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Using molecular imaging to understand early schizophrenia-related psychosis neurochemistry: a review of human studies

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Abstract

Schizophrenia is a chronic psychiatric disorder generally preceded by a so-called prodromal phase, which is characterized by attenuated psychotic symptoms. Advances in clinical research have enabled prospective identification of those individuals who are at clinical high risk (CHR) for psychosis, with the power to predict psychosis onset within the near future. Changes in several brain neurochemical systems and molecular mechanisms are implicated in the pathophysiology of schizophrenia and the psychosis spectrum, including the dopaminergic, γ-aminobutyric acid (GABA)-ergic, glutamatergic, endocannabinoid, and immunologic (i.e. glial activation) system and other promising future directions such as synaptic density, which are possible to quantify *in vivo* using positron emission tomography (PET). This paper aims to review *in vivo* PET studies in the mentioned systems in the early course of psychosis (i.e. CHR and first-episode psychosis (FEP)). The results of reviewed studies are promising; however, the current understanding of the underlying pathology of psychosis is still limited. Importantly, promising efforts involve the development of novel PET radiotracers targeting systems with growing interest in schizophrenia, like the nociceptive system and synaptic density.

Keywords

Positron emission tomography; clinical high risk; ultra-high risk; at risk mental state; first episode; schizophrenia

Introduction

Schizophrenia is a chronic and debilitating brain disorder characterized by positive (i.e. delusions and hallucinations) and negative (i.e. affective flattening, avolition, alogia, anergia, and anhedonia) symptoms, as well as cognitive deficits (Barron, Hafizi, & Mizrahi, 2017). The diagnosis of schizophrenia is generally preceded by a so-called prodromal state (also

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known as high-risk state) (Fusar-Poli, Borgwardt, et al., 2013) which is characterized by negative symptoms and non-specific behavioural and emotional changes with a reduction in the level of functioning. These changes are usually accompanied by attenuated psychotic symptoms (Yung & McGorry, 1996).

Reliable and valid tools are now available to detect help-seeking individuals at high risk for developing psychosis. Based on this, several operational definitions have been proposed; ultra-high risk (UHR), clinical high risk (CHR), prodromal, and at risk mental state (ARMS) (Schultze-Lutter, Schimmelmann, Ruhrmann, & Michel, 2013). These definitions are validated and extensively used around the world (Fusar-Poli, Borgwardt, et al., 2013), enabling the identification of individuals who are at high risk for psychosis with clear and compelling power to predict psychosis onset within the near future (1–3 years) (Addington & Heinssen, 2012). People diagnosed as high risk for psychosis have a high rate of conversion to psychosis, 26% over a mean follow-up period of 2.35 years (across 21 studies) (Fusar-Poli, Bechdolf, et al., 2013), and even those who do not convert were reported to have persistent attenuated psychotic symptoms and poorer social role-functioning, even 2 years following the high-risk diagnosis (Addington et al., 2011). Several factors have been shown to have predictive value for conversion to psychosis, including neuroimaging findings such as structural changes like greater reduction in grey matter volume (Pantelis et al., 2003) and dopamine synthesis capacity (Howes et al., 2011), as well as clinical presentation, such as unusual thought content and suspiciousness and greater decline in social functioning (Cannon et al., 2016).

Several neurochemical systems and molecular mechanisms are implicated in the pathophysiology of psychosis including the dopaminergic, γ-aminobutyric acid (GABA)-ergic, and glutamatergic system (Salavati et al., 2014), as well as the endocannabinoid system (Saito, Ballinger, Pletnikov, Wong, & Kamiya, 2013), microglial activation (Barron, Hafizi, Andreazza, & Mizrahi, 2017), and synaptic density (Egbujo, Sinclair, & Hahn, 2016). *In vivo* quantification of brain proteins (e.g. receptors, transporters, and enzymes) is possible using positron emission tomography (PET) (Jones, Rabiner, & PET Research Advisory Company, 2012).

In this review, we focused on PET studies in the early course of the disease such as first-episode psychosis (FEP) and individuals at high risk for psychosis that investigated the above-mentioned neurochemical systems and molecular mechanisms.

Methodology

The search for this review was conducted using the Medline database in August 2017, with no time span specified for date of publication. We only included *in vivo* studies using human subjects and PET imaging. This review was further confined to include only articles which studied (1) the high risk for psychosis state (including CHR, UHR, and ARMS (Addington et al., 2007; Mizrahi et al., 2014)) as well as (2) patients with FEP (first-episode psychosis with duration of illness less than 5 years). For consistency, the high risk for psychosis state was referred to as CHR in this review.

Exclusively, PET literature was reviewed, with a focus on schizophrenia relevant molecular targets as follows: (1) frontocortical dopaminergic; (2) GABAergic; (3) glutamatergic system; (4) microglial activation; and (5) the endocannabinoid system in FEP and CHR. While we acknowledge that other molecular targets may be important for the development of psychosis, we decided to focus on those which were well researched (Cannon, 2015) and could potentially serve as biomarkers.

PET studies in early psychosis (FEP and CHR)

Dopamine

The striatal hyperdopaminergic state is one of the earliest hypotheses of schizophrenia, studied repeatedly and reviewed frequently (e.g. Abi-Dargham, 2014; Howes, McCutcheon, & Stone, 2015; Seeman & Seeman, 2014). Very recently, the existing PET studies in chronic schizophrenia, FEP, and CHR were reviewed, discussing dopamine synthesis capacity, endogenous dopamine, dopamine release, vesicular monoamine transporter-2 (VMAT2) density, and dopamine receptor density (Howes, McCutcheon, Owen, & Murray, 2017; Weinstein et al., 2017). However, dopamine in cortical regions is rather poorly investigated, although a frontocortical dopamine deficiency is assumed (Davis & Kahn, 1991). The lack of data is partly due to the long absence of appropriate PET radiotracers. Although radiotracers like [^{11}C]raclopride and [^{11}C]-(+)-PHNO are useful to study dopamine transmission in mostly striatal areas, they cannot be used to quantify the low dopamine $D_{2/3}$ receptors density present in cortical regions. The radiotracers [^{11}C]FLB 457 and Fallypride (C-11 or F-18) have a higher $D_{2/3}$ receptor affinity and provide a stronger signal in cortical brain regions, and, in this regard, [^{11}C]FLB 457 was found to be superior as it offers a better resolution with a test–retest variability of ≤15% (Narendran et al., 2009). Thus, in this review, only PET studies which investigated frontocortical dopamine $D_{2/3}$ receptor binding, using [^{11}C]FLB 457 or Fallypride (C-11 or F-18), were included.

Dopamine $D_{2/3}$ receptor density can be estimated by measuring the non-displaceable binding potential (BP_{ND}) of the radiotracer. Various studies were conducted measuring $D_{2/3}$ receptor density in the frontal cortex in patients with schizophrenia (Kessler et al., 2009; Lehrer et al., 2010; Slifstein et al., 2015; Suhara et al., 2002; Talvik, Nordstrom, Olsson, Halldin, & Farde, 2003; Vyas et al., 2017; Yasuno et al., 2005), but only in two studies exclusively patients with FEP were scanned which were included in this review (Table 1). Talvik et al. (2003) included eight healthy controls and nine drug-naïve FEP and Slifstein et al. (2015) scanned 21 healthy controls and 20 unmedicated FEP, with six patients being antipsychotic-naïve. Both studies demonstrated no difference in receptor density in frontocortical regions in patients with FEP compared to healthy controls using [^{11}C]FLB 457 PET. To date, no studies in CHR were conducted, neither with [^{11}C]FLB 457 nor Fallypride (C-11 or F-18).

Dopamine transmission can be studied using paradigms, which combine the assessment of dopamine $D_{2/3}$ receptor binding with a challenge. In those paradigms, the tracer's BP_{ND} is first assessed under a baseline/control condition and again following a challenge of the system, and the percentage change in binding (displacement or depletion) is calculated (ΔBP_{ND}).These paradigms are based on the idea that the challenge either increases or

decreases the concentration of endogenous dopamine, and that the tracer and neurotransmitter compete for the same $D_{2/3}$ receptor binding site (Laruelle, 2000). Only the displacement paradigm was validated in a pre-clinical study in the frontal cortex using [^{11}C]FLB 457 PET and simultaneous microdialysis in non-human primates where dopamine levels and ΔBP_{ND} showed a dose response (Narendran et al., 2014).

To date, there is only one published study measuring dopamine release in FEP (Slifstein et al., 2015) (Table 1). Slifstein et al. (2015) scanned their participants using an oral amphetamine challenge of 0.5 mg/kg which followed the baseline scan performed 3 h earlier. This study supports the frontocortical dopamine deficiency hypothesis by showing a reduction of ΔBP_{ND} in patients with FEP compared to matched healthy controls in frontocortical areas (especially the dorsolateral prefrontal cortex (PFC)). Only our group has studied frontocortical dopamine release in CHR in response to a stress behavioural challenge (Schifani et al., submitted). We detected no differences between CHR (n = 14) and healthy controls (n = 12) in medial PFC or dorsolateral PFC.

Neuroinflammation/microglia activation

Several lines of evidence point to a critical role of immune abnormalities such as microglial activation in the pathophysiology of psychosis (Barron, Hafizi, Andreazza, et al., 2017). Using PET with radioligands that target the 18 kDa translocator protein, TSPO, is currently the best method to quantify microglial activation *in vivo*. The first radioligand developed for PET imaging of TSPO was [^{11}C]PK11195, also known as the first-generation TSPO radioligand. Using [^{11}C]PK11195, Van Berckel et al. (2008) observed significantly higher binding in total grey matter of medicated patients with FEP as compared to healthy controls (Table 2). However, the same group in their more recent study (Van Der Doef et al., 2016) with a larger sample, as well as a very recent study from Di Biase et al. (2017), reported no significant differences in binding of [^{11}C]PK11195 in FEP in comparison to healthy controls.

Due to the methodological limitations of the first-generation TSPO radioligand, such as low penetration into the brain and low specific binding, the second-generation radioligands such as [^{11}C]DPA-713, [^{11}C]PBR28, and [^{18}F]FEPPA were developed, which have a higher affinity to TSPO. A common feature of these radioligands is that their binding to TSPO is affected by a single gene polymorphism in the TSPO gene (rs6971), and, based on this polymorphism, people can be categorized as high-affinity binders (HAB), mixed-affinity binders (MAB), or low-affinity binders (LAB) (Mizrahi et al., 2012; Owen et al., 2012). Using the gold standard outcome measure for the second-generation TSPO radioligands, total volume of distribution (V_T), two studies reported no significant difference in microglial activation between FEP and matched healthy controls (Coughlin et al., 2016; Hafizi et al., 2016). However, a more recent study reported significantly lower binding of [^{11}C]PBR28 in drug-naïve patients with FEP as compared to matched healthy controls (Collste et al., 2017).

To date, three studies investigated microglial activation in the CHR population and reported no significant differences between CHR and matched healthy controls when comparing V_T (Bloomfield et al., 2015; Hafizi et al., in press) or BP_{ND} (Di Biase et al., 2017).

Taken together, the extent and exact nature of the relationship between microglial activation and pathophysiology of psychosis is not yet fully understood. Several reasons have been suggested to contribute to this lack of group effect on microglial activation. First, TSPO is not specific for microglial activation and is also expressed by astrocytes and neurons (Notter et al., in press). Second, using TSPO, it is not possible to differentiate between pro-inflammatory (M1) and anti-inflammatory (M2) states of microglia. Moreover, recent studies suggest that TSPO may be down-regulated in activated microglia (Owen et al., 2017).

Glutamate and GABA

GABA/glutamate imbalance has been implicated in the pathophysiology of schizophrenia, suggesting that hypofunction of the *N*-methyl-D-aspartate (NMDA) receptor causes hypoactivity of GABAergic interneurons. Hypoactivity of these interneurons results in disinhibition of glutamatergic pyramidal neurons, leading to glutamate excitotoxicity (Lewis & Moghaddam, 2006; Lisman et al., 2008). Investigating these neurotransmitter systems *in vivo* with PET imaging has been challenging due to difficulties in the development of reliable radiotracers.

Glutamate is the primary excitatory neurotransmitter in the central nervous system. Both ionotropic glutamate receptors, in particular NMDA receptors, and metabotropic glutamate receptors (mGluRs) play an important role in modulating glutamatergic neurotransmission in the brain (Meldrum, 2000). NMDA receptor and mGluR5 are functionally linked and co-localized in many brain regions implicated in schizophrenia, such as the hippocampus and striatum. Studies have shown that mGluR5 activation leads to the potentiation of NMDA receptor-mediated currents (Matosin & Newell, 2013). Thus, based on the NMDA hypofunction hypothesis of schizophrenia, positive modulation of mGluR5 may provide a therapeutic target to restore NMDA receptor function.

[^{11}C]ABP688 is a glutamatergic radioligand that binds to an allosteric site on mGluR5. In humans, [^{11}C]ABP688 showed high brain uptake and its regional distribution was consistent with known mGluR5 sites (Ametamey et al., 2007). [^{11}C]ABP688 has been used to image mGluR5 in a sample of treated schizophrenia patients, reporting no significant differences in mGluR5 distribution volume ratio (DVR) between patients and healthy controls (Akkus et al., 2017); however, no studies exist in FEP or CHR. Importantly, studies have reported high intrasubject variability across [^{11}C]ABP688 on same day test–re-test scans, suggesting difficulties in using this radioligand to assess group differences (DeLorenzo et al., 2017).

Several radioligands have been synthesized for the *in vivo* imaging of NMDA receptors in the brain. However, most of these ligands are limited by their fast metabolism and high non-specific binding, or have not yet been fully characterized in humans. To date, no PET studies exist which have imaged the NMDA receptor in FEP or CHR, but recent developments may provide the possibility of directly investigating this system in humans (Klein et al., 2017).

GABA is an amino acid neurotransmitter involved primarily in inhibitory synaptic transmission and acts through two main receptors, $GABA_A$ and $GABA_B$. The most widely used radioligand for GABA receptors is [^{11}C]flumazenil, an antagonist with high affinity

and selectivity to the benzodiazepine site of the $GABA_A$ receptor (Maziere et al., 1983). [^{18}F]fluoroflumazenil, a fluoridated derivative of [^{11}C]flumazenil, has been developed to overcome the short half-life of carbon-11 ligands. Evaluation of this ligand in humans suggests a high affinity for $GABA_A$ receptors and comparable biodistribution to [^{11}C]flumazenil (Mitterhauser et al., 2004). Only one study has investigated GABA neurotransmission in CHR individuals using [^{18}F]fluoroflumazenil PET. This study reported reduced [^{18}F]fluoroflumazenil BP_{ND} in CHR relative to healthy controls (Kang et al., 2013). However, the pons was used as a reference region in this study, which is (1) known to be subject to partial volume effects due to its small volume and (2) not completely devoid of $GABA_A$ receptors, challenging the assumption of a true reference region.

It is important to mention that $GABA_A$ receptor sub-types have distinct cellular and regional distributions, suggesting that they may mediate different functions in the brain (Sieghart & Sperk, 2002). However, [^{11}C]flumazenil and [^{18}F]fluoroflumazenil cannot distinguish between $GABA_A$ receptor sub-types, which limits the interpretability of the results.

[^{11}C]Ro15-4513 is a radioligand that binds mostly to the $GABA_A$ α1/α5 benzodiazepine receptor, with a 10-fold higher affinity at α5 than α1 receptor subtypes. Quantification studies reported a high affinity and selectivity of [^{11}C]Ro15-4513 to the α5 sub-unit in humans (i.e. 60–70% of the specific binding); however, binding kinetics were better modelled by alternative quantification methods (i.e. voxel-wise based analyses and simplified tissue reference model) rather than the standard plasma input model (Asai et al., 2009; Myers, Comley, & Gunn, 2017). A study by Asai et al. (2008) reported no significant differences in [^{11}C]Ro15-4513 binding potential between schizophrenia patients and healthy controls; however, this remains to be explored in early psychosis.

Endocannabinoid system

There is strong agreement across epidemiological studies linking cannabis with increased risk of developing schizophrenia (Arseneault et al., 2002; Moore et al., 2007). Moreover, cannabis may reduce the age of onset of psychosis (Di Forti et al., 2014), supporting the involvement of the endocannabinoid system early in the development of psychotic disorders.

The majority of the known psychoactive effects of cannabis act through the cannabinoid CB1 receptor (Huestis et al., 2007) which is expressed densely throughout the brain but is particularly enriched in the cortex, cerebellum, basal ganglia, midbrain, and limbic nuclei (McPartland, Glass, & Pertwee, 2007). In contrast, the CB2 receptor is weakly expressed in the brain, and its functions in humans are poorly understood. The endogenous cannabinoid (endocannabinoid) ligands *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) activate presynaptic CB1 receptors, leading to a reduction of neurotransmitter release from synaptic terminals (Katona & Freund, 2008). Endocannabinoids are produced by *N*-acylphosphatidylethanolamine phospholipase D (NAPE-PLD) or diacylglycerol lipase (DAGL), the biosynthetic enzymes for anandamide and 2-AG, respectively, and brain levels of endocannabinoids are believed to be determined primarily by fatty acid amide hydrolase (FAAH), which degrades anandamide and monoacylglycerol lipase (MAGL) and ab-hydrolysing domain-6 and −12 (ABHD-6 and −12) which degrade 2-AG (Katona & Freund, 2008). Of these primary components of the

endocannabinoid system, to date, only the CB1 receptor and FAAH can be targeted with PET in humans. For CB1 receptors, three radiotracers have been extensively used for PET imaging in humans, [^{11}C]OMAR (Normandin et al., 2015), [^{18}F]MK-9470 (Sanabria-Bohorquez et al., 2010), and [^{11}C]MePPEP (Terry et al., 2009), while novel radiotracers remain under development.

Three PET studies have investigated the CB1 receptor in schizophrenia (Ceccarini et al., 2013; Ranganathan et al., 2016; Wong et al., 2010), and two of these included sub-groups of anti-psychotic-naïve or FEP patients (Table 3). Ceccarini et al. (2013) used [^{18}F]MK-9470 PET with a mixed schizophrenia sample that comprised anti-psychotic-free patients with schizophrenia (9.4 ± 4 months since last antipsychotic exposure) and antipsychotic-naïve patients with FEP, with mean duration of illness of 5 (± 11) and <1 years, respectively. Ranganathan et al. (2016) used [^{11}C]OMAR PET with an unmedicated schizophrenia sub-group that primarily comprised schizophrenia patients that had been antipsychotic-free for 27 ± 24 months. Ranganathan et al. (2016) did not report duration of illness. These studies reported elevated (Ceccarini et al., 2013) and decreased (Ranganathan et al., 2016) CB1 receptors in schizophrenia relative to healthy controls, and sub-group analysis in both studies reported greater magnitude of changes in FEP and anti-psychotic-naïve/unmedicated schizophrenia patients relative to medicated patients. Neither of these PET studies included genotyping of the CNR1 rs2023239 variant that affects CB1 receptor binding. Carriers of the rs2023239 minor allele have as much as ~30% higher binding relative to those homozygous for the wild-type allele (Hirvonen et al., 2013). The reason for the conflicting directions of the change in CB1 receptor availability is unclear as the studies used different ligands ([^{18}F]MK9470 vs [^{11}C]OMAR), different methods of quantification, and different outcome measures (modified standardized uptake values (SUV) vs V_T).

[^{18}F]MK-9470 has high affinity to the CB1 receptor, but exhibits very slow *in vivo* kinetics, posing considerable challenges for its quantification (Sanabria-Bohorquez et al., 2010). Relative to [^{18}F]MK-9470, [^{11}C]OMAR has lower affinity for CB1 receptors and exhibits faster kinetics, aiding modelling, and reducing the scan time required for quantification. In addition, [^{11}C]OMAR binding (V_T) has superior test–re-test reliability and lower betweensubject variability (Normandin et al., 2015).

Future directions for PET studies in early psychosis

Endocannabinoid system

Aside from the CB1 receptor, no other major component of the endocannabinoid system has been imaged *in vivo* in schizophrenia. However, with recent developments, FAAH can now be imaged using [^{11}C]CURB, a C-11 labelled form of the highly selective and specific FAAH inhibitor URB694, that has been validated in humans (Clapper et al., 2009; Rusjan et al., 2013; Wilson et al., 2011). A study demonstrated that more than 95% of [^{11}C]CURB binding can be blocked following pre-treatment with the highly selective FAAH inhibitor PF-04457845 (Boileau, Rusjan, et al., 2015). [^{11}C]CURB PET imaging also demonstrated sensitivity to physiologically relevant changes in FAAH availability by detecting reductions of [^{11}C]CURB binding in carriers of the rs324420 A-allele, a single nucleotide polymorphism that results in lower levels of FAAH protein (Boileau, Tyndale, et al., 2015;

Chiang, Gerber, Sipe, & Cravatt, 2004). In light of strong evidence supporting the hypothesis that the endocannabinoid system is altered in psychosis, [^{11}C]CURB imaging of FEP and CHR individuals is warranted.

Beyond CB1 and FAAH, there is great interest in expanding the repertoire of endocannabinoid PET ligands to interrogate the endocannabinoid system in schizophrenia with notably active development of ligands for MAGL (e.g. Ahamed et al., 2017; Hicks et al., 2014; Wang, Placzek, Van de Bittner, Schroeder, & Hooker, 2016) and the CB2 receptor (e.g. Moldovan et al., 2016; Saccomanni et al., 2015). One of the CB2 ligands has been tested in humans, although its specificity for the CB2 receptor *in vivo* remains to be demonstrated (Ahmad et al., 2016).

Synaptic density

Post-mortem studies have repeatedly detected reduced synaptic density in the PFC and hippocampus in schizophrenia (Egbujo et al., 2016). This is believed to result from exaggerated synaptic pruning during puberty, proposed as a likely mechanism of disease onset (Selemon & Zecevic, 2015). Density of vesicular proteins is commonly used as a marker for synaptic density due to the ubiquitous distribution of synaptic vesicles in the brain, their restricted cellular localization in synaptic boutons, and their high phylogenetic conservation across vertebrates. In patients with schizophrenia, the expression of those proteins (e.g. synaptophysin) in the cerebral cortex was repeatedly found to be decreased (Eastwood, Burnet, & Harrison, 1995; Glantz & Lewis, 1997). Another very abundant vesicular protein is SV2A. Its distribution is homogenous (Bajjalieh, Frantz, Weimann, McConnell, & Scheller, 1994) and well-correlated with the cellular and regional distribution of synaptophysin, the gold standard marker to assess synaptic density (Finnema et al., 2016). Thus, SV2A represents an interesting marker to assess synaptic density (Finnema et al., 2016).

Two PET tracers have recently been developed (Mercier et al., 2014) and studied in humans, [^{18}F]UCB-H (Bretin et al., 2015) and [^{11}C]UCB-J (Finnema et al., 2016). Using rats and non-human primates, two studies reported high uptake and fast kinetics for [^{11}C]UCB-J in the brain, as well as high-affinity, saturable, and specific binding to SV2A (assessed with a displacement study using levetiracetam) (Finnema et al., 2016; Nabulsi et al., 2016). Moreover, [^{11}C]UCB-J's *in vivo* PET binding estimates (V_T) were very well correlated with *in vitro* SV2A densities in brain tissue (Finnema et al., 2016). Also in the human brain, [^{11}C]UCB-J has exceptional imaging qualities, including rapid brain uptake, rapid metabolism, and high-affinity and specific binding to SV2A. Furthermore, [^{11}C]UCB-J has a high and reliably measurable free fraction in plasma, suitable regional time activity curves with high radioactivity concentration in all grey matter regions, and very low uptake in white matter regions, and a very good inter-subject variability (CV = 12% ± 2% (mean ± SD)). A first evaluation in a patient population with temporal lobe epilepsy indicated a significant reduction of [^{11}C]UCB-J binding co-localized with the mesial temporal lobe sclerosis, confirming that [^{11}C]UCB-J PET is sensitive to synaptic loss (Finnema et al., 2016). In comparison, [^{18}F]UCB-H also displayed good kinetics in rodents (Bretin et al., 2013; Warnock et al., 2014) and non-human primates (Zheng et al., 2014), as well as acceptable

dosimetry in humans (Bretin et al., 2015), but there are no human imaging studies yet reported.

To date, no study has investigated SV2A with [^{11}C]UCB-J PET in humans in order to investigate the longstanding hypothesis of synaptic over-pruning in schizophrenia.

Nociceptin receptor system

The nociceptin/orphanin FQ peptide receptor (NOPr) system presents another novel approach to investigate schizophrenia, as there is a relatively large body of pre-clinical and *in vitro* evidence aligning this system with hallmark features of the disorder. The NOPr system plays a role in dopamine (Marti et al., 2004) and glutamate (Nicol, Lambert, Rowbotham, Smart, & McKnight, 1996) regulation, hypothalamic-pituitaryadrenal axis regulation (Leggett, Harbuz, Jessop, & Fulford, 2006), cognition (Higgins et al., 2002), and reward modulation (Rutten, De Vry, Bruckmann, & Tzschentke, 2010) (collectively reviewed by Khan et al., submitted), all of which are significantly altered in schizophrenia (Barch & Ceaser, 2012; Howes et al., 2015; Strauss, Waltz, & Gold, 2014; Walker, Mittal, & Tessner, 2008). Evidence for the implication of this system in the pathogenesis of psychosis is still limited. Yet, one pre-clinical study has demonstrated that the selective NOPr agonist Ro64-6198 disrupts pre-pulse inhibition (PPI) (Ces et al., 2012), a pre-attentive sensory filtering mechanism shown to be deficient in patients with schizophrenia (Braff, 2010; Braff, Geyer, & Swerdlow, 2001). Furthermore, dopamine D_2 receptor antagonism was shown to restore the Ro64-6198-disrupted PPI (Ces et al., 2012). Fortunately, the development and validation of the novel PET tracer [^{11}C]NOP-1A (Lohith et al., 2012) now makes it possible to investigate this system directly in clinical populations.

Conclusion

The increased availability of PET/MRI scanners and radiotracers for unique targets allow PET to be used in various fields of research including neuropsychiatry. The possible areas of quantitative PET application are manifold, including the discovery of disease pathophysiology, diagnosis, drug discovery, disease monitoring, and treatment response, which makes it a unique tool in brain research.

This paper reviewed PET studies in early psychosis (FEP and CHR) concentrating on relevant implicated neurochemical systems and molecular mechanisms such as frontocortical dopaminergic, GABAergic, glutamatergic, endocannabinoid, and immunologic (i.e. glial activation) systems. Initial results with these systems do indicate their potential implication in schizophrenia. Furthermore, promising efforts are being made in the development of PET tracers in novel systems with growing interest in schizophrenia such as the nociceptive system, synaptic density, and even cyclooxygenase (COX)-2 (Kim et al., 2017).

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Table 1.

PET studies quantifying cortical dopamine in early psychosis.

Study	Populations	Anti-psychotic naïve/free	Mean duration of psychotic illness	Radiotracer & challenge	Findings
Talvik et al. (2003)	8 HC 9 FEP	— 9/0	— <5 years	[^{11}C]FLB 457	No group difference in dopamine receptor density in ACC and frontal cortex
Slifstein et al. (2015)	21 HC 20 FEP	— 6/14	— 13.2 ± 11.3 (SD) months	[^{11}C]FLB 457 baseline and with amphetamine	**1** No group difference in dopamine receptor density in cortex (including dlPFC, OFC, mPFC, ACC) **2** Reduced amphetamine-induced dopamine release in patients with FEP in cortex (including dlPFC, OFC, mPFC, ACC), trend to statistical significance only in dlPFC

dlPFC: dorsolateral prefrontal cortex; HC: healthy controls; mPFC: medial prefrontal cortex; ACC: anterior cingulate cortex; OFC: orbifrontal cortex.

Table 2.

PET studies quantifying neuroinflammation in early psychosis.

Study	Populations	Anti-psychotic naïve/free	Mean duration of psychotic illness	Radiotracer	Findings
Van Berckel et al. (2008)	10 HC 10 FEP	— N/A	— 37.2 ± 19.9 (SD) months	[^{11}C]PK11195	Increased binding in total grey matter in FEP
Bloomfield et al. (2015)	14 HC 14 CHR	— 14/0	— —	[^{11}C]PBR28	No group difference in binding using total distribution volume
Coughlin et al. (2016)	14 HC 12 FEP	— N/A	— 26.4 ± 16.8 (SD) months	[^{11}C]DPA-713	No group difference in binding
Hafizi et al. (2016)	20 HC 19 FEP	— 14/5	— 33.6 ± 40.1 (SD) months	[^{18}F]FEPPA	No group difference in binding
van der Doef et al. (2016)	17 HC 19 FEP	— N/A	— 15.6 ± 13.2 (SD) months	[^{11}C]PK11195	No group difference in binding
Collste et al. (2017)	16 HC 16 FEP	— 16/0	— 7.9 ± 9.6 (SD) months	[^{11}C]PBR28	Decreased binding in FEP
Hafizi et al. (in press)	23 HC 24 CHR	— 24/0	— —	[^{18}F]FEPPA	No group difference in binding
Di Biase et al. (2017)	15 HC 10 CHR 18 FEP	— 10/0 4/0	— — 18 ± 12 (SD) months	[^{11}C]PK11195	No differences in binding compared to HC

HC: healthy controls.

Table 3.

PET studies quantifying CB1 receptors in early psychosis.

Study	Populations	Anti-psychotic naive/free	Mean duration of psychotic illness	Radiotracer (outcome measure)	Findings
Ceccarini et al. (2013)	12 HC 16 unmedicated SCZ and 51 medicated SCZ including FEP and chronic SCZ	— 6/10	— Unmedicated SCZ: 5 ± 11 (SD) years unmedicated FEP: <1 year	[^{18}F]MK9470 (modified SUV)	Increased binding in SCZ: unmedicated SCZ > medicated SCZ > HC
Ranganathan et al. (2016)	18 HC 7 unmedicated and 18 medicated SCZ	— 6/1	— NR	[^{11}C]OMAR (VT)	Decreased binding in SCZ: unmedicated SCZ < medicated SCZ < HC

HC: healthy controls; NR: not reported; SCZ: schizophrenia.