Published in final edited form as:
Curr Pharm Des. 2012 ; 18(4): 459–465.

From the prodrome to chronic schizophrenia: the neurobiology underlying psychotic symptoms and cognitive impairments

OD Howes, MRCPsych PhD DM[1,2], **P Fusar-Poli, MD**[2], **M Bloomfield, MBBS**[1], **S Selvaraj, MRCPsych PhD**[1,2], and **P McGuire, FRCPsych PhD**[2]

[1]Psychiatric Imaging Group, Cyclotron Building, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

[2]Box 67, Institute of Psychiatry, London, SE5 8AF, UK

Abstract

Schizophrenia is a chronic psychotic disorder that remains a considerable cause of global disease burden. Cognitive impairments are common and contribute significantly to the morbidity of the disorder. Over the last two decades or so molecular imaging studies have refined understanding of the pathophysiology underlying the development of psychosis and cognitive impairments. Firstly they have consistently implicated presynaptic dopaminergic dysfunction in the disorder, finding that dopamine synthesis capacity, dopamine release and baseline dopamine levels are increased in the illness. Secondly recent findings show that dopamine synthesis capacity is elevated in those that go on to develop psychosis in the following year, but not in those that do not, and appears to increase further with the development of psychosis. Thirdly evidence links greater dopamine synthesis capacity to poorer cognitive performance and altered frontal cortical function measured using functional imaging during cognitive tasks. Finally they have provided data on the nature of other neurofunctional alterations in the disorder, in particular in the serotonergic system and neuroinflammation. We review these findings and discuss their implications for understanding the neurobiology of psychosis and cognitive impairments in schizophrenia.

Keywords

schizophrenia; psychosis; prodrome; cognition; mechanisms; treatment; antipsychotic; imaging; etiology; PET; SPECT; SPET; MRI; functional imaging

Introduction

Schizophrenia is amongst the most common of the severe mental illnesses [1;2], and one of the top ten causes of global disease burden amongst adults [3]. It is a chronic psychotic disorder with a lifetime prevalence of about 0.7%, primarily affecting adults, and having a peak age of onset in the early twenties in men, and three or four years later in women [4]. Women show a later second peak around the time of the menopause, although the lifetime risk for men and women is about equal [4]. In addition to the considerable morbidity and high mortality rate associated with schizophrenia, the health and social care costs for the illness are substantial: equivalent to about 1.6% of the health care budget in the United Kingdom each year, for example [5-7].

oliver.howes@csc.mrc.ac.uk.

CONFLICT OF INTEREST
None.

Europe PMC Funders Author Manuscripts

There are no pathognomic features, or definitive diagnostic tests, for schizophrenia and its symptoms may be seen in other physical or mental illnesses [8]. The typical symptoms have been categorised into 'positive' and 'negative' symptom clusters. 'Positive symptoms', such as hallucinations, delusions and thought disorder, are features of psychosis, whilst alogia, apathy, anergia, and self-neglect are typical of 'negative symptoms' [9]. In addition patients typically show cognitive impairment, with average performance generally 0.5-1.5 standard deviations that of matched controls on a range of cognitive tasks [10].

The pathophysiological basis of schizophrenia is complex, and remains incompletely understood [11;12]. However, better understanding the molecular processes underlying the symptoms of the illness is likely to be essential for improving the use of current drug treatments and to develop new and preventive therapies- as has recently been highlighted [13;14].

Positron emission tomography (PET) and single-photon emission computerised tomography (SPECT) are techniques that have provided *in vivo* data on a number of the neurochemical processes thought to underlie schizophrenia. The availability of selective radiotracers for monoaminergic and several other systems allows has been particularly useful to enable pathophysiological theories of the illness to be investigated. Over the last two decades or so, considerable advances in PET/SPECT technology and its increasingly widespread application has enabled the major aspects of the dopamine hypothesis of schizophrenia to be tested and refined [15]. This review thus focuses on the dopaminergic system, but also considers the role of other brain systems in schizophrenia where there is *in vivo* evidence from molecular imaging studies.

Dopaminergic dysfunction in schizophrenia

The dopamine hypothesis of schizophrenia has been one of the most enduring theories of the pathoaetiology of schizophrenia, and with good reason: several decades of research have served to implicate dysregulated dopaminergic neurotransmission in the disorder [16]. The idea that dopaminergic dysregulation was a central mechanism in the development of schizophrenia initially arose from indirect findings. Firstly, studies of the effects of psychostimulants such as amphetamine, which increases extracellular concentrations of dopamine, found that they can induce psychotic symptoms akin to those seen in schizophrenia (see review [17]). In contrast studies of reserpine, which leads to reduced dopamine neurotransmission [18], found it reduced the symptoms of psychosis, further supporting a causal link between dopamine and psychosis, if not schizophrenia. Studies of dopamine metabolites in the plasma and cerebro-spinal fluid of patients with schizophrenia initially seemed to support this link as well, but it became apparent that the interpretation of these findings is complex, not least because levels of these chemicals also reflect the degradation of other transmitters and, in the case of plasma levels, a substantial contribution from monoamines produced outside of the CNS. The dopamine hypothesis really developed with the discovery that all antipsychotic drugs blocked dopamine receptors, and particularly when, in the 1970s, it was found that the clinical effectiveness of antipsychotic drugs was directly correlated their affinity for dopamine receptors [19;20]. Following this discovery, the hypothesis focussed on dopamine receptors, proposing that receptor density was increased and schizophrenia developed as a consequence of this [21;22].

Consequently molecular imaging studies first focussed on whether D2 receptor density was altered in schizophrenia. There have now been over twenty-two molecular imaging studies in antipsychotic free or naive patients, and, although there have been some inconsistencies, meta-analysis indicates that overall there is an elevation in D2 receptor density in schizophrenia, but the effect size is small [23]. As the radiotracers used in these studies also show appreciable affinity for D3 receptors, this could also reflect some contribution from

D3 alterations. However, the elevation seems to be specific to D2/3 receptors - striatal D1 receptor densities are unaltered [23-26]. The D2 receptor may exist in two intraconvertible affinity states- one with a high affinity and the other with a relatively low affinity for agonists. One suggestion has been that the balance between these two states is altered in schizophrenia [27]. The development of agonist radiotracers has enabled this to be tested- the first study to date finding no difference, indicating that the balance of high and low affinity states is not altered in schizophrenia [28].

Overall the studies of dopamine receptors to date indicate that whilst there is a small elevation in D2/3 receptors the abnormalities are not marked. Consequently subsequent attention has focussed instead on other aspects of dopaminergic neurotransmission: the presynaptic synthesis and release of dopamine into the synapse. Dopamine synthesis capacity can be measured using radiolabeled-*l*-dihydroxyphenylalanine (L-DOPA), which is converted into dopamine and stored in presynaptic vesicles ready for release (see review [29]). Seven out of the nine studies to use this technique to date, including all of the studies where patients were acutely psychotic, have found striatal dopamine synthesis capacity to be elevated in schizophrenia with large effect sizes (in the range 0.6-1.6; see review [30]). The next step in dopaminergic neurotransmission is the release of dopamine into the synapse. Striatal dopamine release can be indexed using molecular imaging with radiotracers such as [11C]raclopride or [123I]IBZM. These radiotracers show reduced binding following dopamine release (and increased binding when dopamine levels are depleted). The competition model accounts for these changes as reflecting the competition between the radiotracer and dopamine to bind to dopamine receptors. Whilst this model is likely to be a simplification, animal studies have found that changes in radiotracer binding do correlate with alterations in extracellular dopamine levels measured using other techniques. Many of the studies using this approach have applied a pharmacological challenge such as amphetamine to probe dopamine release capacity. In schizophrenia the radiotracer displacement following amphetamine has been consistently found to be much greater than that in controls, with effect sizes over 1 [31-33]. The average extent of radiotracer displacement in schizophrenia was more than 100% greater than that in controls, and was directly correlated with the transient worsening of psychotic symptoms induced by amphetamine. Interestingly there is some evidence that this is phase specific- the elevation was most apparent in acutely psychotic patients, and much less marked in stable remitted patients. Another approach is to image the change in radiotracer binding after depletion of presynaptic dopamine stores using a drug such as alpha-methyl-*para*-tyrosine, which blocks dopamine synthesis and reduces extracellular dopamine levels. Studies using this dopamine depletion technique have found that baseline occupancy of D2 receptors by dopamine is elevated in schizophrenia, indicating that extracellular dopamine concentrations are also increased at baseline [34]. Together, these studies provide compelling evidence that presynaptic dopamine availability and dopamine release are increased in schizophrenia. Although at a lower level, increased dopamine availability and release has also been observed in subjects who are at increased risk of developing schizophrenia and who experience mild schizophreniform symptoms, suggesting this dopamine dysregulation may also underlie the development of the illness [35;36].

Animal studies, including in non-human primates, have shown that projections to and from the striatum are topographically organised. Thus limbic cortical areas are linked to ventral and anterior parts of the striatum, whilst projections to and from the sensory and motor cortical regions are localised in more dorsal and posterior striatal regions, and connections to and from associative cortical areas are localised in between. The anatomical localisation of the dopaminergic dysfunction in schizophrenia was initially hypothesised to be mesolimbic, which would suggest the dopaminergic dysfunction would be particularly marked in the part of the striatum that is linked to limbic areas. Limited resolution prevented the early

molecular imaging studies from testing this, but subsequent improvements in scanner technology have enabled these striatal sub-divisions to be reliably imaged. Using a high resolution scanner, we indexed dopamine synthesis capacity in these striatal sub-regions in schizophrenia and compared it to controls. In contrast to the prediction from the mesolimbic hypothesis, the localisation of the dopaminergic dysfunction was most apparent in the part of the striatum linked to associative cortical areas, rather than limbic areas [35]. This associative localisation of the dopaminergic dysfunction in schizophrenia has been subsequently reported in another study using a dopamine depletion approach [37]. This links the dopamine abnormality in schizophrenia to cortical regions such as the dorso-lateral prefrontal cortex that have been implicated in the cognitive dysfunction that is commonly seen in the disorder.

Dopaminergic abnormalities in the prodrome to schizophrenia

What is not apparent from the findings discussed above is whether these abnormalities are secondary to the development of psychosis in schizophrenia, or whether they predate and lead to the onset of psychosis, as has been hypothesised [15]. We sought to test this key tenet of the dopamine hypothesis by imaging dopamine synthesis capacity in people at clinical ultra high risk of going on to develop a psychotic disorder, predominantly schizophrenia, within the next one-two years [35]. These individuals, none of whom were diagnosed with a mental illness, all presented with subtle clinical signs and symptoms that indicate they are likely to be in the prodromal phase of schizophrenia. These prodromal signs of schizophrenia include attenuated psychotic experiences, such as odd beliefs and low-level paranoia, and unusual perceptual experiences. One common symptom cluster has been termed the Truman sign-after the film "*The Truman Show*"- and is characterised by the nagging sense that the world has changed in some disquieting way coupled with the feeling that something significant is about to happen [38]. Individuals in the sample also commonly described subtle subjective and objective cognitive difficulties which impaired their social and occupational function. They all met standardised criteria for being at ultra high risk of psychosis. About one in three people meeting these criteria go on to develop a psychotic disorder, with the vast majority of casing developing a psychotic disorder in the following two years.

In our first study we found that dopamine synthesis capacity at presentation was elevated in a sample of 24 individuals with these at risk signs compared with matched controls [35]. Furthermore greater dopamine synthesis capacity was associated with greater symptom severity at presentation. We also found that the dopaminergic dysfunction was most evident in the associative part of the striatum, just as we had found in schizophrenia [35]. Cognitive impairments have been reported in people presenting at clinical risk of psychosis and impairments in performance on verbal fluency and other tasks of executive function appear to be particularly marked [10]. Based on this we tested verbal fluency performance in the at risk individuals and found an indirect relationship between verbal fluency performance and striatal dopamine synthesis capacity: greater dopamine synthesis capacity was associated with worse performance on the verbal fluency task.

We subsequently enlarged this cohort and conducted repeated clinical assessment to determine their subsequent clinical outcome. About one in three of the subjects have developed a psychotic disorder (almost all meeting DSM-IV criteria for schizophrenia) after clinical follow-up for over two years. We found that compared to matched controls, baseline dopamine synthesis capacity was elevated in the individuals who subsequently developed psychosis [39]. In contrast, those individuals who did not go on to develop psychosis showed no difference in dopamine synthesis capacity from controls, and showed significantly lower dopamine synthesis capacity than individuals who went on to develop psychosis.

Furthermore, dopamine synthesis capacity was associated symptom severity in those who went on to develop psychosis, but showed no relationship with symptom severity in those who did not go on to develop psychosis. We also sought to determine if there was a change in dopamine synthesis capacity associated with the development of psychosis. Individuals at clinical high risk of psychosis were scanned at presentation and again after they developed the first psychotic episode, or, in the case of the at risk individuals who did not develop a psychotic disorder, after the high risk period. In this study we found that there was a longitudinal increase in dopamine synthesis capacity from presentation to the first psychotic episode [40]. Thus these findings indicate that dopamine synthesis capacity is elevated in the prodromal phase of schizophrenia, is linked to the symptoms, and increases with the development of the first psychotic episode.

In summary, it is apparent from the studies reviewed above that the most consistent body of molecular imaging research implicates the presynaptic side of dopamine neurotransmission. Furthermore the effect sizes tend to be much larger for the measures of presynaptic dopamine dysfunction than those of the D2/3 receptors, and evidence suggests that this may preferentially impact on associative cortical circuits.

How these dopaminergic abnormalities translate into the symptoms seen in the clinic still remains to be fully explained. However, one model has recently been described [16;41]. It is based on the extensive animal literature describing the role of dopamine in learning the contingencies between the presence of environmental stimuli and rewarding or aversive events. The model proposes the dopaminergic dysfunction in schizophrenia results in dopamine release occurring in the absence of relevant stimuli. This, it is proposed, would result in the aberrant attribution of salience to innocuous stimuli, which would explain clinical phenomena seen in the development of schizophrenia such as the Truman sign, and, over time, forms the basis of delusions and other psychotic symptoms.

Whilst the consistent findings of abnormal presynaptic dopaminergic function in schizophrenia suggest that this could lead to a diagnostic test, PET and SPECT scans have not proven sufficiently sensitive to be used diagnostically in the past. However, new approaches to analysing imaging data using multivariate inputs and neural network analysis have been found to offer high specificity and sensitivity in identifying people with schizophrenia [42]. These developments, together with improvements in scanner resolution, suggest that imaging may be used diagnostically in the future.

The link between dopaminergic dysfunction and cognitive impairment

A large body of evidence indicates that prefrontal dysfunction may underlie aspects of the cognitive impairment, in particular working memory function, seen in schizophrenia (see meta-analyses by Lee et al [43] and Glahn et al [44]). Over the past few years it has become evident that both alterations in prefrontal activation [45] and impairments in working memory [46] are already present in people at clinical high risk of psychosis [47]. Furthermore, the severity of working memory impairments may predict the subsequent onset of schizophrenia in clinical high risk subjects [48]. Working memory is normally mediated by a distributedneural network that includes the parietal and prefrontal cortices (for meta-analyses see Wager et al [49] and Owen et al [50]), with consistent engagement of dorsolateral prefrontal regions [50]. Working memory function is normally modulated by central dopaminergic activity [51;52]. For example, systemic administration of dopamine agonists enhances working memory performance [53] and modulates task dependent neuronal activity within the prefrontal cortex [54;55]. In Parkinson's disease [53] and in animal models [56], the loss or depletion of dopamine neurons is associated with impaired performance. Furthermore prefrontal function during working memory tasks appears to be most efficient at a particular level of afferent dopaminergic activity, and suboptimal if

dopaminergic activity is either too low or too high [57]. This particular relationship can be described as following an inverted U shaped curve [57].

We sought to test the relationship between dopaminergic function and prefrontal functioning in subjects at clinical risk for psychosis using a multimodal PET-fMRI. Subjects received an [18F]-DOPA PET scan of dopamine synthesis capacity and functional magnetic resonance imaging during a working memory task [58]. We found that there was a negative relationship between prefrontal activation during the working memory task and striatal dopamine synthesis capacity in the subjects at clinical risk for psychosis, whereas in matched healthy controls, the correlation was positive. When clinical high risk subjects and controls were combined in one sample, there was a quadratic relationship between striatal dopamine synthesis capacity and prefrontal activation. Thus, prefrontal activation was maximal in subjects with mid-range levels of dopamine synthesis capacity, but less marked in subjects in whom dopamine function was either relatively low, or relatively high. This relationship parallels the inverted U relationship between prefrontal cortical function during working memory tasks and afferent dopamine activity as described in experimental animals and in healthy human subjects [52;57;59]. The finding that prefrontal function is related to striatal dopamine synthesis capacity in controls as well as in patients, and that the relationship in both groups follows a quadratic relationship, suggests that the same mechanism underlies working memory in controls and clinical high risk subjects. Our results extend previous findings in patients with established schizophrenia [60;61], by showing that an alteration in the relationship between prefrontal cortical function and striatal dopamine synthesis capacity is evident when people have prodromal symptoms, prior to the full clinical expression of the disorder.

The cross-sectional nature of our study and those in established schizophrenia mean the direction of causality between the prefrontal and striatal findings can not be determined. Basic research indicates that activity in dopaminergic projections to the striatum is influenced by the prefrontal cortex [62;63]. A primary dysfunction of prefrontal cortex could thus underlie cognitive impairments and lead to increased subcortical dopaminergic activity [60] and the development of psychosis. However, selective disruption of dopaminergic neurotransmission in the striatum in mice can impair working memory performance and alters dopamine levels and D1 receptor activation in the prefrontal cortex [64], suggesting that changes in striatal dopaminergic neurotransmission can have secondary effects in prefrontal cortex. Overall the preclinical evidence indicates that either direction of causality is possible. Of course, it is also possible that another factor underlies both (see [65;66] and the sections below and in the review by Egerton et al in this issue). Nevertheless, these findings highlight presynaptic dopaminergic dysfunction as a target for drugs to ameliorate the cognitive impairments seen in schizophrenia.

Serotonin (5-HT) and Schizophrenia

The idea that serotonergic alterations might have a role in the pathophysiology of schizophrenia initially developed from several indirect findings. Firstly the observation that Lysergic Acid Diethylamide (LSD), a psychedelic agent which shares structural similarities with 5-HT, can cause schizophrenia-like symptoms such as hallucination and perceptual abnormalities. This led to the hypothesis that psychosis may be caused by brain serotonergic dysfunction [67-69]. However the findings from the LSD studies were later found to be more complex to interpret, not least because some of the effects of LSD on 5-HT receptors result in enhanced glutamate transmission [70]. Secondly a number of the second generation antipsychotic drugs were found to have higher affinity for 5-HT receptors than dopamine receptors [71]. Thirdly studies of 5-HT metabolites in the plasma and cerebro-spinal fluid have found evidence of alterations in schizophrenia (see review: [72]).

Although there is evidence for there being 14 sub-types of the 5-HT receptor [73], the main PET tracers that have been used to investigate the serotonin system in schizophrenia have targeted the 5-HT2A and 5-HT1A receptors and the 5-HT transporter (5-HTT).

The 5-HT2A receptor is located post-synaptically and widely distributed throughout the brain with high density in neocortical areas and relatively low density in subcortical areas such as striatum, caudate nucleus, thalamus, and pons. The majority (11 out of 15) of post-mortem 5-HT2A studies in schizophrenia show decreased binding in frontal cortex (see review in: [74]). However the results of 5-HT2A imaging studies have been inconsistent: four studies reported no difference [75-78], whilst two studies found decreased frontal cortex 5-HT2 availability in medication-free patients with schizophrenia compared to healthy control subjects [74;79]. Several of the negative studies have either used radiotracers with relatively low selectivity for 5HT2A receptors, or had relatively small sample sizes and so may have been under-powered. In this respect, Rasmussen et al, who earlier reported no change (n=15) [78], found about 10% decreased frontal cortex BP when they included more first episode medication-naïve patients (n=30) [74]. Finally Hurleman et al studied a relatively small group (n=14) of young people who were at high risk of psychosis and found decreased 5-HT2A availability in some regions [80]. Whilst this result warrants replication, the study highlights that serotonergic alterations may predate the onset of psychosis.

5-HT1A receptors are present pre-synaptically on 5-HT cell bodies and dendrites in mid-brain and brainstem raphe nucleus and act as autoreceptors. They are also localised post-synaptically, particularly in the hypothalamus, hippocampus, limbic and neocortical areas. Preclinical evidence suggests that 5-HT acts on 5-HT1A receptors to exert negative feedback on neuronal firing and thus maintains homeostatic control. The PET radiotracer [^{11}C]-WAY100632 has been used to index 5HT1A receptors in schizophrenia. The first study found increased cortical 5-HT1A availability- up to 20% in medial temporal areas- in 14 antipsychotic drug–naïve patients with schizophrenia [81]. In contrast, Yasuno et al found a decrease in 5-HT1A availability in eleven schizophrenia patients who were either drug-naïve or drug free [82]. Two other studies however reported no difference between patients and controls (n=22 medication-free) [83] and (n= 11 medicated) [84].

The 5-HT transporter plays a key role in regulating synaptic 5-HT neurotransmission. The two studies that have investigated the 5-HT transporter binding in schizophrenia have found no difference in 5-HTT availability compared to healthy control subjects [85;86] indicating that serotonin reuptake is not altered in schizophrenia. One key issue that remains to be investigated is whether serotonin release is altered in schizophrenia. It has proven difficult to reliably image serotonin release *in vivo* in man, but radiotracers currently under evaluation may enable this in the future.

Glutamatergic alterations and schizophrenia

Clinical observations that drugs such as ketamine that block N-methyl-D-aspartate (NMDA) type glutamate receptors result in transient schizophreniform symptoms led to proposals that a primary NMDA hypofunction underlies schizophrenia [87]. The investigation of NMDA receptor function in schizophrenia using molecular imaging has been limited by the relatively low brain penetration and receptor specificity of the radiotracers available, although more specific tracers are under development [88]. To fully understand the nature of glutamatergic alterations it will also be necessary to image glutamate levels. A recent study in baboons that suggests that molecular imaging may be used to do this *in vivo* [89]. Although this method has yet to be tested in man and requires further validation, it is a promising new approach that has the potential to greatly extend understanding of glutamatergic alterations in schizophrenia (see Egerton et al in this issue for a further discussion of glutamatergic dysfunction in the disorder).

Inflammation, microglia and Schizophrenia

Microglial cells are found throughout the CNS and activate in response to neuronal injury and inflammation. It has been proposed that microglial dysfunction may underlie the development of schizophrenia [90]. Post-mortem studies have demonstrated increased levels of activated microglia in patients with schizophrenia compared with controls [91;92]. Microglia show an increase in the expression of peripheral benzodiazepine receptor (also known as the translocator protein) sites when they undergo activation. The radiotracer [^{11}C]-PK1195 is selective for this binding site and has been widely used in PET studies of CNS inflammation.

Three PET studies with sample sizes from 7 to 16 have found increased [^{11}C]-PK1195 binding in medicated patients with psychotic illnesses, predominantly schizophrenia. Van Berckel et al [93] found a global increase in [^{11}C]-PK1195 grey matter binding in patients with schizophrenia who were within 5 years of onset of illness (n=10) with an effect size of 0.84. Banati et al [94] found increased [^{11}C]-PK1195 binding in schizophrenia across frontal and temporal regions. The largest effect size in the cortex was 2.5, for the superior frontal lobe, although there was also a large elevation in caudate of patients. Patients in this study (n=16) were a mixture of chronic and acute patients who were taking a range of antipsychotic medications. Finally, Doorduin et al [95] found evidence for an increase in activated microglia in the hippocampi of patients with schizophrenia (n=7). These studies thus indicate that there is increased microglial activation in schizophrenia which could be in response to prior or on-going neuronal injury or inflammation.

Conclusions and Future Directions

This review has highlighted key findings from functional imaging studies that have considerably advanced understanding of the neurobiology of psychotic disorders. Presynaptic striatal dopaminergic dysfunction is a consistent and widely replicated finding in PET and SPECT studies of schizophrenic molecular pathology. However, serotonergic alterations are much less consistent, and there is currently little or no molecular data on a number of other key neurotransmitter systems. The development of techniques to reliably image the release of serotonin and glutamate is an area of active research and will be invaluable in refining understanding of the pathophysiology of psychotic disorders. It is apparent that changes in dopamine synthesis capacity and stimulated dopamine release are consistently reported across different schizophrenic patient populations and experimental settings, whilst alterations in the density of post-synaptic D2/3 receptors are less marked. This implicates presynaptic dopaminergic dysfunction as the major dopaminergic abnormality in schizophrenia. Presynaptic dopaminergic dysfunction may therefore provide a practical biomarker for diagnosis of schizophrenia. Recent studies also indicate that microglial activation is increased in schizophrenia, suggesting that neuroinflammation may constitute part of the pathophysiology of the disorder. The evidence that elevated dopamine synthesis capacity is evident in the prodrome to schizophrenia and increases further the development psychosis provides a neurobiological target for preventive intervention. Furthermore, abnormal dopamine synthesis capacity in prodromal psychosis is associated with prefrontal dysfunction, accounting for the neurocognitive impairments observed in this phase of the disease. The high sensitivity and specificity of PET imaging for schizophrenia using the neural net approach suggests that this may be a useful biomarker to predict who will go on to develop psychosis, enabling intervention to be targeted on those truly at risk .

LIST OF ABBREVIATIONS

CNS	Central Nervous System

DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
FMRI	Functional Magnetic Resonance Imaging
IBZM	Iodobenzamide
L-DOPA	L-dihydroxyphenylalanine
LSD	Lysergic Acid Diethylamide
MRI	Magnetic Resonance Imaging
NMDA	N-methyl-D-aspartate
PET	Positron Emission Tomography
SPECT	Single Photon Emission Computed Tomography

REFERENCES

1. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, et al. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychol Med Monogr Suppl. 1992; 20:1–97. [PubMed: 1565705]
2. Jablensky A. Epidemiology of schizophrenia: the global burden of disease and disability. Eur Arch Psychiatry Clin Neurosci. 2000; 250(6):274–285. [PubMed: 11153962]
3. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet. 1997; 349(9063):1436–1442. [PubMed: 9164317]
4. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005; 2(5):e141. [PubMed: 15916472]
5. Hu TW. Perspectives: an international review of the national cost estimates of mental illness, 1990-2003. J Ment Health Policy Econ. 2006; 9(1):3–13. [PubMed: 16733267]
6. Guest JF, Cookson RF. Cost of schizophrenia to UK Society. An incidence-based cost-of-illness model for the first 5 years following diagnosis. Pharmacoeconomics. 1999; 15(6):597–610. [PubMed: 10538332]
7. Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. Schizophr Bull. 2004; 30(2): 279–293. [PubMed: 15279046]
8. Schultz SK, Andreasen NC. Schizophrenia. Lancet. 1999; 353(9162):1425–1430. [PubMed: 10227239]
9. Moller HJ. Course and long-term treatment of schizophrenic psychoses. Pharmacopsychiatry. 2004; 37(Suppl 2):126–135. [PubMed: 15546064]
10. Simon AE, Cattapan-Ludewig K, Zmilacher S, Arbach D, Gruber K, Dvorsky DN, et al. Cognitive functioning in the schizophrenia prodrome. SchizophrBull. 2007; 33(3):761–71.
11. Howes OD, McDonald C, Cannon M, Arseneault L, Boydell J, Murray RM. Pathways to schizophrenia: the impact of environmental factors. Int J Neuropsychopharmacol. 2004; 7(Suppl 1):S7–S13. [PubMed: 14972079]
12. Broome MR, Woolley JB, Tabraham P, Johns LC, Bramon E, Murray GK, et al. What causes the onset of psychosis? Schizophr Res. 2005; 79(1):23–34. [PubMed: 16198238]
13. Lewis DA, Gonzalez-Burgos G. Pathophysiologically based treatment interventions in schizophrenia. Nat Med. 2006; 12(9):1016–1022. [PubMed: 16960576]
14. McGuire P, Howes OD, Stone J, Fusar-Poli P. Functional neuroimaging in schizophrenia: diagnosis and drug discovery. Trends Pharmacol Sci. 2008; 29(2):91–98. [PubMed: 18187211]
15. Howes OD, Montgomery AJ, Asselin MC, Murray RM, Grasby PM, McGuire PK. Molecular imaging studies of the striatal dopaminergic system in psychosis and predictions for the prodromal phase of psychosis. Br J Psychiatry Suppl. Dec.2007 51:s13–8. [PubMed: 18055930]
16. Kapur S, Mizrahi R, Li M. From dopamine to salience to psychosis--linking biology, pharmacology and phenomenology of psychosis. Schizophr Res. 2005; 79(1):59–68. [PubMed: 16005191]

17. Lieberman JA, Kane JM, Alvir J. Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology (Berl). 1987; 91(4):415–433. [PubMed: 2884687]
18. Carlsson A, Lindqvist M, Magnusson T. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature. 1957; 180(4596):1200. [PubMed: 13483658]
19. Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science. 1976; 192(4238):481–483. [PubMed: 3854]
20. Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature. 1976; 261(5562):717–719. [PubMed: 945467]
21. Matthysse S. Antipsychotic drug actions: a clue to the neuropathology of schizophrenia? Fed Proc. 1973; 32(2):200–205. [PubMed: 4348519]
22. Snyder SH. The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. Am J Psychiatry. 1976; 133(2):197–202. [PubMed: 1251927]
23. Laruelle M. Imaging dopamine transmission in schizophrenia. A review and meta-analysis. Q J Nucl Med. 1998; 42(3):211–221. [PubMed: 9796369]
24. Kestler LP, Walker E, Vega EM. Dopamine receptors in the brains of schizophrenia patients: a meta-analysis of the findings. Behav Pharmacol. 2001; 12(5):355–371. [PubMed: 11710751]
25. Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, et al. Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. Nature. 1997; 385(6617):634–636. [PubMed: 9024661]
26. Karlsson P, Farde L, Halldin C, Sedvall G. PET study of D(1) dopamine receptor binding in neuroleptic-naive patients with schizophrenia. Am J Psychiatry. 2002; 159(5):761–767. [PubMed: 11986129]
27. Seeman P, Schwarz J, Chen JF, Szechtman H, Perreault M, McKnight GS, et al. Psychosis pathways converge via D2high dopamine receptors. Synapse. 2006; 60(4):319–346. [PubMed: 16786561]
28. Graf-Guerrero A, Romina M, Agid O, Marcon H, Barsoum P, Rusjan P, et al. The dopamine D2 receptors in high-affinity state and D3 receptors in schizophrenia: a clinical [11C]-(+)-PHNO PET study. Neuropsychopharmacology. 2009; 34(4):1078–86. [PubMed: 18987627]
29. Moore RY, Whone AL, McGowan S, Brooks DJ. Monoamine neuron innervation of the normal human brain: an 18F-DOPA PET study. Brain Res. 2003; 982(2):137–145. [PubMed: 12915249]
30. Howes OD, Egerton A, Allan V, McGuire P, Stokes P, Kapur S. Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. Curr Pharm Des. 2009; 15(22):2550–9. [PubMed: 19689327]
31. Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. Am J Psychiatry. 1998; 155(6):761–767. [PubMed: 9619147]
32. Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de BA, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc Natl Acad Sci U S A. 1997; 94(6):2569–2574. [PubMed: 9122236]
33. Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, et al. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci U S A. 1996; 93(17):9235–9240. [PubMed: 8799184]
34. Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc Natl Acad Sci U S A. 2000; 97(14):8104–8109. [PubMed: 10884434]
35. Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P, et al. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. Arch Gen Psychiatry. 2009; 66(1): 13–20. [PubMed: 19124684]
36. Abi-Dargham A, Kegeles LS, Zea-Ponce Y, Mawlawi O, Martinez D, Mitropoulou V, et al. Striatal amphetamine-induced dopamine release in patients with schizotypal personality disorder studied with single photon emission computed tomography and [123I]iodobenzamide. Biol Psychiatry. 2004; 55(10):1001–1006. [PubMed: 15121484]

37. Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M, et al. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. Arch Gen Psychiatry. Mar; 2010 67(3):231–9. [PubMed: 20194823]

38. Fusar-Poli P, Howes O, Valmaggia L, McGuire P. 'Truman' signs and vulnerability to psychosis. Br J Psychiatry. Aug.2008 193(2):168. [PubMed: 18670010]

39. Howes OD, Bose S, Valli I, Turkheimer F, Egerton A, Valmaggia L, et al. Dopamine synthesis capacity before onset of psychosis: a prospective [18]-DOPA PET imaging study. Am J Psychiatry. In Press.

40. Howes O, Bose S, Turkheimer F, Valli I, Egerton A, Stahl D, et al. Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. Mol Psychiatry. Mar 1.2011 PMID: 21358709 Epub ahead of print.

41. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry. 2003; 160(1):13–23. [PubMed: 12505794]

42. Bose SK, Turkheimer FE, Howes OD, Mehta MA, Cunliffe R, Stokes PR, et al. Classification of schizophrenic patients and healthy controls using [18F] fluorodopa PET imaging. Schizophr Res. 2008; 106(2-3):148–55. [PubMed: 18849151]

43. Lee J, Park S. Working memory impairments in schizophrenia: a meta-analysis. J Abnorm Psychol. Nov; 2005 114(4):599–611. [PubMed: 16351383]

44. Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, et al. Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. Hum Brain Mapp. May; 2005 25(1):60–9. [PubMed: 15846819]

45. Broome MR, Matthiasson P, Fusar-Poli P, Woolley J, Johns L, Tabraham P, et al. Neural correlates of executive function and working memory in the 'at-risk mental state'. Br J Psychiatry. 2009; 194(1):25–33. [PubMed: 19118321]

46. Pflueger MO, Gschwandtner U, Stieglitz RD, Riecher-Rossler A. Neuropsychological deficits in individuals with an at risk mental state for psychosis - working memory as a potential trait marker. Schizophr Res. Dec; 2007 97(1-3):14–24. [PubMed: 17936587]

47. Phillips LJ, McGorry PD, Yung AR, McGlashan TH, Cornblatt B, Klosterkotter J. Prepsychotic phase of schizophrenia and related disorders: recent progress and future opportunities. Br J Psychiatry Suppl. Aug.2005 48:S33–44. [PubMed: 16055805]

48. Pukrop R, Ruhrmann S, Schultze-Lutter F, Bechdolf A, Brockhaus-Dumke A, Klosterkotter J. Neurocognitive indicators for a conversion to psychosis: comparison of patients in a potentially initial prodromal state who did or did not convert to a psychosis. Schizophr Res. 2007; 92(1-3): 116–25. [PubMed: 17344028]

49. Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci. Dec; 2003 3(4):255–74. [PubMed: 15040547]

50. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp. May; 2005 25(1):46–59. [PubMed: 15846822]

51. Egerton A, Mehta MA, Montgomery AJ, Lappin JM, Howes OD, Reeves SJ, et al. The dopaminergic basis of human behaviors: A review of molecular imaging studies. Neurosci Biobehav Rev. Jul; 2009 33(7):1109–32. [PubMed: 19481108]

52. Marie RM, Defer GL. Working memory and dopamine: clinical and experimental clues. Curr Opin Neurol. Dec; 2003 16(Suppl 2):S29–35. [PubMed: 15129848]

53. Costa A, Peppe A, Dell'Agnello G, Carlesimo GA, Murri L, Bonuccelli U, et al. Dopaminergic modulation of visual-spatial working memory in Parkinson's disease. Dement Geriatr Cogn Disord. 2003; 15(2):55–66. [PubMed: 12566593]

54. Meisenzahl EM, Schmitt GJ, Scheuerecker J, Moller HJ. The role of dopamine for the pathophysiology of schizophrenia. Int Rev Psychiatry. Aug; 2007 19(4):337–45. [PubMed: 17671867]

55. Goldman-Rakic PS. Regional and cellular fractionation of working memory. Proc Natl Acad Sci U S A. Nov 26; 1996 93(24):13473–80. [PubMed: 8942959]

56. Miyoshi E, Wietzikoski S, Camplessei M, Silveira R, Takahashi RN, Da Cunha C. Impaired learning in a spatial working memory version and in a cued version of the water maze in rats with

MPTP-induced mesencephalic dopaminergic lesions. Brain Res Bull. May; 2002 58(1):41–7. [PubMed: 12121811]

57. Williams GV, Castner SA. Under the curve: critical issues for elucidating D1 receptor function in working memory. Neuroscience. Apr 28; 2006 139(1):263–76. [PubMed: 16310964]
58. Fusar-Poli P, Howes OD, Allen P, Broome M, Valli I, Asselin MC, et al. Abnormal frontostriatal interactions in people with prodromal signs of psychosis: a multimodal imaging study. Arch Gen Psychiatry. Jul; 2010 67(7):683–91. [PubMed: 20603449]
59. Goldman-Rakic PS, Muly EC 3rd, Williams GV. D(1) receptors in prefrontal cells and circuits. Brain Res Brain Res Rev. Mar; 2000 31(2-3):295–301. [PubMed: 10719156]
60. Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, et al. Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nat Neurosci. Mar; 2002 5(3):267–71. [PubMed: 11865311]
61. Bertolino A, Breier A, Callicott JH, Adler C, Mattay VS, Shapiro M, et al. The relationship between dorsolateral prefrontal neuronal N-acetylaspartate and evoked release of striatal dopamine in schizophrenia. Neuropsychopharmacology. 2000; 22(2):125–32. [PubMed: 10649825]
62. Bennay M, Gernert M, Schwabe K, Enkel T, Koch M. Neonatal medial prefrontal cortex lesion enhances the sensitivity of the mesoaccumbal dopamine system. Eur J Neurosci. Jun; 2004 19(12): 3277–90. [PubMed: 15217384]
63. Flores G, Wood GK, Liang JJ, Quirion R, Srivastava LK. Enhanced amphetamine sensitivity and increased expression of dopamine D2 receptors in postpubertal rats after neonatal excitotoxic lesions of the medial prefrontal cortex. J Neurosci. Nov 15; 1996 16(22):7366–75. [PubMed: 8929443]
64. Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V, et al. Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. Neuron. 2006; 49(4):603–15. [PubMed: 16476668]
65. Stone JM, Howes OD, Egerton A, Kambeitz J, Allen P, Lythgoe DJ, et al. Altered relationship between hippocampal glutamate levels and striatal dopamine function in subjects at ultra high risk of psychosis. Biol Psychiatry. 2010; 68(7):599–602. 2010 Oct 1. [PubMed: 20638047]
66. Bramon E, Shaikh M, Broome M, Lappin J, Berge D, Day F, et al. Abnormal P300 in people with high risk of developing psychosis. Neuroimage. 2008; 41(2):553–60. [PubMed: 18387827]
67. Woolley DW, Shaw E. An antiserotonin which is active when fed. J Pharmacol Exp Ther. May; 1953 108(1):87–93. [PubMed: 13053426]
68. Gaddum JH. Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine. J Physiol. Jul.1953 121(1):15P.
69. Amin AH, Crawford TB, Gaddum JH. The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. J Physiol. Dec 10; 1954 126(3):596–618. [PubMed: 13222357]
70. Aghajanian GK, Marek GJ. Serotonin model of schizophrenia: emerging role of glutamate mechanisms. Brain Res Brain Res Rev. Mar; 2000 31(2-3):302–12. [PubMed: 10719157]
71. Meltzer HY. Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. Psychopharmacology (Berl). 1989; 99:S18–27. Suppl. [PubMed: 2682729]
72. Abi-Dargham A, Laruelle M, Aghajanian GK, Charney D, Krystal J. The role of serotonin in the pathophysiology and treatment of schizophrenia. J Neuropsychiatry Clin Neurosci. 1997; 9(1):1–17. Winter. [PubMed: 9017523]
73. Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav. Apr; 2002 71(4):533–54. [PubMed: 11888546]
74. Rasmussen H, Erritzoe D, Andersen R, Ebdrup BH, Aggernaes B, Oranje B, et al. Decreased frontal serotonin2A receptor binding in antipsychotic-naive patients with first-episode schizophrenia. Arch Gen Psychiatry. Jan; 2010 67(1):9–16. [PubMed: 20048218]
75. Lewis R, Kapur S, Jones C, DaSilva J, Brown GM, Wilson AA, et al. Serotonin 5-HT2 receptors in schizophrenia: a PET study using [18F]setoperone in neuroleptic-naive patients and normal subjects. Am J Psychiatry. Jan; 1999 156(1):72–8. [PubMed: 9892300]

76. Trichard C, Paillere-Martinot ML, Attar-Levy D, Blin J, Feline A, Martinot JL. No serotonin 5-HT2A receptor density abnormality in the cortex of schizophrenic patients studied with PET. Schizophr Res. May 4; 1998 31(1):13–7. [PubMed: 9633832]
77. Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, et al. Serotonin 5-HT2 receptors in schizophrenic patients studied by positron emission tomography. Life Sci. 2000; 66(25):2455–64. [PubMed: 10894088]
78. Erritzoe D, Rasmussen H, Kristiansen KT, Frokjaer VG, Haugbol S, Pinborg L, et al. Cortical and subcortical 5-HT2A receptor binding in neuroleptic-naive first-episode schizophrenic patients. Neuropsychopharmacology. Sep; 2008 33(10):2435–41. [PubMed: 18288096]
79. Ngan ET, Yatham LN, Ruth TJ, Liddle PF. Decreased serotonin 2A receptor densities in neuroleptic-naive patients with schizophrenia: A PET study using [(18)F]setoperone. Am J Psychiatry. Jun; 2000 157(6):1016–8. [PubMed: 10831488]
80. Hurlemann R, Matusch A, Kuhn KU, Berning J, Elmenhorst D, Winz O, et al. 5-HT2A receptor density is decreased in the at-risk mental state. Psychopharmacology (Berl). Jan; 2008 195(4):579–90. [PubMed: 17899021]
81. Tauscher J, Kapur S, Verhoeff NP, Hussey DF, Daskalakis ZJ, Tauscher-Wisniewski S, et al. Brain serotonin 5-HT(1A) receptor binding in schizophrenia measured by positron emission tomography and [11C]WAY-100635. Arch Gen Psychiatry. Jun; 2002 59(6):514–20. [PubMed: 12044193]
82. Yasuno F, Suhara T, Ichimiya T, Takano A, Ando T, Okubo Y. Decreased 5-HT1A receptor binding in amygdala of schizophrenia. Biol Psychiatry. Mar 1; 2004 55(5):439–44. [PubMed: 15023569]
83. Frankle WG, Lombardo I, Kegeles LS, Slifstein M, Martin JH, Huang Y, et al. Serotonin 1A receptor availability in patients with schizophrenia and schizo-affective disorder: a positron emission tomography imaging study with [11C]WAY 100635. Psychopharmacology (Berl). Dec; 2006 189(2):155–64. [PubMed: 16953380]
84. Bantick RA, Montgomery AJ, Bench CJ, Choudhry T, Malek N, McKenna PJ, et al. A positron emission tomography study of the 5-HT1A receptor in schizophrenia and during clozapine treatment. J Psychopharmacol. Sep; 2004 18(3):346–54. [PubMed: 15358978]
85. Frankle WG, Narendran R, Huang Y, Hwang DR, Lombardo I, Cangiano C, et al. Serotonin transporter availability in patients with schizophrenia: a positron emission tomography imaging study with [11C]DASB. Biol Psychiatry. Jun 15; 2005 57(12):1510–6. [PubMed: 15953487]
86. Laruelle M, Abi-Dargham A, van Dyck C, Gil R, D'Souza DC, Krystal J, et al. Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [(123)I]beta-CIT. Biol Psychiatry. Mar 1; 2000 47(5):371–9. [PubMed: 10704949]
87. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry. 1995; 52(12):998–1007. [PubMed: 7492260]
88. Arstad E, Platzer S, Berthele A, Pilowsky LS, Luthra SK, Wester HJ, et al. Towards NR2B receptor selective imaging agents for PET-synthesis and evaluation of N-[11C]-(2-methoxy)benzyl (E)-styrene-, 2-naphthyl- and 4-trifluoromethoxyphenylamidine. Bioorg Med Chem. Sep 15; 2006 14(18):6307–13. [PubMed: 16777419]
89. Miyake N, Skinbjerg M, Easwaramoorthy B, Kumar D, Girgis RR, Xu X, et al. Imaging changes in glutamate transmission in vivo with the metabotropic glutamate receptor 5 tracer [11C] ABP688 and N-acetylcysteine challenge. Biol Psychiatry. May 1; 2011 69(9):822–4. [PubMed: 21288506]
90. Munn NA. Microglia dysfunction in schizophrenia: an integrative theory. Med Hypotheses. Feb; 2000 54(2):198–202. [PubMed: 10790752]
91. Bayer TA, Buslei R, Havas L, Falkai P. Evidence for activation of microglia in patients with psychiatric illnesses. Neurosci Lett. Aug 20; 1999 271(2):126–8. [PubMed: 10477118]
92. Radewicz K, Garey LJ, Gentleman SM, Reynolds R. Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. J Neuropathol Exp Neurol. Feb; 2000 59(2):137–50. [PubMed: 10749103]
93. van Berckel BN, Bossong MG, Boellaard R, Kloet R, Schuitemaker A, Caspers E, et al. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. Biol Psychiatry. Nov 1; 2008 64(9):820–2. [PubMed: 18534557]

94. Banati R, Hickie IB. Therapeutic signposts: using biomarkers to guide better treatment of schizophrenia and other psychotic disorders. Med J Aust. Feb 16; 2009 190(4 Suppl):S26–32. [PubMed: 19220170]

95. Doorduin J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC. Neuroinflammation in schizophrenia-related psychosis: a PET study. J Nucl Med. Nov; 2009 50(11):1801–7. [PubMed: 19837763]

Europe PMC Funders Author Manuscripts