic patients: a continuous arterial spin-labeling 3.0-T MR study. *Radiology* 256, 253–260
32 Pinkham, A. *et al.* (2011) Resting quantitative cerebral blood flow in schizophrenia measured by pulsed arterial spin labeling perfusion MRI. *Psychiatry Res.* 194, 64–72
33 Horn, H. *et al.* (2009) Structural and metabolic changes in language areas linked to formal thought disorder. *Br. J. Psychiatry* 194, 130–138
34 Holt, D.J. *et al.* (2006) Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophr. Res.* 82, 153–162
35 Holt, D.J. *et al.* (2005) Sustained activation of the hippocampus in response to fearful faces in schizophrenia. *Biol. Psychiatry* 57, 1011–1019
36 Hall, J. *et al.* (2008) Overactivation of fear systems to neutral faces in schizophrenia. *Biol. Psychiatry* 64, 70–73
37 Tamminga, C.A. *et al.* (2012) Hippocampal novelty activations in schizophrenia: disease and medication effects. *Schizophr. Res.* 138, 157–163
38 Heinz, A. and Schlagenhauf, F. (2010) Dopaminergic dysfunction in schizophrenia: salience attribution revisited. *Schizophr. Bull.* 36, 472–485
39 Marsman, A. *et al.* (2013) Glutamate in schizophrenia: a focused review and meta-analysis of (1)H-MRS studies. *Schizophr. Bull.* 39, 120–129
40 Kraguljac, N.V. *et al.* (2013) Increased hippocampal glutamate and volumetric deficits in unmedicated patients with schizophrenia. *JAMA Psychiatry* 70, 1294–1302
41 Bustillo, J.R. *et al.* (2011) Glutamate as a marker of cognitive function in schizophrenia: a proton spectroscopic imaging study at 4 Tesla. *Biol. Psychiatry* 69, 19–27
42 Theberge, J. *et al.* (2002) Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. *Am. J. Psychiatry* 159, 1944–1946
43 Theberge, J. *et al.* (2007) Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. *Br. J. Psychiatry* 191, 325–334
44 Choe, B.Y. *et al.* (1996) Observation of metabolic changes in chronic schizophrenia after neuroleptic treatment by in vivo hydrogen magnetic resonance spectroscopy. *Invest. Radiol.* 31, 345–352
45 Ongur, D. *et al.* (2010) Elevated gamma-aminobutyric acid levels in chronic schizophrenia. *Biol. Psychiatry* 68, 667–670
46 Goto, N. *et al.* (2009) Reduction of brain gamma-aminobutyric acid (GABA) concentrations in early-stage schizophrenia patients: 3T Proton MRS study. *Schizophr. Res.* 112, 192–193
47 Yoon, J.H. *et al.* (2010) GABA concentration is reduced in visual cortex in schizophrenia and 47 with orientation-specific surround suppression. *J. Neurosci.* 30, 3777–3781

48 Stan, A.D. *et al.* (2014) Magnetic resonance spectroscopy and tissue protein concentrations together suggest lower glutamate signaling in dentate gyrus in schizophrenia. *Mol. Psychiatry* Published June 10, 2014. . (http://dx.doi.org/10.1038/mp.2014.54
49 Brugger, S. *et al.* (2011) Proton magnetic resonance spectroscopy and illness stage in schizophrenia–a systematic review and meta-analysis. *Biol. Psychiatry* 69, 495–503
50 Kegeles, L.S. *et al.* (2000) Hippocampal pathology in schizophrenia: magnetic resonance imaging and spectroscopy studies. *Psychiatry Res.* 98, 163–175
51 Fusar-Poli, P. *et al.* (2013) Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci. Biobehav. Rev.* 37, 1680–1691
52 Navari, S. and Dazzan, P. (2009) Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychol. Med.* 39, 1763–1777
53 Ho, B.C. *et al.* (2011) Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch. Gen. Psychiatry* 68, 128–137
54 Abbott, C.C. *et al.* (2013) Antipsychotic drug effects in schizophrenia: a review of longitudinal FMRI investigations and neural interpretations. *Curr. Med. Chem.* 20, 428–437
55 Handley, R. *et al.* (2013) Acute effects of single-dose aripiprazole and haloperidol on resting cerebral blood flow (rCBF) in the human brain. *Hum. Brain Mapp.* 34, 272–282
56 de la Fuente-Sandoval, C. *et al.* (2013) Glutamate levels in the associative striatum before and after 4 weeks of antipsychotic treatment in first-episode psychosis: a longitudinal proton magnetic resonance spectroscopy study. *JAMA Psychiatry* 70, 1057–1066
57 Fusar-Poli, P. *et al.* (2012) Predicting psychosis meta-analysis of transition outcomes in individuals at high clinical risk. *Arch. Gen. Psychiatry* 69, 220–229
58 Howes, O.D. *et al.* (2009) Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch. Gen. Psychiatry* 66, 13–20
59 Egerton, A. *et al.* (2013) Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: findings in a second cohort. *Biol. Psychiatry* 74, 106–112
60 Howes, O.D. *et al.* (2011) Dopamine synthesis capacity before onset of psychosis: a prospective [(18)F]-DOPA PET imaging study. *Am. J. Psychiatry* 168, 1311–1317
61 Allen, P. *et al.* (2012) Transition to psychosis associated with prefrontal and subcortical dysfunction in ultra high-risk individuals. *Schizophr. Bull.* 38, 1268–1276
62 Howes, O. *et al.* (2011) Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Mol. Psychiatry* 16, 885–886
63 Phillips, L.J. *et al.* (2002) Non-reduction in hippocampal volume is associated with higher risk of psychosis. *Schizophr. Res.* 58, 145–158
64 Borgwardt, S.J. *et al.* (2007) Regional gray matter volume abnormalities in the at risk mental state. *Biol. Psychiatry* 61, 1148–1156
65 Witthaus, H. *et al.* (2010) Hippocampal subdivision and amygdalar volumes in patients in an at-risk mental state for schizophrenia. *J. Psychiatry Neurosci.* 35, 33–40
66 Wood, S.J. *et al.* (2010) Hippocampal pathology in individuals at ultra-high risk for psychosis: a multi-modal magnetic resonance study. *Neuroimage* 52, 62–68
67 Wood, S.J. *et al.* (2005) Hippocampal and anterior cingulate morphology in subjects at ultra-high-risk for psychosis: the role of family history of psychotic illness. *Schizophr. Res.* 75, 295–301
68 Hurlemann, R. *et al.* (2008) Interrelated neuropsychological and anatomical evidence of hippocampal pathology in the at-risk mental state. *Psychol. Med.* 38, 843–851
69 Velakoulis, D. *et al.* (2006) Hippocampal and amygdala volumes according to psychosis stage and diagnosis – a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Arch. Gen. Psychiatry* 63, 139–149
70 Fusar-Poli, P. *et al.* (2011) Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neurosci. Biobehav. Rev.* 35, 1175–1185
71 Smieskova, R. *et al.* (2010) Neuroimaging predictors of transition to psychosis: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 34, 1207–1222
72 Pantelis, C. *et al.* (2003) Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 361, 281–288
73 Mechelli, A. *et al.* (2011) Neuroanatomical abnormalities that predate the onset of psychosis: a multicenter study. *Arch. Gen. Psychiatry* 68, 489–495
74 Allen, P. *et al.* (2011) Altered prefrontal and hippocampal function during verbal encoding and recognition in people with prodromal symptoms of psychosis. *Schizophr. Bull.* 37, 746–756
75 Fusar-Poli, P. *et al.* (2011) Altered brain function directly related to structural abnormalities in people at ultra high risk of psychosis: longitudinal VBM-fMRI study. *J. Psychiatr. Res.* 45, 190–198
76 Seiferth, N.Y. *et al.* (2008) Increased neural response related to neutral faces in individuals at risk for psychosis. *Neuroimage* 40, 289–297
77 Modinos, G. *et al.* (2014) Overactivation of emotional brain systems predicts severity of positive symptoms and global functioning in prodromal and first-episode psychosis. In *Presented at the 9th International Conference on Early Psychosis*. Tokyo, Japan, November 2014, International Early Psychosis Association (IEPA). http://www.iepaconference.org/
78 Schobel, S.A. *et al.* (2009) Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. *Arch. Gen. Psychiatry* 66, 938–946
79 Stone, J.M. *et al.* (2009) Glutamate dysfunction in people with prodromal symptoms of psychosis: relationship to gray matter volume. *Biol. Psychiatry* 66, 533–539
80 Egerton, A. *et al.* (2014) Relationship between brain glutamate levels and clinical outcome in individuals at ultra high risk of psychosis. *Neuropsychopharmacology* 39, 2891–2899
81 de la Fuente-Sandoval, C. *et al.* (2011) Higher levels of glutamate in the associative-striatum of subjects with prodromal symptoms of schizophrenia and patients with first-episode psychosis. *Neuropsychopharmacology* 36, 1781–1791
82 de la Fuente-Sandoval, C. *et al.* (2013) Striatal glutamate and the conversion to psychosis: a prospective 1H-MRS imaging study. *Int. J. Neuropsychopharmacol.* 16, 471–475
83 Natsubori, T. *et al.* (2014) Reduced frontal glutamate + glutamine and n-acetylaspartate levels in patients with chronic schizophrenia but not in those at clinical high risk for psychosis or with first-episode schizophrenia. *Schizophr. Bull.* 40, 1128–1139
84 Marin, O. (2012) Interneuron dysfunction in psychiatric disorders. *Nat. Rev. Neurosci.* 13, 107–120
85 Day, M. *et al.* (2003) Glutamate-receptor-mediated encoding and retrieval of paired-associate learning. *Nature* 424, 205–209
86 Valli, I. *et al.* (2011) Altered medial temporal activation related to local glutamate levels in subjects with prodromal signs of psychosis. *Biol. Psychiatry* 69, 97–99
87 Fusar-Poli, P. *et al.* (2011) Thalamic glutamate levels as a predictor of cortical response during executive functioning in subjects at high risk for psychosis. *Arch. Gen. Psychiatry* 68, 881–890
88 Allen, P. *et al.* (2014) Functional outcome in people at high risk for psychosis predicted by thalamic glutamate levels and prefronto-striatal activation. *Schizophr. Bull.* pii: sbu115 [Epub ahead of print]
89 Stone, J.M. *et al.* (2010) Altered relationship between hippocampal glutamate levels and striatal dopamine function in subjects at ultra high risk of psychosis. *Biol. Psychiatry* 68, 599–602
90 Allen, P. *et al.* (2012) Abnormal relationship between medial temporal lobe and subcortical dopamine function in people with an ultra high risk for psychosis. *Schizophr. Bull.* 38, 1040–1049
91 Roiser, J.P. *et al.* (2013) Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis. *Schizophr. Bull.* 39, 1328–1336
92 Kapur, S. *et al.* (2005) From dopamine to salience to psychosis–linking biology, pharmacology and phenomenology of psychosis. *Schizophr. Res.* 79, 59–68
93 Fusar-Poli, P. *et al.* (2010) Abnormal frontostriatal interactions in people with prodromal signs of psychosis: a multimodal imaging study. *Arch. Gen. Psychiatry* 67, 683–691
94 Fusar-Poli, P. *et al.* (2011) Abnormal prefrontal activation directly related to pre-synaptic striatal dopamine dysfunction in people at clinical high risk for psychosis. *Mol. Psychiatry* 16, 67–75
95 Godsil, B.P. *et al.* (2013) The hippocampal-prefrontal pathway: the weak link in psychiatric disorders? *Eur. Neuropsychopharmacol.* 23, 1165–1181

96 Schobel, S.A. *et al.* (2013) Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. *Neuron* 78, 81–93
97 Choi, D.W. (1994) Calcium and excitotoxic neuronal injury. *Ann. N. Y. Acad. Sci.* 747, 162–171
98 Lodge, D.J. and Grace, A.A. (2012) Divergent activation of ventromedial and ventrolateral dopamine systems in animal models of amphetamine sensitization and schizophrenia. *Int. J. Neuropsychopharmacol.* 15, 69–76
99 Alexander, G.E. *et al.* (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 9, 357–381
100 Volk, D.W. *et al.* (2000) Decreased glutamic acid decarboxylase67 messenger RNA expression in a subset of prefrontal cortical gamma-aminobutyric acid neurons in subjects with schizophrenia. *Arch. Gen. Psychiatry* 57, 237–245
101 Yaakub, S.N. *et al.* (2013) Preserved working memory and altered brain activation in persons at risk for psychosis. *Am. J. Psychiatry* 170, 1297–1307
102 Brune, M. *et al.* (2011) An fMRI study of 'theory of mind' in at-risk states of psychosis: comparison with manifest schizophrenia and healthy controls. *Neuroimage* 55, 329–337
103 Mondelli, V. *et al.* (2011) Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume. *J. Clin. Psychiatry* 72, 1677–1684
104 Mondelli, V. and Howes, O. (2014) Inflammation: its role in schizophrenia and the potential anti-inflammatory effects of antipsychotics. *Psychopharmacology* 231, 317–318
105 Gill, K.M. *et al.* (2014) Prior antipsychotic drug treatment prevents response to novel antipsychotic agent in the methylazoxymethanol acetate model of schizophrenia. *Schizophr. Bull.* 40, 341–350
106 Nyffeler, M. *et al.* (2006) Maternal immune activation during pregnancy increases limbic GABAA receptor immunoreactivity in the adult offspring: implications for schizophrenia. *Neuroscience* 143, 51–62
107 Jaaro-Peled, H. *et al.* (2010) Review of pathological hallmarks of schizophrenia: comparison of genetic models with patients and nongenetic models. *Schizophr. Bull.* 36, 301–313
108 Lipska, B.K. and Weinberger, D.R. (2000) To model a psychiatric disorder in animals: schizophrenia as a reality test. *Neuropsychopharmacology* 23, 223–239
109 Krystal, J.H. *et al.* (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch. Gen. Psychiatry* 51, 199–214
110 Lahti, A.C. *et al.* (1995) Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology* 13, 9–19
111 Lodge, D.J. and Grace, A.A. (2009) Gestational methylazoxymethanol acetate administration: a developmental disruption model of schizophrenia. *Behav. Brain Res.* 204, 306–312
112 Lodge, D.J. *et al.* (2009) A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. *J. Neurosci.* 29, 2344–2354
113 Gastambide, F. *et al.* (2012) Selective remediation of reversal learning deficits in the neurodevelopmental MAM model of schizophrenia by a novel mGlu5 positive allosteric modulator. *Neuropsychopharmacology* 37, 1057–1066
114 Akbarian, S. *et al.* (1995) Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. *Arch. Gen. Psychiatry* 52, 258–266
115 Hammad, H. and Wagner, J.J. (2006) Dopamine-mediated disinhibition in the CA1 region of rat hippocampus via D3 receptor activation. *J. Pharmacol. Exp. Ther.* 316, 113–120
116 Gonzalez-Burgos, G. and Lewis, D.A. (2012) NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. *Schizophr. Bull.* 38, 950–957
117 Cohen, M.X. *et al.* (2009) Connectivity-based segregation of the human striatum predicts personality characteristics. *Nat. Neurosci.* 12, 32–34
118 Bunzeck, N. and Duzel, E. (2006) Absolute coding of stimulus novelty in the human substantia nigra/VTA. *Neuron* 51, 369–379
119 Winton-Brown, T.T. *et al.* (2014) Dopaminergic basis of salience dysregulation in psychosis. *Trends Neurosci.* 37, 85–94
120 Carr, D.B. and Sesack, S.R. (1996) Hippocampal afferents to the rat prefrontal cortex: synaptic targets and relation to dopamine terminals. *J. Comp. Neurol.* 369, 1–15
121 Seamans, J.K. and Yang, C.R. (2004) The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog. Neurobiol.* 74, 1–58
122 Giusti-Rodriguez, P. and Sullivan, P.F. (2013) The genomics of schizophrenia: update and implications. *J. Clin. Invest.* 123, 4557–4563
123 Callaghan, B.L. and Richardson, R. (2011) Maternal separation results in early emergence of adult-like fear and extinction learning in infant rats. *Behav. Neurosci.* 125, 20–28
124 Gao, J. *et al.* (2014) Glutamate and GABA imbalance promotes neuronal apoptosis in hippocampus after stress. *Med. Sci. Monit.* 20, 499–512
125 Caldji, C. *et al.* (2000) The effects of early rearing environment on the development of GABAA and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. *Neuropsychopharmacology* 22, 219–229
126 Zimmerman, E.C. *et al.* (2013) Abnormal stress responsivity in a rodent developmental disruption model of schizophrenia. *Neuropsychopharmacology* 38, 2131–2139
127 Du, Y. and Grace, A.A. (2013) Peripubertal diazepam administration prevents the emergence of dopamine system hyperresponsivity in the MAM developmental disruption model of schizophrenia. *Neuropsychopharmacology* 38, 1881–1888
128 Day, F. *et al.* (2014) Blunted cortisol awakening response in people at ultra high risk of developing psychosis. *Schizophr. Res.* 158, 25–31
129 Thompson, K.N. *et al.* (2007) HPA axis functioning associated with transition to psychosis: combined DEX/CRH test. *J. Psychiatr. Res.* 41, 446–450
130 Walker, E.F. *et al.* (2013) Cortisol levels and risk for psychosis: initial findings from the North American prodrome longitudinal study. *Biol. Psychiatry* 74, 410–417
131 Mondelli, V. *et al.* (2010) Higher cortisol levels are associated with smaller left hippocampal volume in first-episode psychosis. *Schizophr. Res.* 119, 75–78
132 Watabe-Uchida, M. *et al.* (2012) Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron* 74, 858–873
133 Belujon, P. *et al.* (2013) Disruption of prefrontal cortical-hippocampal balance in a developmental model of schizophrenia: reversal by sulpiride. *Int. J. Neuropsychopharmacol.* 16, 507–512
134 Belujon, P. *et al.* (2014) Role of the prefrontal cortex in altered hippocampal-accumbens synaptic plasticity in a developmental animal model of schizophrenia. *Cereb. Cortex* 24, 968–977
135 Modinos, G. *et al.* (2014) Effect of dorsomedial prefrontal GABA levels on brain perfusion in people at ultra high risk for psychosis. In *Presented at the 9th International Conference on Early Psychosis*. Tokyo, Japan, November 2014, International Early Psychosis Association (IEPA). http://www.iepaconference.org/