Molecular imaging studies of the striatal dopaminergic system in psychosis and predictions for the prodromal phase of psychosis

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Summary  The dopamine hypothesis has been the major pathophysiological theory of psychosis in recent decades. Molecular imaging studies have provided in vivo evidence of increased dopamine synaptic availability and increased presynaptic dopamine synthesis in the striatum of people with psychotic illnesses. These studies support the predictions of the dopamine hypothesis, but it remains to be determined whether dopaminergic abnormalities pre-date or are secondary to the development of psychosis. We selectively review the molecular imaging studies of the striatal dopaminergic system in psychosis and link this to models of psychosis and the functional subdivisions of the striatum to make predictions for the dopaminergic system in the prodromal phase of psychosis.

Declaration of interest  None.

THE DOPAMINE HYPOTHESIS OF PSYCHOSIS

The predominant pathophysiological theory of psychosis postulates that dopamine dysfunction is the final common pathway driving its development (Carlsson & Lindqvist, 1963; Davis et al, 1991; Kapur, 2003). It is hypothesised that hyperactivity of the dopamine system leads to the psychotic symptoms seen in conditions such as schizophrenia (Kapur, 2003). Recent elaborations of this model propose that striatal hyperdopaminergia results in aberrant salience being attached to what would normally be innocuous stimuli that then form the basis of the hallucinations and delusions of psychosis (Kapur, 2003). Additionally it has been proposed that there is an interaction between striatal dopamine overactivity and frontal dopamine hypoactivity, with the latter associated with some of the neurocognitive deficits seen in schizophrenia (Willner, 1997; Laruelle et al, 2003; Abi-Dargham, 2004). This is supported by a mouse model in which dopamine D2 receptor overexpression in the striatum is associated with selective working memory deficits, and decreased dopamine turnover and D1 receptor activation in the frontal cortex (Kellendonk et al, 2006).

There is considerable indirect or ex vivo evidence of dopamine dysfunction in psychosis based on studies of dopaminergic agonists, antagonists, and post-mortem studies reviewed by Carlsson and colleagues (Carlsson et al, 1997). Pharmacological studies show a correlation between clinical doses of antipsychotic drugs and their potency for blocking D2 receptors, and provide further evidence for the involvement of dopamine in psychosis through the psychotogenic effects of dopamine enhancing drugs (Seeman & Lee, 1975; Meltzer & Stahl, 1976; Haracz, 1982; Lieberman et al, 1987). These studies strongly suggest, but do not establish, the existence of a dysregulation of dopamine transmission in psychosis. Post-mortem findings of chronic psychotic conditions have been mixed. Although direct tissue measures of dopamine and D2 receptor levels have been found to be elevated in the striatum, this has not been consistent, and post-mortem studies are confounded by antipsychotic exposure (Kleinman et al, 1988; Reynolds, 1989; Davis et al, 1991; Zakianis & Hansen, 1998).

IN VIVO MOLECULAR IMAGING OF STRIATAL DOPAMINERGIC SYSTEMS

Studies of dopamine receptors and dopamine release

Developments in human molecular imaging over the past 20 years have allowed aspects of dopaminergic function to be examined in vivo. The early studies in psychosis, predominantly schizophrenia, examined the striatal postsynaptic dopamine D2 receptor density using positron emission tomography (PET) and single photon emission computed tomography (SPECT) tracers including various radiolabelled analogues of spiperone, [11C]raclopride and [123I]IBZM. The findings of these studies are inconsistent, with some reporting increased D2 receptor binding in schizophrenia (Crawley et al, 1986; Wong et al, 1986; Gjedde & Wong, 1987) and others no difference from controls (Farde et al, 1990; Martinot et al, 1990). However a meta-analysis of these studies concluded that there is a modest elevation in the D2 receptor densities in people with psychotic illnesses, with an effect size of approximately 0.5 (Laruelle, 1998). The two studies that have investigated D1 receptor densities in the striatum of patients with psychotic illnesses report no difference from controls, indicating that striatal D1 receptor levels are unchanged in psychosis, although there may be differences in other brain regions (Okubo et al, 1997; Karlsson et al, 2002).

Other studies have examined the striatal synaptic availability and release of dopamine (Laruelle et al, 1996, 1999; Breier et al, 1997; Abi-Dargham et al, 1998, 2000) by employing radiotracers whose binding is sensitive to endogenous dopamine levels such as [11C]raclopride and [123I]IBZM. These studies have used amphetamine to probe the responsivity of the striatal dopaminergic system. Amphetamine acts to stimulate dopamine release from vesicles and reverse the dopamine transporter, increasing extracellular levels of dopamine (Sulzer et al, 1993; Jones et al, 1998). The competition model predicts that dopamine competes for binding to the D2 receptors with the radioligand and therefore that the amphetamine-induced increase in dopamine levels results in a reduction in radioligand binding and a change in the signal compared to baseline conditions. Stimulated dopamine release using amphetamine has consistently been found to be increased in psychotic conditions by 1–2 standard deviations, and is related to both the severity of induced psychotic symptoms, and to the response to subsequent antipsychotic treatment (Laruelle et al, 1996, 1999; Breier et al, 1997; Abi-Dargham et al, 1998). However this increased radioligand displacement has not been seen in...
patients with schizophrenia during remission, suggesting that the increased dopamine release is a feature of the psychotic phases of the illness (Laruelle et al., 1999).

These studies have been interpreted as indicating increased dopamine release, on the basis that animal studies show a correlation between increased dopamine concentration as measured by microdialysis and radiotracer binding (Breier et al., 1997; Houston et al., 2004). To determine whether baseline levels of dopamine are different, Abi-Dargham and colleagues (2000) examined the effect of dopamine depletion, using alpha-methyl-para-tyrosine, on [123I]IBZM binding (Abi-Dargham et al., 2000). They report greater [123I]IBZM binding following dopamine depletion in first-episode psychosis and patients with chronic disorder during an acute relapse compared with controls. This is taken as indicating greater baseline D2 receptor occupancy by dopamine in psychosis. Additionally, the degree of change correlated with response to treatment with antipsychotics. Patients in remission need to be studied to determine whether this is related to illness phase.

Studies of presynaptic striatal dopaminergic function

Presynaptic striatal dopaminergic function can be measured using the PET radiotracers [β-11C]L-dopa and 6-[18F]fluoro-L-dopa (FDOPA). These radiotracers are converted by aromatic L-amino acid decarboxylase (AADC) into [14C]dopamine and 6-[18F]fluoro-dopamine, respectively, and trapped in vesicles in the presynaptic dopamine neurons. Their accumulation can be detected through the emission of annihilation photons as the radioisotopes decay via positron emission. Their uptake is typically quantified as an influx constant (Ki) value relative to a reference region devoid of specific uptake (Patlak & Blasberg, 1985; Moore et al., 2003; McGowan et al., 2004). High Ki values occur in areas of dense dopamine nerve terminals such as the striatum, reflecting the structural and functional integrity of the nigrostriatal dopaminergic system. Although tyrosine hydroxylase, and not AADC, is the rate-limiting step in the synthetic pathway for dopamine, AADC activity influences the rate of dopamine synthesis (Cumming et al., 1995, 1997). FDOPA uptake has been shown to correlate with nigral dopamine neuron numbers in both animal and human studies (Pate et al., 1993; Snow et al., 1993).

These radiotracers have been used to investigate the dopaminergic system in a number of central nervous system conditions, particularly Parkinson’s Disease (Brooks, 1998; Morrish et al., 1998; Piccini and Brooks, 1999; Brooks et al., 2000; Rakshi et al., 2002).

Eight studies have measured pre-synaptic striatal dopamine synthesis and storage capacity using [β-11C]L-dopa or FDOPA in psychotic conditions (Table 1). Six found elevated striatal DOPA uptake in psychotic disorders (Reith et al., 1994; Hietala et al., 1995, 1999; Lindstrom et al., 1999; Meyer-Lindenberg et al., 2002; McGowan et al., 2004), with effect sizes in the positive studies ranging from 0.63 to 1.89. All studies that investigated patients who were psychotic at the time of PET scanning reported elevated striatal dopamine synthesis capacity (Hietala et al., 1995, 1999; Lindstrom et al., 1999). The two inconsistent studies were in chronically treated patients who were not acutely psychotic, although Dao-Castellana and colleagues (1997) report a non-significant elevation in the striatum and greater variance in the Ki values in the group with schizophrenia (Dao-Castellana et al., 1997; Elkashef et al., 2000). The other study found a significant decrease in Ki value in the ventral striatum of the group with untreated schizophrenia, but an increase in the posterior cingulate (Elkashef et al., 2000). Thus all the studies have found indications of increased DOPA uptake in individuals with schizophrenia, although not all in the striatum.

Relationship between striatal dopamine synthesis capacity and symptom profiles

There are indications that the elevation in dopamine synthesis capacity is not specific to schizophrenia alone but is associated with episodes of positive psychotic symptoms. Reith et al. (1994) studied patients with complex partial seizures, and compared those with a history of psychosis to those who did not have a history of psychosis. The group with psychosis showed elevated striatal Ki values, similar to the elevation seen in a group with schizophrenia, while the striatal Ki value in the non-psychotic group was similar to that in controls (Reith et al., 1994). Hietala and colleagues (1995) have suggested that there is a difference in FDOPA uptake which depends on the subtype of schizophrenia.

This was based on the finding that a single subject with catatonia showed markedly lower striatal FDOPA uptake than controls and those with paranoid schizophrenia. Dao-Castellana et al. (1997) subsequently found a similar reduction in a subject with catatonia. Hietala and colleagues (1999) also found a negative correlation between depressive symptoms and striatal FDOPA uptake, and a trend for positive psychotic symptoms to be associated with higher striatal FDOPA uptake. Further support for elevated FDOPA uptake being associated with positive psychotic symptoms could be inferred from the two studies that found no significant elevation in striatal Ki value in chronic, stable patients (Dao-Castellana et al., 1997; Elkashef et al., 2000). However, elevated striatal Ki values have been reported in chronic patients in remission (Reith et al., 1994), indicating that it is not as simple as acute psychosis being associated with increased dopamine synthesis capacity. McGowan et al. (2004) have found that dopamine synthesis capacity is elevated in individuals chronically treated for schizophrenia (McGowan et al., 2004) to a similar degree to that reported in antipsychotic-naïve patients in their first episode of psychosis (Hietala et al., 1995, 1999; Lindstrom et al., 1999). Furthermore, the findings reported by Hietala et al. (1999) supporting an association between positive psychotic symptoms and elevated FDOPA uptake are at a trend level in small groups of patients, indicating that further studies are needed to determine if the association is found in other samples.

SPECIFICITY OF STRIATAL DOPAMINERGIC ABNORMALITIES TO PSYCHOSIS

Striatal dopaminergic function is not elevated in non-psychotic patients with other psychiatric or neurological conditions, including mania (without psychotic symptoms), Tourette’s syndrome and depression (Reith et al., 1994; Turjanski et al., 1994; Ernst et al., 1997; Martinot et al., 2001; Parsey et al., 2001; Yatham et al., 2002). Ernst and colleagues report no significant difference in striatal FDOPA uptake between children or adults with attention-deficit hyperactivity disorder and controls, although there may be differences in other brain regions (Ernst et al., 1998, 1999). The findings in these studies indicate that
prior to the development of psychosis, the majority of patients experience a pro-
dromal state and developing a psychotic illness within 1 year, indicating that they are at high risk of developing psychotic illness in people with an at-risk mental state, who are at high risk of imminently developing psychosis.

Subjects with an at-risk mental state are experiencing attenuated psychotic symptoms and are also at high risk of developing psychosis in the near future, therefore an initial prediction would be that the at-risk mental state would be associated with striatal hyperdopaminergia. However, as most individuals with an at-risk mental state will not develop a psychotic illness, a further prediction might be that the magnitude of this elevation will be greater in those that go on to develop a psychotic illness than in subjects who do not.

Models of psychosis (above) propose that elevated dopaminergic function may lead to the development of hallucinations and delusions through effects on cognitive processes like appraisal. Reasoning is a component of appraisal and those with at-risk mental state show a bias in probabilistic reasoning (‘jumping to conclusions’) that is similar to that seen in psychotic disorders (Garety et al., 2003; Peters & Garety, 2006). This suggests that the magnitude of the hypothesised increase in dopaminergic function may be correlated with a tendency to jump to conclusions. In addition, because elevated dopaminergic function may be specifically linked to hallucinations and delusions, hyperdopaminergia in the at-risk mental state would be predicted to be particularly correlated with the severity of these symptoms as opposed to other psychotic features or the level of general psychopathology.

Finally, it has been suggested that the cognitive impairment and negative symptoms of schizophrenia are a function of hypodopaminergia in the dorsolateral prefrontal cortex (Abi-Dargham et al., 2002). It is difficult to assess cortical dopamine function using FDOPA due to its low signal-to-noise ratio in the cortex (McGowan et al., 2004). However, it has been proposed that hypodopaminergia in the dorsolateral prefrontal cortex in schizophrenia is related to excess subcortical dopamine levels (Tanaka, 2006), and striatal FDOPA uptake in patients with schizophrenia has been inversely correlated with dorsolateral prefrontal cortex activation during the Wisconsin Card Sort test (Meyer-Lindenberg et al., 2002) and with impaired performance.
on the symbol-digit modalities test (McGowan et al., 2004). Thus the hypothesised increase in striatal dopaminergic function in the at-risk mental state may be inversely correlated with impaired prefrontal cortical function, as indicated through impaired performance on tasks of executive functions and by abnormal dorsolateral prefrontal cortex activation in functional neuroimaging studies.

**FUNCTIONAL SUBDIVISIONS OF THE STRIATUM**

The striatum shows a topographic organisation reflecting connections with the limbic, frontal executive and motor brain regions that does not correspond to traditional anatomical subdivisions into caudate, putamen and nucleus accumbens (Haber, 2003). Ventral areas of the striatum (the nucleus accumbens, and ventral caudate and putamen rostral to the anterior commissure) are part of limbic circuits involving medial prefrontal and orbitofrontal cortex, and thalamic loops, and have been termed the 'limbic striatum' (Joel & Weiner, 2000; Martinez et al., 2003). The dorsal areas of the caudate and putamen rostral to the anterior comissure and the postcommissural caudate form circuits involving the dorsolateral prefrontal cortex, and ventral anterior thalamus, and are involved in cognitive function ('the associative striatum') (Joel & Weiner, 2000; Martinez et al., 2003). Finally the postcommissural putamen ('the sensorimotor striatum') is linked to the motor and premotor cortex and ventral anterior thalamus (Joel & Weiner, 2000; Martinez et al., 2003).

Striatal functional connectivity suggests that the consequences of dopaminergic dysfunction may vary depending on the area of the striatum affected. Because of its place in circuits involving the dorsolateral prefrontal cortex, the associative striatum would be predicted to be critical to the cognitive processes leading to psychosis, and the cognitive dysfunction seen in schizophrenia. Recent advances in imaging technology have enabled these functional subdivisions to be delineated (Martinez et al., 2003). Preliminary evidence has recently been presented indicating that the alpha-methyl-para-tyrosine induced increase in D2 receptor availability was significantly higher in the associative striatum of patients with schizophrenia, but not the other striatal subregions (Laruelle, 2006).

If dopaminergic dysfunction is driving the development of psychosis through cognitive effects, we would predict that the associative striatum would show the largest increase in dopaminergic function in people with an at-risk mental state, and that this would correlate with dorsolateral prefrontal cortex function, such as performance on working memory tasks.

**IN VIVO STUDIES OF STRIATAL DOPAMINERGIC FUNCTION IN PEOPLE AT RISK OF PSYCHOSIS**

Dopamine function has not been studied in individuals with an at-risk mental state, but there have been studies in other groups at increased risk of psychotic illness, notably the unaffected relatives of people with schizophrenia, and people with schizotypal personality disorder. D2 receptor levels have been found to be elevated in the caudate to an intermediate degree in the non-psychotic monozygotic co-twins of patients with schizophrenia compared to controls (Hirvonen et al., 2005), although there was no evidence of alterations in the D1/D2 receptor ratio (Hirvonen et al., 2006). People with schizotypal personality disorder, who can experience intermittent attenuated psychotic symptoms, have been found to have increased [11C]raclopride displacement following amphetamine challenge (Abi-Dargham et al., 2004). Interestingly the authors note that the degree of [11C]raclopride displacement seen in the schizotypal personality disorder group was similar to that seen in remitted patients with schizophrenia, but much less than that seen in patients with acute psychosis.

The investigation of striatal dopaminergic function in individuals with an at-risk mental state has a number of advantages over further studies of striatal dopaminergic function in people with psychotic illnesses. Firstly it will help determine the time-point at which dopaminergic abnormalities occur, indicating whether dopaminergic abnormalities are primary or secondary to other factors. Similarly the relationship between dopaminergic function and cognitive processes thought to be related to the development of psychosis, and the development of the cognitive deficits seen in psychosis, can be investigated. Additionally the effects of antipsychotic drugs on dopaminergic function are not a complicating factor as this group is largely antipsychotic naive, and a substantial proportion of individuals with an at-risk mental state are in the prodromal phase of a psychotic illness, which is not the case in other ‘risk groups’, such as relatives of those with schizophrenia or people with schizotypy, as these groups contain many individuals who may be trait carriers but who will not develop psychosis. There has been considerable debate concerning the ethics of offering people with an at-risk mental state antipsychotic medication to treat attenuated psychotic symptoms and reduce the risk of developing psychotic illness (McGorry et al., 2001; Haroun et al., 2006). Studies of the dopaminergic system in individuals with an at-risk mental state would indicate whether a dopaminergic abnormality that might be modified by antipsychotic treatment exists prior to the development of psychosis.

**CONCLUSIONS**

There is a fairly substantial and consistent body of in vivo molecular imaging evidence indicating that striatal presynaptic dopamine synthesis and synaptic dopamine availability is increased in psychotic illnesses. Striatal dopamine D2 receptor levels may also be modestly increased in people with psychotic illnesses, although there have been a number of inconsistent studies, and striatal D1 receptor levels are similar. The relationship between psychotic symptoms and dopaminergic function is less well established, as few studies have investigated this, and the results among those to have done so are inconsistent. Although the imaging data reviewed supports the dopaminergic hypothesis, the studies cannot exclude the possibility that the abnormalities in the dopamine system are secondary to other factors, such as glutamatergic dysfunction (Laruelle et al., 2003). Studies in people with at-risk mental states, some of whom are in the prodromal phase of psychosis, are needed to determine whether the dopaminergic abnormalities found in psychotic illness are state or trait features. Furthermore these studies will enable a number of predictions about the relationship between dopaminergic abnormalities and cognitive biases and cognitive impairments commonly associated with psychosis to be tested. Investigating the pathophysiology of the prodromal phase is important both to understand the pathophysiology of
psychosis and for the development of better treatments to prevent the development of psychosis and ameliorate symptoms in the prodrome.

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