

## Editorial

## Insights into schizophrenia using positron emission tomography: building the evidence and refining the focus



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**Summary**

Schizophrenia involves dysregulation in dopaminergic transmission. Studies show heightened presynaptic striatal dopaminergic function and elevated striatal  $D_2/D_3$  receptor density in the brain. Cognitive impairments result from hypostimulation of  $D_1$  receptors and are associated with dysfunction in the prefrontal cortex. Here we discuss

relevant positron emissions tomography (PET) studies and provide future directions.

**Declaration of interest**

None.

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Schizophrenia is a severe and complex neuropsychiatric disorder with a lifetime risk of 1%. The disorder usually presents in early adolescence to early adulthood, with the majority of patients showing psychosocial dysfunction over the course of the syndrome. Although this polygenic disorder has a high heritability (80%) the aetiology remains unclear. It is believed that the emerging signs and symptoms of schizophrenia are a result of altered dopamine transmission. Since schizophrenia has a biological basis the natural progression is to apply functional imaging techniques to gain better insights into its pathophysiology. The functional technology of positron emission tomography (PET) was developed in the early 1970s and has been extensively used in research and diagnostic applications. Combined with computed tomography (PET–CT), this is a non-invasive metabolic and neuroreceptor imaging technique that provides anatomical and functional information which may help improve understanding of neural function and aetiological factors. Over the past decade PET neuroimaging has been used to examine dopamine function in schizophrenia. However, since PET requires an on-site or close-by cyclotron unit to produce the receptor ligand, and causes exposure of those investigated to ionising radiation, other molecular imaging techniques such as functional magnetic resonance imaging (fMRI) have gained preference. Not only does fMRI not entail the use of ionising radiation, it is also more readily available and cheaper than PET–CT. Nevertheless, based on technological advances and an upsurge of research interest in the role of dopamine in schizophrenia, the field of PET–CT neuroimaging has extensively progressed, providing substantial insights into neural function and *in vivo* brain chemistry.

**Brain neurochemical dysfunction in schizophrenia**

The classical dopamine hypothesis of schizophrenia proposes that positive symptoms are related to a dopaminergic imbalance in the

brain. Positive symptoms such as hallucinations and delusions are considered to be a result of increased subcortical release of dopamine causing greater stimulation of  $D_2$  receptors, and a primary target of many antipsychotic drugs therefore is antagonism at striatal  $D_2$  receptors. Cognitive deficits and negative symptoms are resistant to treatment by most typical antipsychotic drugs and arise from reduced  $D_1$  receptor stimulation. Experimental investigations have demonstrated an association of  $D_2$  receptors and cognitive processes, particularly planning ability and tasks with a working-memory component. The hypothesis is supported by the observation that long-term use of  $D_2$  receptor agonists such as amphetamines can induce psychotic-like symptoms, and effective antipsychotic drugs have been shown to block  $D_2$  receptors. Recently, the theoretical grounds of the dopamine hypothesis have somewhat altered following influential findings stemming from several disciplines, including imaging studies identifying brain anatomical and connectivity abnormalities, cognitive deficits affecting multiple networks, advances in molecular genetics and the influence of putative environmental risk factors.<sup>1</sup>

Regional brain abnormalities in schizophrenia have been identified with PET. The radiotracer [ $^{18}\text{F}$ ]fluorodopa is taken up by spared serotonergic nerve terminals, converted into dopamine and then released into the synaptic cleft. Its neurochemical pathway can be used to generate a map of presynaptic dopamine synthesis. Elevated dopaminergic levels have been reported in the presynaptic striatum in schizophrenia,<sup>2</sup> with an increase in turnover,<sup>3</sup> which may be associated with symptom severity. These studies have reported effect sizes for presynaptic striatal dopamine ranging from moderate (0.63) to large ( $>1$ ). Additionally, numerous studies and meta-analyses have replicated the finding that patients with schizophrenia show increased dopamine content and excessive  $D_2/D_3$  receptor density,<sup>4</sup> although there are decreased  $D_2/D_3$  receptor densities in extrastriatal regions such as the thalamus, amygdala, temporal cortex and anterior cingulate.<sup>5</sup> Striatal  $D_1$  receptor density appears unaffected. These studies have been reviewed in detail elsewhere.<sup>6</sup>

**Dopamine: cognition, genes, environment**

Cognitive impairment is a characteristic feature noted since the earliest descriptions of the disorder. Impairments in higher-order cognitive functions are associated with poor functional outcome. Since the discovery of dopamine almost 50 years ago, imaging

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studies have shown that such deficits are associated with the prefrontal cortex, an executive control site of the brain which has a central role in neurochemical systems such as those mediated by dopamine and serotonin. Although prefrontal cortical function is highly responsive to other neurotransmitters, it is particularly sensitive to modulation of D<sub>1</sub> receptors, which are associated with prefrontal cortical cognitive networks. Dopamine D<sub>2</sub> receptors have been linked with cognitive processes involving cognitive set-shifting ability, working memory (i.e. the ability to maintain information 'online' for a short span of time during the execution of a task) and planning ability.

Dopaminergic dysregulation has been associated with cognitive impairments subserved by neural systems such as the frontal cortex, striatum and other anatomical structures. Several PET studies have reported differences in dopamine content between patients and normal controls in the prefrontal cortex, anterior cingulate cortex and hippocampus. Some studies have noted greater [<sup>18</sup>F]fluorodopa uptake in the dorsal anterior cingulate in patients during performance on the Stroop task in comparison with normal controls.<sup>2</sup> These findings may highlight the important role of the anterior cingulate dopamine function in suppression of attention processes and response inhibition. A few PET studies have investigated the relationship between D<sub>1</sub> dysfunction and working memory performance in medication-naïve patients with schizophrenia. However, the findings have been inconsistent. One study reported a decrease in prefrontal cortical D<sub>1</sub> receptor binding,<sup>7</sup> whereas a second study showed an increase in D<sub>1</sub> receptor binding.<sup>8</sup> A third study reported no difference between patients and controls.<sup>9</sup> A plausible explanation for the variation in findings may be the use of different PET radioligands, which show a differential response of dopamine depletion on internalisation and binding to the ligand. As mentioned above, animal and human studies have shown an association between D<sub>2</sub> receptors and cognitive functioning. Decreased striatal D<sub>2</sub> receptor density is associated with attentional processing in schizophrenia, especially in tasks with a time-restriction element. Studies in schizophrenia have shown a relationship between increased D<sub>1</sub> receptor density binding and poor performance on working memory tasks related to the prefrontal cortex.<sup>9</sup> An explanation of these cognitive distortions might be the inability to modify behaviour effectively with the demands of a task, resulting in inflexibility and impulsivity in performance in schizophrenia.

It has been difficult to elucidate the genetic basis of schizophrenia owing to the likely complexities of its pathophysiology, involvement of environmental factors (e.g. social adversity, cannabis use, obstetric complications) which are difficult to measure, probable genetic heterogeneity, variable penetrance and expressivity. Evidence supports an aetiological role for mutations or polymorphisms in a number of genes, pointing to a multifactorial inheritance which posits that no one gene or environmental factor causes schizophrenia, but rather that predisposition is influenced by a combination of multiple genes, in contrast to a monogenic or Mendelian inheritance model. The most promising candidate genes currently include neuregulin-1 (*NRG1*), dysbindin (*DTNBPI*) and D-amino acid oxidase activator (*DAOA*, also known as *G72*). The association between schizophrenia and these genes appears to be modest, possibly because of the effect of a given gene being differentially associated with a specific neurobiological component of schizophrenia. This is supported by the functional roles of the identified genes that relate to dopaminergic, serotonergic,

glutamatergic and monoaminergic neurotransmission and neurodevelopment. Recent molecular genetic advances have focused on copy-number variation in schizophrenia, which are rare, penetrant, at the familial end of the disease spectrum, and are important sources of sequence variations between individuals.<sup>10</sup> Considerable effort in identifying these genes is ongoing. Therefore the precise nature and functional role of these genes for the dopaminergic pathway is less clear.

In summary, PET-CT can help to identify structural and functional abnormalities in schizophrenia. Future PET-CT studies in schizophrenia should investigate the role of genes, neurochemistry and cognitive processes in relation to brain anatomical structures. It would not be unreasonable to expect that this might help to identify genetic, biochemical, imaging and neurocognitive biomarkers for schizophrenia. In turn, it would be useful to study how such biomarkers are altered in relation to functional connectivity and brain networks, how they vary with factors such as age, and the effects upon them of putative treatments. This would help produce a strong scientific basis for the development of preventive measures and new therapies for this debilitating psychiatric disorder.

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