The Use of Positron Emission Tomography Imaging in Studying Cognition, Genetics, and Pharmacotherapeutic Interventions in Schizophrenia

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Summary

Positron emission tomography (PET) offers a strategic imaging platform to provide a map of functional neural correlates associated with underlying the cognitive deficits in schizophrenia. It enables regional cerebral glucose metabolism and dopaminergic and serotonergic receptor function to be studied. PET neuroimaging can therefore be used in drug development and to study putative treatments. Recent PET studies have been carried out of the first-generation antipsychotics flupentixol and haloperidol, and of the second-generation antipsychotics risperidone, aripiprazole, quetiapine, sertindole, ziprasidone, paliperidone, and olanzapine; modulation of limbic circuitry has been found to be a predictor of treatment response. PET can also be used to predict and monitor likely extrapyramidal side-effects from antipsychotic treatment. PET and neuropsychological testing can together also allow putative molecular genetic changes associated with schizophrenia to be studied. Advances in the imaging, cognition, and molecular genetics are likely to lead to the development of future diagnostics, treatments, and novel pharmacological agents.

Key words: antipsychotics; cognition; COMT; dopamine receptors; memory; PET; prefrontal cortex; schizophrenia; serotonin.

Positron Emission Tomography: Fundamental Aspects

In the 1970s Dr Ron Nutt and Dr David Townsend invented PET. Since then, a number of configurations incorporating new and faster detector technology have advanced the field, in combination with a variety of multi-slice computed tomography (CT) configuration in one device, hence the term PET/CT [1]. 1976 saw the advent of the use in humans of the most commonly used radiopharmaceutical, ^{18}F-2-fluoro-2-deoxyglucose ([^{18}F]FDG), which indexes glucose metabolism, which enables metabolism studies to be conducted. Once the tracer is injected, the subject is asked to lie in a quite room whilst the tracer redistributed itself in the areas of interest. The subject is then placed in a PET/CT scanner and imaged. The positrons emitted from the radiotracer interact with electrons in the patient's tissues to produce gamma rays which are detected by crystals in the PET scanner. These coincidence 'events' are then organized by a computer to form an image illustrating the radiotracer uptake of the various tissues in the body (see Figure 1). The scan protocol consists of a scout scan for positioning, followed by a low-dose CT scan for attenuation correction and density information, and finally a PET scan. The major clinical applications of PET are in lung cancer and lymphoma, but recently there has been a growing interest of PET in the field of neuroimaging where it vividly illustrates areas of activity differences between patients with disease and healthy controls, as well as allowing various neurotransmitter receptors to be imaged. The advent of new tracers and increased sensitivity of PET/CT have revealed different aspects of metabolism and function that were previously unknown (see Table 1). Functional changes may be detected sooner compared to anatomical changes, which take longer to manifest.

The uptake and binding characteristics of a particular PET radiotracer can be determined with the use of compartmental models. The tracer kinetic models separate the receptor binding effects from those related to tracer transport, and can be created for both reversible and irreversible radiotracers. The primary model for the utilization of glucose by the central nervous system using [^{18}F]FDG was developed in 1977 by Sokoloff et al. [2]. This model comprised three compartments which represented the reversible exchange of [^{18}F]FDG in tissue with blood, and irreversible characteristics showing formulation of phosphorylated [^{18}F]FDG in rat brain tissue. This animal model was then adapted for use in humans [3]. However, owing to modeling assumptions, limitations, and the need to estimated parameters from the entire tissue tracer uptake curve [4], Patlak graphical analysis has been preferred to evaluate glucose metabolism [5,6].

PET enables two rather different types of imaging study of the brain to be carried out. First, it can be used as a functional imaging tool to study regional cerebral blood flow (rCBF) and glucose metabolism. As mentioned above, this was the first use to which PET was put historically. Indeed, many would now argue that, since the advent of blood oxygen level-dependent echoplanar imaging functional magnetic resonance imaging (fMRI) in the 1990s, with its absence of ionizing radiation (paramagnetic deoxyhemoglobin is used as an endogenous contrast agent), it is becoming difficult to justify the use of PET as a functional imaging tool to study rCBF, although PET allows measurement of brain activity within a single condition and, unlike fMRI, it does not require a contrast with a baseline signal [7].

However, fMRI is certainly not able to replace the second application, in which PET can be used as a powerful neurochemical tool which enables the activity of

multiple neurotransmitter receptors to be imaged. Radioligands that are currently accessible include those for receptors that may be of importance in the pathophysiology of schizophrenia, including dopamine, serotonin, glutamate, $GABA_A$, and acetylcholine (nicotinic).

Here, both these different uses are considered in respect of schizophrenia, with particular reference to recently published studies. Additionally, PET and neuropsychological testing can together also allow putative molecular genetic changes associated with schizophrenia to be studied; these two applications are discussed in this paper.

Recent PET Imaging Findings in Schizophrenia

The use of PET/CT in schizophrenia has provided new avenues for neuroimaging research in schizophrenia. PET has been used to elucidate dopamine dysfunction [8] as well as the role of serotonin [9] in the brain and provide a better understanding of possible differential neuroanatomical activations during neurocognitive tasks in patients with schizophrenia compared with healthy controls.

The most common PET tracer is [^{18}F]FDG. This tracer can be used for the assessment of glucose metabolism in the brain. Patients with schizophrenia have been shown to have decreased uptake of [^{18}F]FDG in the frontal cortex, primary sensory regions and the anterior cingulate cortex, and possible functional imbalance in the fronto-striatal-thalamic circuitry including the cingulate cortex [10] and the cortico-cerebellar-thalamic cortical circuit [11]. Fujimoto et al. [10] also suggested gender-related dysfunction in the anterior cingulate and thalamus. The disadvantage of using a tracer like [^{18}F]FDG is that it is not specific; as several lines of evidence have

demonstrated dopamine dysfunction in the pre-frontal cortex (PFC), anterior cingulate gyrus and hippocampus of patients with schizophrenia [12,13] there is an increasing demand for novel tracers that map brain dopamine metabolism. One such tracer is 6-^{18}F-fluorodopa ([^{18}F]FDOPA), which can be used to examine presynaptic dopamine metabolism. Studies with [^{18}F]FDOPA have shown that the synthesis of dopamine in the left caudate nucleus, and dopaminergic transmission in the right temporal cortex, as well as the turnover of radiolabeled dopamine, are elevated in patients with schizophrenia [14,15]; this study also demonstrated a positive correlation between symptomatology and the level of dopamine. A study by Bose and colleagues [16] showed that the sensitivity and specificity of [^{18}F]FDOPA imaging for schizophrenia classification can be increased with the application of artificial neural networks.

PET studies using [^{11}C]raclopride have demonstrated elevated levels of dopamine D_2 receptor/dopamine D_3 receptor (D_2R/D_3R) densities primarily in the striatum [17]. Furthermore, all currently licensed antipsychotic drugs block the striatal D_2 receptors [12,18]. Therefore it would be appropriate to study schizophrenia using a highly selective and high-affinity PET ligands such as [^{11}C]raclopride or [^{18}F]fallypride, which preferentially bind to D_2R/D_3R. Whereas [^{18}F]fallypride measures both striatal and extrastriatal brain regions, [^{11}C]raclopride allows such exploration of striatal regions but not extrastriatal brain regions. Raclopride has a particularly high affinity to D_2R, and once injected, is rapidly cleared from the plasma and crosses the blood-brain barrier to settle in the basal ganglia and stereoselectively in the caudate and the putamen, regions with high dopamine receptor density, with very low binding in cortical areas or in the cerebellum [19]. It has also been used to evaluate the cortical receptor

occupancy of antipsychotic drugs, the efficacy of which are positively correlated with the degree of selective D_2R occupancy.

PET co-registered with MRI can provide a map of dopamine receptors in the brain [12]. Such studies on normal unmedicated controls, using [^{18}F]fallypride, show the highest receptor concentration in the putamen followed by (in descending order) the caudate, thalamus, amygdala, substriatal region, hippocampus = temporal cortex, and orbitofrontal cortex. Studies on unmedicated schizophrenia patients have shown reduced binding potential of [^{18}F]fallypride in the medial dorsal nucleus and thalamic pulvinar compared with healthy controls [20]. Patients also show reduced D_2Rs/D_3Rs in extrastriatal regions such as the amygdala, temporal lobe, and cingulate gyrus. Furthermore, there is a positive correlation between positive symptomatology and reduced D_2R binding in the thalamus [20].

MRI studies have shown that schizophrenia is often associated with progressive loss of grey matter. Buchsbaum and colleagues [21] used co-registered [^{18}F]FDG PET and matching T_1-weighted MRI scans in unmedicated patients to show that this vulnerable group have an increase in the relative metabolic uptake in white matter (WM), with WM damage, and decrease in the grey matter metabolism. This loss has been investigated using (R)-[^{11}C]-PK11195, a tracer that accumulates in areas where microglial activation occurs, which accompanies neural damage within the first 5 years of disease onset [22]. Several studies have shown WM impairment following administration of D_2R antagonists, suggesting an involvement of D_2Rs in working memory. Non-human mammalian studies suggest that dopaminergic neurotransmission plays an important role in the function of normal spatial working memory through a pathway located in the hippocampus [23].

PET in Drug Development and Treatments for Schizophrenia

A number of studies have used the percentage occupancy of D_2Rs elucidated by PET to determine the optimum antipsychotic dose for treatment of schizophrenia. The ability of PET to image in-vivo regional medication-receptor binding to investigate efficacy and drug side-effects has been demonstrated [24-30] As mentioned in the section on pharmacotherapy below, PET can help in the study of EPSEs caused by antipsychotic medication, and can be a good predictor of patient response to treatment following drug intervention.

There has recently been growing interest in using repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, for the treatment of schizophrenia for those patients who do not respond well to medication [31-33]. Horacek and colleagues [31] used [^{18}F]FDG PET to study the effect of rTMS on brain metabolism; rTMS led to a decreased rate of metabolism in the cortex. A recent study made use of the tracer [^{11}C]-FLB 457 PET, a tracer with a high affinity for dopamine D_2R, to show a reduced binding potential in the dorsolateral prefrontal cortex (DLPFC), indicative of dopamine modulation, following rTMS of DLPFC.

In respect of drug development, there has recently been interest in the role of serotonin (5-HT) in the pathophysiology of schizophrenia. First-episode antipsychotic-naïve schizophrenia patients have been found to have increased 5-HT_{2A}R binding in the caudate nucleus, with no difference in cortical receptor binding when compared to normal healthy controls [34]. This study used the PET tracer [^{18}F]altanserin, a 5-HT_{2A}R antagonist. For drugs with a higher affinity for 5-HT_{2A}Rs compared with D_2Rs, PET has been used to study the relationship between receptor occupancy, side-effects and the optimum dosage. One such drug is ziprasidone. A dual isotope study using

[^{11}C]raclopride for dopamine occupancy, and [^{18}F]setoperone for 5-HT$_{2A}$R occupancy, showed that ziprasidone has a similar occupancy profile to risperidone and olanzapine, with no evidence of extrastriatal dopamine receptor occupancy [35]. On the other hand, a study by Frankle and colleagues [37] using [^{11}C]WAY 100635 showed no difference in 5-HT$_{2A}$R binding between schizophrenia patients and healthy controls, questioning the role of serotonin in schizophrenia, while a recent study reported a decrease in serotonin receptors in schizophrenia [35].

PET Studies in Other Neurotransmitter Systems in Schizophrenia

Glutamatergic models of schizophrenia, originally based on the effects of phencyclidine (PCP) and ketamine, which were shown to induce their unique psychotomimetic effects by blocking neurotransmission at NMDA-type glutamate receptors, have been strongly supported by NMDA antagonists studies in non-human mammals, as well as ketamine challenge studies in humans [38]. While [^{18}F]FDG PET has been used to study metabolic hyperfrontality and psychopathology in the ketamine model of psychosis, with increased metabolic activity in the frontomedial and anterior cingulate cortex being found to correlate positively with psychotic symptom formation (in particular with ego pathology) [39], there have not yet been any published studies of the use of PET directly to assess glutamate function in the brain in schizophrenia. Fortunately, suitable radioligands are now becoming available [40,41], so that such studies should become feasible. Similarly, no direct PET studies of GABA$_A$ receptors or of nicotinic acetylcholine receptors in schizophrenia have yet been published, but, given the potential importance of these in the pathophysiology of this illness and the development

of novel corresponding radioligands, it is to be hoped that such human studies will be forthcoming [42,43]

Cognitive Functioning in Schizophrenia: Recent Advances using PET

Cognitive deficits are a prominent feature of the disorder with impairments consistently identified in a wide array of ability domains, including verbal learning and memory, general intellectual ability (intelligence quotient), verbal/visual learning and memory, speed of processing, reasoning and problem solving, attention, executive function, motor function, and language [44-46]. The Vulnerability Indicators in Psychosis study (VIPS) showed that visual information processing is significantly compromised in patients with schizophrenia in comparison with healthy volunteers [47]. Similar to adult-onset patients, early-onset schizophrenia cases show a selective deficit in sustained attentional processes [48]. The most intriguing finding which has led to an upsurge of interest into the treatment and management of neurocognitive deficits in schizophrenia is the associated functional disability observed which profoundly affects psychosocial and occupational functioning [49,50]. Neuropsychological performance may be a better predictor of functional integrity than symptom presentation and may be a valuable target for interventions [51]. The neurochemical determinants of cognitive deficits in schizophrenia have been partially explained by the dopamine hypothesis, postulating that positive symptoms result from heightened subcortical dopamine release subsequently enhancing stimulation of D_2Rs, while cognitive deficits and negative symptomatology result from reduced D_1R stimulation [52,53]. PET offers a strategic imaging platform to provide a map of neural correlates associated with underlying cognitive deficits in schizophrenia. Here, we evaluate recently published studies

investigating cognitive function in schizophrenia using PET (for a detailed review of keynote studies, see Table 2).

PFC dysfunction plays a central role in working memory deficits in schizophrenia [54]. Information in working memory is maintained for a short span of time based on task-relevant information requiring “online” access [55]. Schizophrenia patients show impairments on tasks demanding higher-order cognitive processes including sequential thinking, task switching, cognitive set shifting, and abstraction.

[^{18}F]FDG PET has been used to study metabolism in brain regions selectively activated during performance on neuropsychological tasks. An increase in [^{18}F]FDG in the thalamus has been observed in healthy controls during performance on a spatial attention task [56]. In schizophrenia, diminished regional glucose metabolism was reported in the medial dorsal nucleus (i.e. the largest nucleus in the thalamus which has major connections with the PFC), the posterior thalamus, and the PFC, compared with normal subjects [57]. There is a high positive correlation between task and thalamic dopamine release, implicating the involvement of extrastriatal dopamine in normal cognition and neuropsychiatric disorders [56,57]. One study investigated the anatomical location of auditory verbal hallucinations in patients with first-episode schizophrenia [58]. Parellada and colleagues [58] studied nine neuroleptic-naïve first-episode schizophrenia patients using [^{18}F]FDG PET, while they experienced frequent auditory verbal hallucinations. During the PET scan, bilateral linguistic auditory activation was mimicked (single words, continuous speech, emotional component) based on the patients’ own hallucinations. The authors reported a significant activation of the motor area, anterior cingulum, medial superior frontal area, and cerebellum during the auditory verbal hallucinations. Interestingly, activation was also shown in the left superior frontal

area, right superior temporal pole and right orbitofrontal region. Furthermore, during bilateral linguistic auditory activation (induced by mimicking of hallucinatory content), heightened FDG uptake was found in the right and left superior and middle temporal cortices, left hippocampus, and left parahipppocampal regions. The authors suggested that cortical regions may be implicated in the production of inner speech in acute schizophrenia patients.

Recently, a positive correlation between performance on frontal lobe tasks, such as verbal fluency and executive function, and hippocampal D_2R binding has been reported using the short half-life tracer, [^{11}C]FLB457 PET [59]. D_2R in the hippocampus may also affect PFC functions [23]. There is a paucity of PET studies showing the correlation between hippocampal D_2R binding and performance on tasks that explicitly assess working memory. A motor response study revealed increased primary visual cortical stimulation in patients with schizophrenia during a motor learning task, while healthy controls expressed increased blood flow in the primary motor cortex and supplementary motor area during the same task [60]. Ko and colleagues [61] demonstrated the role working memory played by prefrontal dopamine during an executive task using [^{11}C]FLB457. A reduction in tracer uptake was observed in the right dorsal anterior cingulate cortex, indicative of increased dopamine neurotransmission in the ACC during executive tasks. An interesting study by Fernandez et al. [62] showed that patients with schizophrenia exhibit a non-task specific amygdalar metabolic hyperactivation compared to matched controls during a facial emotion recognition task.

Sabri and colleagues [63] simultaneously used [^{15}O]H_2O PET and functional transcranial Doppler (fTCD) sonography to investigate working memory deficits in

clinically stable chronic schizophrenia patients and healthy controls using the N-back sequential number task. The schizophrenia patients activated larger cortical volumes but with lower blood flow increases in these volumes than did the healthy controls; they did not increase blood flow velocity during cognitive activation. The authors reported no significant correlations between neuropsychological performance scores and PET blood flow or fTCD changes. In harmony with previous neuropsychological findings [64], the authors concluded that patients with schizophrenia show less efficient problem-solving and search strategies which lead to working memory deficits which are observed over the course of the disorder.

To investigate executive-control related neural activity in schizophrenia, Brewer and co-workers [65] examined a group of neuroleptic-naïve first-episode schizophrenia patients and age-, premorbid IQ-, and gender-matched healthy controls while performing the Stroop color-word interference task [66] (a tool utilized for engagement and evaluation of executive functions, directed attention, and inhibition) which engages frontal function, during a $[^{15}O]H_2O$ PET scan. The first-episode patients were randomly treated with either haloperidol or risperidone and then re-scanned after an 8-week follow-up period. There was a differential activation of brain regions for task performance at follow-up with enhanced activation of posterior brain regions in normal subjects, and heightened activation in frontal regions in schizophrenia. The authors concluded that although the findings may suggest that PFC abnormalities, commonly found in schizophrenia, may be associated with the expression of acute symptomatology, the causal pathways for increased frontal activity remain unknown, since it could be caused by the effects of medication, a lack of neurophysiological learning with test/re-test, a combination of the two, or other plausible factors. These

findings may suggest that individuals with schizophrenia do not effectively engage in "tuning" neurophysiological effort in relation to task difficulty compared to normal subjects.

Schizophrenia is associated with abnormalities in emotional processing and social cognition. Using [^{15}O]H_2O PET, Kim and colleagues [67] investigated similarities and differences in decision making involved in emotionally conflicting stimuli, as measured using the word-stem completion task, between schizophrenia patients, depression patients, and healthy subjects. The task involved forced and non-forced choice conditions and consisted of a study phase and a test phase. Healthy subjects showed increased activation in the PFC and cerebellum, the schizophrenia group showed negligible activity within these two regions, while the depression group showed an altered pattern with evidence of a functional compensatory recruitment of inferior parietal regions. The authors suggested that 'the prefrontal cortex seems to be associated with the cognitive control to resolve the conflict toward the ambivalent stimuli, whereas the cerebellum reflects the sustained working memory to search for compromise alternatives'. Individuals with schizophrenia showed deficits of cerebellar activation. The authors explained that this may result from the inability to search and consider compromising responses for conflict resolution. This study supports Maher [68] who suggested that delusions experienced in schizophrenia may be an attempt to resolve the imbued conflicting and confused state of mind.

Other studies have attempted to provide a deeper understanding of the role of the amygdala on emotional processing in schizophrenia. Fernandez-Egea et al. [69] used [^{18}F]FDG PET to study amygdalar response during performance on the facial emotional recognition task in a group of patients with schizophrenia and healthy controls. The

emotional task involved happy and sad faces (equal number of men and women) in which the participant responded “sadness” or “happiness”, while the control task was a gender-discrimination task which involved pictures of men and women with neutral expressions where they were asked to respond ‘man’ or ‘woman’. Compared to healthy subjects, patients with schizophrenia showed task-independent hyperactivation of the left amygdala. Patients also exhibited similar hyperactivation in the amygdala for both emotional and non-emotional facial recognition tasks. Although these findings are interesting, the authors acknowledged that the emotional task only accounted for sad and happy faces which may be a restrictive component, as opposed to a task measuring a range of expressed emotions, such as the Ekman’s face recognition task.

Higher doses of antipsychotic medications could lead to poor neurocognitive performance in adults with schizophrenia. Uchida and colleagues [30] investigated the impact of antipsychotic medication on cognitive functioning in patients with late-life schizophrenia undergoing a [^{11}C]raclopride PET scan. The Dementia Rating Scale-2 (DRS-2) consisted of five scores: attention, initiation/perseveration, construction, conceptualization, and memory. The DRS-2 attention scores negatively correlated with D_2R blockage but were found to be positively associated with non-displaceable binding potential. The backward digit span, a measure of working memory, negatively correlated with D_2R blockage. No correlation was reported for the other subscales within the DRS. These findings are consistent with previous studies showing working memory impairment following administration of D_2R antagonists, and suggests an involvement of the dopaminergic system (particularly D_2Rs) in working memory [70]. Non-human mammalian studies suggest that dopaminergic neurotransmission plays an important role in the function of normal spatial working memory through a pathway

located in the hippocampus [23]. Interestingly, a recent study reported a positive correlation between performance on frontal lobe tasks, such as verbal fluency and executive function, and hippocampal D_2R binding using [^{11}C]FLB457 PET [59].

Neurocognition is considered an endophenotype for schizophrenia [71-73]. As discussed above, recent PET cognitive studies in schizophrenia have focused on working memory, attention, and emotional processing. The studies reviewed here suggest that patients with schizophrenia have selective deficits in performing tasks demanding high levels of attentional capacity, decision making, and problem solving. They demonstrate emotional dysfunction, poor attention, and inhibition. PET studies investigating emotional processing in schizophrenia have reported either insignificant activation in the PFC and cerebellum or left amygdala hyperactivation for emotional and non-emotional components of a task; however, some of the tasks used to study emotional processing have been limited by the variation of emotional content and the relatively small number of subjects studied.

Some neurocognitive traits of schizophrenia, such as working memory deficits, are moderately heritable (43−49%), which points to the need to investigate the critically important role of genetic factors in understanding cognitive functioning in schizophrenia [74].

Genetic Underpinnings for Schizophrenia: The Role of PET Neuroimaging

Schizophrenia is a highly genetic disorder with a heritability of approximately 80%. As mentioned above, the dopaminergic system plays a vital role in the pathophysiological mechanisms of schizophrenia. Some genes that are currently of high interest in schizophrenia include *NRG1* (neuregulin 1), *DTNBP1* (dysbindin), *DRD* (dopamine

receptors 1−4), *DISC1* (disrupted in schizophrenia 1) and *COMT* (catechol-O-methyltransferase). COMT is an enzyme which plays an important role in cortical dopamine metabolism. The most common single nucleotide polymorphism (SNP) studied in the *COMT* gene is rs4680, Val168Met polymorphism. This polymorphism causes a common substitution from a valine (Val) to a methionine (Met) at amino acid position 158, leading to a 3-to-4 fold reduced activity of the COMT enzyme. Individuals with the Val allele show heightened COMT activity and lower dopaminergic signaling in the PFC in comparison to Met carriers. A few studies have investigated the impact of specific genes using PET imaging in schizophrenia. Abi-Dargham's group investigated the impact of the *COMT* genotype on D_1R availability using [^{11}C]NNC 112, which has a high affinity for D_1R [75]. This work stemmed from the same group's previous study showing heightened D_1R availability, using [^{11}C]NNC 112, in the DLPFC in schizophrenia [52]. They also reported an association of increased [^{11}C]NNC 112-binding and worse performance on a working memory task. In a group of healthy subjects, Slifstein and colleagues found that Val homozygotes produced greater cortical [^{11}C]NNC 112-binding compared with Met homozygotes and heterozygotes, but showed no differences in striatal dopamine. They concluded that COMT plays a role in regulating dopaminergic transmission in the cortex but not the striatum, and the [^{11}C]NNC 112 may be an important and reliable marker for low dopamine tone, as documented in previous schizophrenia studies [72]. More recently, Bertolino et al. [76] used single-photon emission computerized tomography (SPECT) with [^{123}I]IBZM and [^{123}I]FP-CIT to the study the effect of a functional intronic SNP (rs1076560) of the *DRD2* gene on working memory, as measured using the N-back task, in healthy subjects. They reported that the 'functional SNP within *DRD2* predicts striatal binding

of the two radiotracers to dopamine transporters and D_2 receptors as well as the correlation between striatal D_2 signaling with prefrontal cortex activity during performance on the working memory task'.

An earlier study [77] using [^{15}O]H_2O PET investigated the role of the COMT Val^{158}Met polymorphism on several executive function and working memory measures in schizophrenia patients compared with healthy controls. Executive function and working memory were measured using the Wisconsin Card Sort Test, digit span forward, Trail making test and N-back task. There was no effect of genotype or a genotype x diagnosis interaction; however, Val158 homozygotes showed higher frontal lobe activation than Met158 homozygotes and heterozygotes during the one-back task. The authors concluded that there was a modest role of *COMT* in increasing susceptibility for schizophrenia, although 'age-related changes and phenotypic heterogeneity of schizophrenia may influence the complex relationship between *COMT* genotype and cognition'.

Current hypothesis suggest dopaminergic imbalance in schizophrenia. Overstimulation of subcortical *DRD2* dopamine receptors and reduced activation of the frontal cortical *DRD1* dopamine receptors is well documented in schizophrenia [78]. Several genes involved in dopamine metabolism storage, release and uptake (e.g. COMT) have been associated with schizophrenia. However the association of specific genes for increasing susceptibility of schizophrenia appears modest, possibly due to the non-Mendelian inheritance of this disorder.

High-Risk Population

It is well known that schizophrenia aggregates in families [79]. Studies of twins provide

an opportunity to understand the relative importance of the combination of genetic and environmental influences in disease etiology. In a Finnish population-based twin cohort study, Hirvonen and colleagues [80] used [^{11}C]raclopride PET to study performance on neuropsychological tasks sensitive to frontal lobe function in six monozygotic (MZ) and five dizygotic (DZ) unaffected co-twins of individuals with schizophrenia, in addition to four MZ and three DZ healthy controls twins with no family history of psychosis. The unaffected MZ co-twins showed elevated caudate D_2R density compared to the unaffected DZ co-twins and healthy controls. Individuals who performed less well on the cognitive tasks showed heightened caudate D_2R binding, based on the degree of schizophrenia vulnerability in the entire sample. More recent investigations into the impact of dopaminergic dysregulation on cognition in individuals with high genetic risk of schizophrenia have been conducted. Lee and colleagues studied 11 unaffected relatives (with two or more first- or second-degree relatives with schizophrenia or an MZ schizophrenic twin) and 11 healthy controls using [^{11}C]raclopride PET while they underwent several neuropsychological tasks [81]. High-risk subjects did not show rightward asymmetry of D_2 binding potential in the putamen, as reported in healthy controls. In addition, relatives of patients with schizophrenia showed worse performance on measures of executive function and visuo-spatial memory function. A similar neuroimaging study was conducted on siblings of patients with schizophrenia in response to acute metabolic stress [82]. This study found that siblings had a significant left > right asymmetry in stress-induced dopamine release which was more pronounced in the ventral striatum, suggesting that asymmetrical uptake is associated with genetic risk which may be a consequence of the dysconnectivity present in this group of vulnerable patients [21].

A study using [^{18}F]FDOPA was conducted on first-degree relatives of patients with schizophrenia, and found that they also expressed changes in synthesis of striatal presynaptic dopamine previously reported in schizophrenia [83].

In summary, dopamine imbalances in specific brain regions are related to vulnerability to schizophrenia. This may provide a fundamental rationale for early interventions and the development of dopamine D_2R blocking drugs.

Pharmacotherapy

Antipsychotic medication is the mainstay of pharmacotherapy in schizophrenia. In this section we shall begin with a consideration of recent PET studies of the effects on the brain, including receptor occupancy, of the older typical, or first-generation, antipsychotic drugs, and then consider recent PET studies of the newer atypical, or second-generation, antipsychotic drugs. Other findings gleaned from recent PET studies will then be described.

First-generation antipsychotic medication

The butyrophenone haloperidol is a commonly used first-generation antipsychotic, while flupentixol, a thioxanthine, is a first-generation antipsychotic drug which is commonly administered in depot form (as well as orally). Given that the neurotransmitters dopamine and serotonin may play an important part in the pathophysiology of schizophrenia, Reimold and colleagues have compared the occupancy of cerebral D_1R, D_2R, and 5-HT_{2A}R of these two medications (and also with a second-generation antispsychotic drug), having chosen receptor subtypes that are particularly implicated in this illness [84]. Eleven patients solely treated with flupentixol

were entered into the study: three were assessed for striatal D_1R and D_2R occupancy using [^{11}C]SCH 23390 and [^{11}C]raclopride, respectively; another three for striatal D_1R and frontal 5-HT_{2A}R occupancy, the latter using 3-N-[^{11}C]methylspiperone; four patients for striatal D_2R and frontal 5-HT_{2A}R occupancy, although two of these were found to have a positive urine drug test; and one for just striatal D_1R occupancy (this patient did not go on to have a second PET scan). Eleven patients solely treated with haloperidol were also entered into the study, and 26 age-matched antipsychotic-medication-free healthy controls each underwent one PET scan with one of the above three radiotracers. This study showed moderate 5-HT_{2A}R and D_1R occupancy under clinically relevant doses of flupentixol, with mean receptor occupancy of approximately 20% for each receptor type, which was clearly below saturation. The authors concluded that if the efficacy of flupentixol on negative symptoms of schizophrenia is based on its interaction with 5-HT_{2A} and/or D_1 receptors, it should be highly dependent on serum concentration and thus on dosage and metabolism, but their data also suggested that mechanisms other than D_1 or 5-HT_{2A} antagonism may contribute to its efficacy on negative symptoms [84]. For haloperidol, D_2R occupancy was closely related to serum concentration; there was 14% D_1R occupancy and negligible 5-HT_{2A}R occupancy.

Buchsbaum's group carried out a six-week double-blind crossover trial of haloperidol and sertindole (a second-generation antipsychotic) in 15 patients with schizophrenia, followed by [^{18}F]FDG PET (and anatomical MRI) [27]. Haloperidol was associated with a rise in metabolic rates in the medial and orbital PFC. (Sertindole results are given below.)

Second-generation antipsychotic medication

At the time of writing, risperidone is one of the most commonly used second-generation (atypical) antipsychotic drugs; indeed it is the first such drug to be made available in a long-acting depot formulation in addition to its oral formulation. This benzisoxazole derivative is known to have high affinity for D_2R, alpha-1 and alpha-2 adrenergic receptors and histamine H_1 receptors [85]. Ito and colleagues have studied the effects of risperidone on dopamine synthesis in a dozen healthy male volunteers using L-[β-^{11}C]DOPA; the latter allows the regional activity of the dopamine biosynthetic enzyme aromatic L-amino acid decarboxylase, and hence dopamine synthesis capacity, to be indexed [86]. This scanning was carried out just after PET imaging with [^{11}C]raclopride, and these sequential PET studies were carried out both under a resting condition (baseline) and following oral administration of risperidone (drug challenge) on separate days. Occupancy of D_2Rs corresponding to the dose of risperidone was observed, no significant changes in dopamine synthesis capacity by the administration of risperidone were reported, nor was the relation between the occupancy of D_2Rs and these changes significant. On the other hand, a significant negative correlation was reported between baseline dopamine synthesis capacity and changes in dopamine synthesis capacity associated with risperidone, indicating that this drug probably stabilizes dopamine synthesis capacity. The authors concluded that the therapeutic effects of risperidone in schizophrenia might be related to such stabilizing effects on dopaminergic neurotransmission responsivity [87]. As mentioned above, Uchida and colleagues have used [^{11}C]raclopride PET to study the effects of risperidone on older patients with schizophrenia (those aged at least 50 years) and have reported that the age-corrected score on the attention subscale of the DRS-2 neuropsychological test was

negatively correlated with D_2R blockade. A secondary finding was that the attentional deficits were observed above 74% blockade (corresponding to a risperidone dosage higher than 3 mg/day) in this patient group. Unfortunately, this was a small cross-sectional study, of 11 subjects, in which the use of concomitant medication was not controlled. Nevertheless, the authors concluded that these results suggest the critical importance of a systematic determination of the lowest effective dose of antipsychotic drugs in order to minimize their negative impact on cognition in late-life schizophrenia [30]. They have also separately reported that extrapyramidal side-effects were observed in seven subjects at D_2R occupancy rates of between 34% and 79%, lower than previously reported for younger patients in whom such side-effects are rare at occupancies lower than 80% [29].

Mamo and colleagues conducted PET studies with [^{11}C]raclopride, [^{18}F]setoperone and [^{11}C]WAY 100635 in 12 patients with schizophrenia who were randomly assigned to receive four different doses of aripiprazole, in order to characterize the simultaneous effects of this second-generation antipsychotic on D_2R, 5-HT_2R and 5-$HT_{1A}R$ [88]. They reported very high occupancy at striatal D_2Rs (average putamen, 87%; caudate, 93%; and ventral striatum, 91%), lower occupancy at 5-HT_2Rs (54%–60%), and even lower occupancy at 5-$HT_{1A}Rs$ (16%). D_2R occupancy levels were significantly correlated with plasma drug concentrations, with even the lowest dose of aripiprazole administered (10 mg) leading to 85% D_2R occupancy. Moreover, extrapyramidal side-effects were observed in only two of the four subjects who had occupancies exceeding 90%. This triple tracer PET study therefore confirmed the unique occupancy profile of this second-generation antipsychotic and also its low propensity to cause extrapyramidal side-effects [88]. Kegeles and colleagues [89] used

[^{18}F]fallypride PET to study 19 patients with schizophrenia or schizoaffective disorder. Occupancy levels were higher in extrastriatal than striatal regions; pituitary measures of aripiprazole effect correlated with doses and were unrelated to prolactin levels, which remained within the normal range under medication (thereby indicating a low propensity to cause side-effects related to hyperprolactinaemia). Positive schizophrenia symptom improvement with aripiprazole correlated with striatal but not extrastriatal D_2R occupancies. The correlations of ratings of clinical improvement with regional occupancy suggest that aripiprazole benefits positive symptoms of schizophrenia most directly through its modulation of striatal rather than cortical or other extrastriatal dopamine activity [89]. Gründer and colleagues [90] also carried out a [^{18}F]fallypride PET study in 16 patients with schizophrenia or schizoaffective disorder receiving aripiprazole and in eight age-matched medication-free schizophrenia patients; they were thereby able to ascertain receptor occupancy as a percentage reduction in binding potential relative to unblocked values derived from the medication-free patients [90]. They reported that mean dopamine D_2R/D_3R occupancy was high in all brain regions investigated, with no binding difference across brain regions, while nonlinear regression analysis showed maximum attainable receptor occupancy values close to saturation. The dissociation from these receptors was slow; the authors calculated that in patients with serum concentrations in the clinical range, D_2Rs/D_3Rs remain nearly saturated for as long as one week following the last dose of aripiprazole.

The dibenzodiazepine derivative quetiapine has been studied by Nikisch and colleagues in five drug-naïve patients suffering from schizophrenic disorder using [^{18}F]fallypride PET [91]. Quetiapine produced preferential occupancy of parietal cortex vs. putamenal D_2R (41%). D_2R occupancies in the occipital and parietal cortices were

positively correlated with cerebrospinal fluid (CSF) levels of quetiapine and norquetiapine (a quetiapine metabolite with high affinity for 5-HT_{2A}R, which may contribute to the antipsychotic action of quetiapine). CSF monoamine metabolites were significantly increased after treatment and correlated with regional receptor occupancies in the putamen, caudate nucleus, thalamus and temporal cortex, suggesting that they reflect the effects of quetiapine treatment on neurotransmitters in vivo and indicating that monitoring plasma and CSF quetiapine and norquetiapine levels may be of clinical relevance [91].

The dibenzepine clozapine is the archetypal atypical antipsychotic. The finding that its antipsychotic actions were accompanied by only minimal extrapyramidal side-effects helped spur the development of other second-generation antipsychotics. Even now, on balance, it could be argued that clozapine might be the most efficacious second-generation antipsychotic currently available. Thus, in spite of its propensity to cause agranulocytosis in a small minority of patients, there is still an important place for the use of this antipsychotic drug in the pharmacotherapy of schizophrenia, including treatment-resistant cases, so long as regular blood monitoring is carried out. PET neuroimaging has shown that, while all currently prescribed antipsychotics bind to D_2Rs, clozapine actually has the least such binding [92]; this may well be related to its low level of extrapyramidal side-effects and may suggest that D_2R binding is not the most important factor in antipsychotic action of clozapine. Indeed, D_2R binding may be the most important factor for eliciting extrapyramidal side-effects in the context of PET neuropsychopharmacological studies. Nordström and colleagues studied 17 patients with schizophrenia treated with clozapine using PET and one to three radioligands: [^{11}C] SCH23390, [^{11}C]raclopride, and [^{11}C]N-methylspiperone [92]. Patients treated

with clozapine expressed a unique combination of high D_1, low D_2, and very low 5-HT_{2A} receptor occupancy. The authors showed that clozapine serum concentrations do not predict clinical effects, and therefore suggested that 'clinical titration cannot be replaced by monitoring of drug concentrations for optimisation of clozapine treatment in individual patients' [93].

Sertindole is a second-generation antipsychotic which was suspended for use in the UK owing to concerns about arrhythmias; at the time of writing it has been re-introduced in the UK but its use is restricted to those patients who are enrolled in clinical studies and who are not able to tolerate at least one other antipsychotic drug. The [^{18}F]FDG PET study of Buchsbaum's group of haloperidol and sertindole, mentioned above, reported a greater relative metabolic rate in the dorsolateral and anterior prefrontal regions in schizophrenia patients receiving sertindole [27].

An [^{18}F]fallypride PET study in 15 patients with schizophrenia or schizoaffective disorder receiving treatment with the second-generation antipsychotic ziprasidone, combined with a parallel [^{11}C]raclopride PET study in eight healthy subjects receiving single antipsychotic oral doses, showed that ziprasidone plasma concentrations correlated with D_2R/D_3R occupancy in all regions of interest [94]. Occupancy in extrastriatal regions was around 10% higher than in striatal regions, while single ziprasidone doses resulted in higher occupancies exceeding the 95% prediction limits of the occupancy versus plasma concentrations for chronic dosing.

An [^{11}C]raclopride PET study of 13 schizophrenia patients taking part in a six-week multiple-dosing study of the second-generation antipsychotic paliperidone ER (the extended-release formulation) showed that a dosage of paliperidone ER of 6 to 9

mg/day leads to a D_2R occupancy of 70 to 80%, with the magnitude of the occupancy being similar between the striatum and temporal cortex [95].

Other studies

By measuring the time course of regional cerebral blood flow patterns generated by haloperidol and the second-generation antipsychotic olanzapine in patients with schizophrenia during a six-week treatment trial, Lahti and colleagues have used [^{15}O]H_2O PET to show that modulation of limbic circuitry predicts treatment response to antipsychotic medication [96]. This innovative study will doubtless spawn similar future studies.

Mizrahi and colleagues have used PET to show that higher D_2R occupancy is associated with negative subjective experience in patients taking risperidone or olanzapine [97]. Since this may be related to poor compliance clinically, further investigation of this finding will be of importance for clinical practice.

Uchida and colleagues studied four patients with schizophrenia who underwent [^{11}C]raclopride PET on two occasions five to 14 months apart, while receiving treatment with a stable dose of risperidone [28]. They reported that plasma risperidone levels were consistent between scans and that the consistencies of non-displaceable D_2 binding potential and D_2R occupancy was good, thereby pointing to the long-term stability of measuring D_2Rs in schizophrenia patients treated with antipsychotic medication [28].

Finally, a patient data meta-analysis of SPECT and PET in vivo receptor imaging studies by Stone and colleagues concluded that cortical D_2R/D_3R occupancy is indeed involved in antipsychotic efficacy, with striatal D_2R/D_3R occupancy having a

likely therapeutic role in addition to being related to extrapyramidal side-effects; no evidence was found for 5-HT_{2A}R blockade involvement in antipsychotic action [98].

Expert commentary

In light of the above findings, it is clear that PET has a strategic role to play in new clinical strategies and the development and assessment of new pharmaceutical products for schizophrenia. With appropriate ligands, and in combination with structural MRI scans (for anatomical co-registration), PET allows the stability of key dopaminergic and serotonergic receptors to be quantified and the likely clinical efficacy of putative pharmacotherapeutic agents to be predicted. The role of D_2R antagonism in antipsychotic action is controversial; as mentioned above, one of the most, if not the most, efficacious antipsychotics currently available for prescription, namely clozapine, has the least binding of any of these drugs to D_2Rs. However, it seems probable that D_2R binding is related to the level of extrapyramidal side-effects. For the time being at least, therefore, it is likely that studies of D_2R binding agents will continue in the search for new drugs for use in schizophrenia. To this end, it is noteworthy that novel interactions at D_2Rs are being discovered which will necessitate the formulation of a new and better understanding of ligand interactions at these receptors [99].

Certain unwanted actions, in particular EPSEs, can also be both predicted and quantitatively and objectively assessed directly from the brain. We have demonstrated how PET offers a powerful way of assessing the brain changes that take place during performance on neuropsychological tasks. The critically important role of genetics, particularly the *COMT* Val158Met polymorphism and the functional SNP (rs1076560) of the *DRD2* gene provide a better understanding of the PFC as an important cortical

substrate of working memory processes. The recent SchizophreniaGene (SzGene) database publication showed that four of the top 10 gene variants most strongly associated with schizophrenia are directly involved in dopaminergic pathways. Recent advances in high-density genome-wide microarrays have enabled the identification of copy number variation (CNVs) in schizophrenia [48], which may provide a better explanation into the role of other dysfunctional neurotransmitter systems (e.g. glutamate, GABA, and serotonin) involved in the pathophysiology of schizophrenia. The genetic etiology of schizophrenia is very complex owing to difficulty in determining the relationship between genotype and phenotype, probable genetic heterogeneity with variable penetrance and expressivity of candidate genes.

Five-year view

The use of PET neuroimaging in schizophrenia research, particularly in relation to neuropsychological changes, molecular genetic polymorphisms, drug side-effects, treatment response, and the development of novel pharmacotherapeutic agents, is likely to increase during the next five years. This will be aided by the continued novel PET tracer development. The pathophysiology of schizophrenia is obscure owing to no laboratory tests or biological markers associated with core etiopathology traits. The identification of neuroimaging (including high-resolution MRI brain scanning), biochemical, neurocognitive, and also genetic biomarkers in relation to abnormal neuronal connectivity and brain networks will advance diagnosis and treatment evaluations in the field. D_2Rs are crucial targets of antipsychotic drugs for the treatment and management of schizophrenia**.** There is likely to be a greater emphasis on neurotransmitter systems additional to the dopaminergic and serotonergic ones in

studies conducted during the next five years. It is likely that amino acid neurotransmitters, which have a strong presence in the human brain, will the focus of some of these exciting studies. There is evidence pointing to the putative role of the excitatory neurotransmitter glutamate in schizophrenia and therefore the recent development of glutamatergic radiotracers for PET, such as [18F]FPECMO [100], may be valuable not only to probe the integrity of this system but to investigate its interactions with the dopaminergic system. Advances in the aforementioned disciplines are likely to lead to the development of future diagnostics, treatments, and new pharmacological agents.

Key issues

- PET is an effective functional imaging technique that utilizes radioactive tracers to help identify regions associated with brain functioning and cognitive functioning.
- PET can be used to measure both cerebral blood flow (using [^{15}O]H_2O) and glucose metabolism (using [^{18}F]FDG) during performance on neuropsychological tasks which activate the PFC and adjacent regions in the brain.
- Schizophrenia is associated with dopaminergic imbalances in the brain. Brain imaging studies using PET provide a detailed functional-anatomical map of brain function.
- Several studies demonstrate that patients with schizophrenia show decreased uptake of [^{18}F]FDG in the frontal cortex, anterior cingulate cortex, and fronto-striatal-thalamic circuitry.

- Neurocognitive deficits are observed before presentation of the clinical symptomatology in schizophrenia. PET provides an effective means of underpinning these cognitive deficits by studying functional abnormalities in relation to neurochemical imbalances in the brain, identified by changes in networks of specific brain regions, of individuals with schizophrenia.
- Working memory (maintaining a limited amount of information 'online' for a brief period of time for conscious recollection) deficits are a prominent feature of schizophrenia, found to be associated with prefrontal cortical dysfunction. PET studies have shown amygdalar metabolic hyperactivation during working memory task performance in schizophrenia in comparison to healthy controls.
- Individuals with schizophrenia show impairments in directed attention, inhibition and working memory-related cognitive tasks. PET studies indicate that patients do not effectively engage in "tuning" neurophysiological effort in relation to task difficulty compared with healthy subjects.
- The amgydala plays an important role in emotional processing. [^{18}F]FDG PET studies report hyperactivation in the amygdala for both emotional and non-emotional neurocognitive paradigms, consistent with the hypothesis that schizophrenia is associated with emotional dysfunction and impairments in social cognition.
- Schizophrenia has a strong genetic component. Several genes for schizophrenia have been identified including *NRG1*, *DTNBP1*, *DRD1-4*, *DISC1* and *COMT*. PET studies have shown that individuals with *COMT* Val158 homozygozity produce greater cortical binding compared to Met carriers. PET studies show that the functional intronic SNP (rs107660) of the *DRD2* predicts striatal binding

and there appears to be a correlation between striatal D2 signaling with PFC activity during performance on working memory paradigms.

- PET elucidates the differential actions of first- and second-generation antipsychotics on different dopaminergic, serotonergic and glutamatergic receptors in the brain.
- Advances in the aforementioned disciplines are likely to lead to the development of future diagnostics, treatments, and new pharmacological agents.

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Figure 1. Coincidence Detection in Positron Emission Tomography

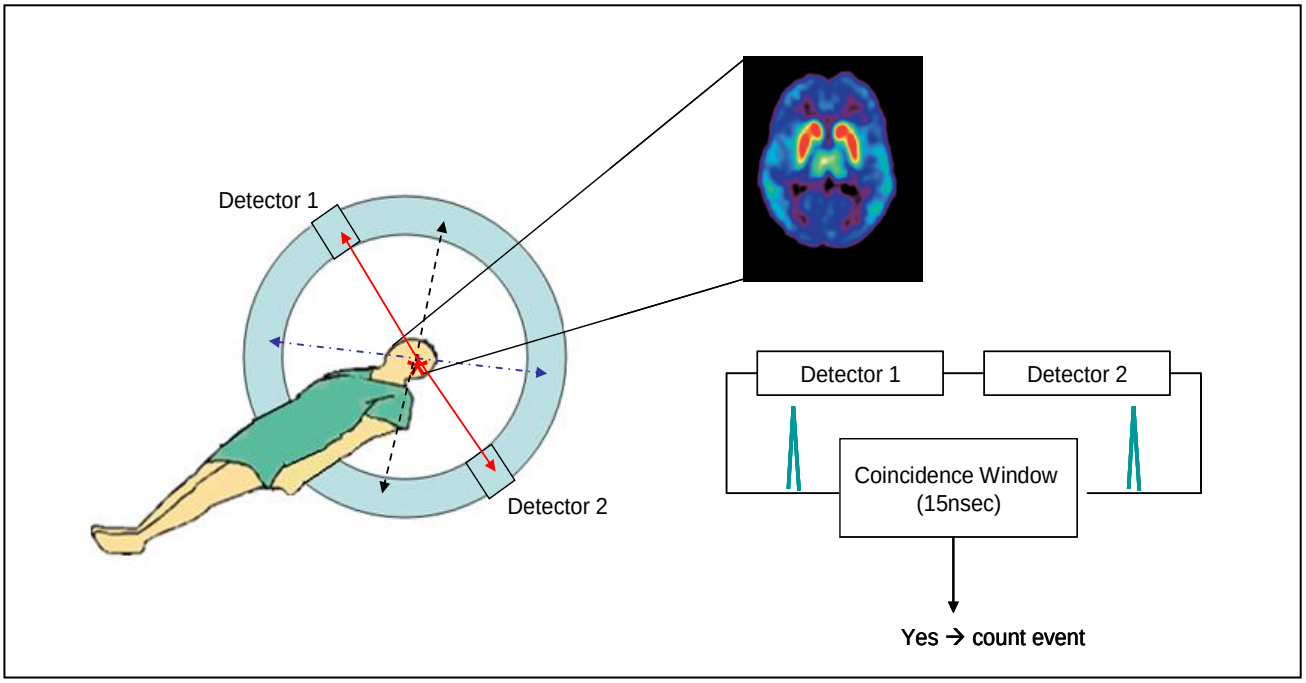

Table 1. Different Neuro-Radiotracers and their Targets

Radioisotope	Ligand	Half-life	Physiological Measurement and Target	Availability
^{18}F	FDG	110 min	Glucose transporters and hexokinases	Commercially available*
	FDOPA		Decarboxylase; L-type amino acid transporter system. High affinity for dopamine receptors (D_1R-D_4R)	Commercially available*
	Fallypride		Dopamine receptors (D_2R, D_3R)	Commercially available*
	Altanserin		5-HT_{2A} serotonin receptors	Limited availability
	Setoperone		5-HT_{2A} serotonin receptors	Limited availability
^{15}O	Water	2 min	Cerebral blood flow and oxygen metabolism	Limited availability
^{11}C	Fallypride	20 min	Fatty acid metabolism	Commercially available*
	Raclopride		Dopamine receptors (D_2R, D_3R)	Commercially available*
	PK11195		Peripheral-type benzodiazepine receptor	Limited availability
	FLB 457		Dopamine receptors (D_2R)	Limited availability
	WAY 100635		5-HT_{1A} serotonin receptors	Limited availability
	NNC 112		Dopamine receptors (D_1R)	Limited availability
	SCH 23390		Dopamine receptors (D_1R)	Limited availability
	Methylspiperone		Dopamine receptors (D_2R) and 5-HT_{2A} serotonin receptors	Limited availability
	DOPA		Decarboxylase; L-type amino acid transporter system. High affinity for dopamine receptors (D_1R-D_4R)	Commercially available*

* For research purposes only

Table 2. A Selective Review of Studies Investigating Cognitive Function in Schizophrenia using Position Emission Tomography.

Author(s)	Subjects	Mean Age (SD)	Methods *(PET tracer and Assessment)*	Results	Comments
Sabri *et al.* [63]	11 chronic SZ 10 NC	30.6 (11.9) 30.7 (10.7)	fTCD [^{15}O]H_2O PET N-back task number-version *0-back:* press the button whenever the number 3 appears. *2-back:* respond according to a number presented 2 stimuli before.	SZ activated larger cortical volumes but lower blood flow increases in these volumes than NC; they did not increase blood flow velocity during cognitive activation.	
Hirvonen *et al.* [80]	Unaffected co-twins from pairs discordant for SZ: 6 MZ 5 DZ Healthy control twins: 4 MZ NC, 3 DZ NC (n=14 twins from 7 healthy pairs)	 52.8 (5.3) 50.5 (4.7) 50.2 (3.9)	PET with [^{11}C] raclopride Spatial working memory (immediate recall of spatial locations, total backward and forward orders of presentations, visual span subtest, WMS-R), Divided Attention (single-task performance in Brown-Peterson dual task paradigms), CVLT (intrusions) and Posner paradigm (choice reaction times to visual targets).	MZ co-twins exhibited higher binding potential values than NC. Unaffected co-twins showed heightened caudate D_2 density compared with unaffected DZ co-twins and healthy control twins. Higher D_2R binding in caudate predicted poor performance on cognitive tasks. Negative correlation between D_2 binding potential and scores obtained on cognitive tests in caudate nucleus.	Population-based twin cohort study
Ho *et al.* [77]	159 SZ 84 NC	26.5 (7.35) 27.0 (7.03)	[^{15}O]H_2O PET WAIS-R (FSIQ, digit span backward subtest), WCST, N-back task, TMT A&B.	Met homozygotes showed longer reaction times than Val homozygotes on the one-back, although this did not reach significance. Patients with Met homozygozity showed greater rCBF than Val homozygotes. Val homozygotes showed greater activation in the DLPFC and the right mesial frontal lobe, compared with Met homozygotes.	Influence of *COMT* Val158Met polymorphism on cognition.
Lehrer *et al.* [57]	12 never-medicated SZ 13 NC	29.0 (9.8) 28.5 (8.0)	[^{18}F]FDG PET BPRS, GAF, CASH, Abnormal Involuntary Movement Scale.	SZ showed diminished regional glucose metabolism in the medial dorsal nucleus, posterior thalamus, and prefrontal cortex relatives to NC.	
Brewer *et al.* [65]	8 FES 8 NC	21.2 (3.0) 22.6 (2.0)	[^{15}O]H_2O PET SCID, PANSS Stroop colour-word interference task, NART (estimated premorbid IQ).	At follow-up, SZ showed greater activation in dorsal and inferior regions of the lateral PFC compared to baseline testing.	Neuroleptive-naïve FES. Predominantly male sample. Follow-up study

Author(s)	Subjects	Mean Age (SD)	Methods *(PET tracer and Assessment)*	Results	Comments
Lee *et al.* [81]	11 genetic HR 11 NC	25.1 (5.2) 25.5 (5.2)	PET with [^{11}C]raclopride SCID (or SCID-NP), FIGS; WCST, TMT, COWA, RCFT, K-WAIS (IQ).	Genetic HR subjects showed a loss of asymmetry binding in the putamen, while NC showed hemispheric asymmetry in the putamen (greater D_2R binding potential in right than left putamen).	
Kim *et al.* [67]	12 SZ 12 depression 12 NC	24.6(3.0) 23.9 (3.0) 24.8 (2.3)	[^{15}O]H_2O PET PANSS, Beck Depression Inventory; Modified word-stem completion task (forced/non-forced choice conditions)	Although NC showed heightened activation in the PFC and cerebellum, activity in the SZ group in these region were less pronounced. During the non-forced condition, NC showed increased activity of the right cerebellum compared with SZ. In the forced condition, increased activation in the right frontopolar area and orbitofrontal cortex was found in NC compared to SZ. Compared to NC, patients with SZ showed no significant correlations between regional activation and cerebellum and orbitofrontal cortex.	
Uchida *et al.* [30]	11 late-life SZ or SZaff	63.5 (8.1)	PET with [^{11}C]raclopride PANSS, MMSE; Abnormal Involuntary Movement Scale, the Barnes Rating Scale for Drug-Induced Akathisia, SAS; DRS: attention, conceptualization, construction, initiation/preservation, memory.	DRS-attention negatively correlated with the D_2R blockade. SZ patients who showed 74.9% or higher D_2R blockade performed worse on the attention subscale, than those with lower D_2R blockade.	
Fernandez-Egea *et al.* [69]	11 SZ 10 NC	28.64 (7.1) 27.50 (2.7)	[^{18}F]FDG PET SCID, PANSS Facial emotion recognition tasks: emotional task (50 happy and 50 sad faces), control task (gender discrimination task: pictures of 50 men and 50 women with neutral expressions).	SZ showed task-independent left amygdala hyperactivation than NC. SZ showed amygdala hyperactivation during the control task.	

Note: BPRS, British Psychological Rating Scale; CASH, Comprehensive Assessment of Symptoms and History; COWA, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; DLPFC, dorsal lateral prefrontal cortex; DSM-IV, Diagnostic and Statistical Manual, 4th edition ; DRS, Dementia Rating Scale-2; FES, first episode schizophrenia; FIGS, Family Interview for Genetic Study; fTCD, functional transcranial Doppler sonography; GAF, Global Assessment of Functioning Scale; HR, high-risk; IQ, intelligence quotient; K-WAIS, Korean version of Wechsler Adult Intelligence Scale; MINI, Mini International Neuropsychiatric Interview; MIS, Magical Ideation Scale; MMSE, Mini-Mental State Examination; NART, National Adult Reading Test; NC, normal controls; PAS, Perceptual Aberration Scale; PANSS, positive and negative syndrome scale; PFC, prefrontal cortex; RCFT, Rey-Osterrieth Complex Figure Test; SAS, Simpson-Angus Scale; SZ, schizophrenia; SZaff, schizoaffective disorder; SCID, Structured Clinical Interview for DSM-IV; SCID-NP, Structured Clinical Interview for DSM-IV, non-patient version; TMT, Trail making test; WCST, Wisconsin card sorting test.