Neurochemistry of Schizophrenia: The Contribution of Neuroimaging Postmortem Pathology and Neurochemistry in Schizophrenia

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Abstract: The advent of molecular neuroimaging has greatly impacted on understanding the neurochemical changes occurring in the CNS from subjects with psychiatric disorders, especially schizophrenia. This review focuses on the outcomes from studies using positron emission tomography and single photon emission computer tomography that have measure levels of neurotransmitter receptors and transporters in the CNS from subjects with schizophrenia. One outcome from such studies is the confirmation of a number of findings using postmortem tissue, but in the case of neuroimaging, using drug naïve and drug free subjects. These findings add weight to the argument that findings from postmortem studies are not an artifact of tissue processing or a simple drug effect. However, there are some important unique findings from studies using neuroimaging studies. These include evidence to suggest that in schizophrenia there are alterations in dopamine synthesis and release, which are not accompanied by an appropriate down-regulation of dopamine D2 receptors. There are also data that would support the notion that decreased levels of serotonin 2A receptors may be an early marker of the onset of schizophrenia. Whilst there is a clear need for on-going development of neuroimaging ligands to expand the number of targets that can be studied and to increase cohort sizes in neuroimaging studies to give power to the analyses of the resulting data, current studies show that existing neuroimaging studies have already extended our understanding of the underlying pathophysiology of psychiatric disorders such as schizophrenia.

Keywords: Schizophrenia, Neuroimaging, Dopamine, Serotonin, Muscarinic, Glutamate, Cannabinoid.

1. INTRODUCTION

The advent of molecular neuroimaging has opened up the possibility of studying changes in the molecular structure of the human CNS in the living, allowing new insights into potential pathophysiological processes in subjects with disorders of the CNS [1]. Thus, at one level, these technologies have given the capability to confirm and expand findings from postmortem CNS studies, which had been the only approach to studying molecular changes in the brain prior to the advent of molecular neuroimaging. However, in psychiatry, neuroimaging of the molecular cytoarchitecture of the human CNS has also provided unique opportunities to i) study people in a drug naïve and drug free state and ii) delve into dynamic processes occurring in the human CNS that cannot be studied in postmortem tissue. This review will focus on how molecular neuroimaging has influence our understanding of changes in CNS neurochemistry in people with psychoses, with a particular focus on schizophrenia, where molecular imaging has been extensively utilized to understand the pathophysiology of that disorder.

It is now widely accepted that many psychiatric disorders manifest in individuals with a genetic predisposition with progress towards the frank disorder being triggered by encounters with as yet to be established environmental factors [2, 3]. In the case of schizophrenia, such complex interactions

between variations in the human gene sequence and the environment has led to the suggestion that that disorder may be a disorder restricted to humans [4, 5]. This logic strongly supports the argument that uncovering the underlying pathophysiology of the disorder requires the on-going and extensive study of the human CNS. Significantly, there are now numerous studies that have shown that neurochemical pathways in the human CNS are affected by the pathophysiology of disorders such as schizophrenia [6, 7, 8] and bipolar disorder [9]. It is therefore not surprising that the advent of neuroimaging techniques saw these technologies used to study neurochemical markers in the brains of people with psychiatric disorders, in particular neurotransmitter receptors and transporters. This review will particularly focus on how neuroimaging studies have complemented and expanded findings using postmortem CNS to increase our understanding of the pathophysiology of psychotic disorders. It will also highlight how molecular neuroimaging of neurotransmitter systems has given new data on potential causes of psychiatric disorders such as schizophrenia. This review does not include other important neuropsychopharmacological based studies using neuroimaging techniques to understand how drug receptor occupancy in the living human CNS affects therapeutic response and side-effect profiles.

2. NEUROIMAGING AND THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

The early availability of ligands that targeted receptors enabled these important molecules to be imaged in the CNS using single-photon emission computed tomography

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(SPECT) or positron emission tomography (PET). These technologies were first used in psychiatry to challenge the long standing dopamine hypothesis of schizophrenia that argued that over-activity of dopaminergic pathways contributed to the pathophysiology of schizophrenia [10].

2.1. Findings on Dopamine-D2 Like Receptors

Studies on the human genome had shown that there were a family of 5 dopamine receptors, all of which are expressed in the human CNS [11]. However, ligands that have been developed for molecular neuroimaging can only delineate these receptors into two major sub-classes, the dopamine D2-like receptors comprising of the dopamine D2, D3 and D4 receptors (DADR2) and the dopamine D1-like receptors, made up of the dopamine D1 and D5 receptors (DADR1). It has long been recognized that DADR2 were critical to the therapeutic benefits obtained when using antipsychotic drugs [12] and, it was proposed, to the pathophysiology of schizophrenia [7]. Hence initial studies of neurotransmitter systems in schizophrenia focused on this important dopaminergic marker in the dopamine rich region of the human CNS, the caudate nucleus.

The first study using PET to measure DADR2 in schizophrenia showed a 151% and 161% increase in (3-*N*-[¹¹C]methyl)sipiperone ([¹¹C]NMS) to the caudate nucleus from drug naïve and antipsychotic drug treated people with the disorder, respectively [13] (Table 1). However, a subsequent study using [¹¹C]raclopride to measure DADR2 reported no changes in the levels of radioligand binding in the putamen from drug naïve people with schizophrenia [14]; a finding supported using [⁷⁶Br]bromospiperone to measure DADR2 [15].

Following these initial studies, the majority of studies using [¹¹C]NMS have reported increased binding in the caudate-nucleus from drug naïve and drug free people with schizophrenia [16-19] and in late onset schizophrenia [20]. By contrast, two studies reported no change in the binding of that radioligand in schizophrenia [21, 22]. Studies using [¹¹C]raclopride [21, 23, 24] and [⁷⁶Br]bromospiperone [25] have all reported no significant differences in binding in the caudate-nucleus in drug naïve and drug free people with schizophrenia. The findings of unaltered levels of DADR2 is also supported by studies using single photon emission computer tomography of drug naïve and drug free people with schizophrenia using [¹²³I]-iodobenzamide as the radioligand [26-30]. Significantly, it has recently reported that the binding of this radioligand was not altered in the CNS of subjects at ultra-high risk for developing schizophrenia [31]. Hence, overall, it would appear that it is most likely that neuroimaging studies support the hypothesis that there is no change in DADR2 in the dopaminergic rich regions of the human CNS associated with schizophrenia.

The conflicting results using different DADR2 ligands in neuroimaging is not novel as studies using postmortem tissue had consistently reported an increased levels of [³H]sipiperone binding to the caudate-putamen from subjects with schizophrenia [32, 33] but this difference was not apparent when [³H]raclopride was used at appropriate concentrations for receptor saturation [34]. This suggests that the differences in findings on dopamine DADR2 may be related

to methodological considerations and / or the pharmacology of the radioligands used.

DADR2 are most predominant in the caudate-nucleus but can be detected in other regions of the human central nervous system [35] and a few neuroimaging studies have been carried out to determine if DADR2 are altered in regions of the CNS other than the caudate-putamen. Two of these studies have failed to provide any evidence for changed dopamine DADR2 in the cortex of people with schizophrenia [24, 29]. By contrast, a PET study using [¹⁸F]fallypride reported a decrease in DADR2 in the anterior cingulate in people with schizophrenia [36] and a SPECT study using [¹²³I]epidepride reported that DADR2 were decreased in the left and right temporal cortex of people with schizophrenia [37]. Hence, it is possible that there are region-specific changes in the levels of DADR2 in regions other than the caudate nucleus in people with schizophrenia. This notion is support by some postmortem studies that also suggest there may be region-specific changes in DADR2 in the cortex of subjects with schizophrenia [38-40].

The notion of region-specific changes in DADR2 in people with schizophrenia becomes even more refined based on studies in the thalamus. Thus, one study using PET and [¹⁸F]fallypride reported a decrease in binding in right medial thalamus in schizophrenia without finding any change in binding in the left thalamus [24]. A second study using the same radioligand failed to show a change in binding across the entire thalamus but reported a decrease in binding in the left medial dorsolateral nucleus (-18%) and pulvinar (-18%) [41]. Finally, a study using [¹¹C]raclopride reported a generalized decrease in binding in the right thalamus but not left thalamus from subjects with the disorder [42]. These data suggest the changes in DADR2 in the CNS from subjects with schizophrenia are complex and will require studies of larger populations before the hypothesis that changes in DADR2 in the CNS from people with schizophrenia can be thoroughly tested.

Two studies have measured DADR2 in the CNS of subjects with schizophrenia and bipolar disorder (BPD) to determine whether changes in receptor density were associated with diagnoses or symptom profiles (Table 1). These studies reported an increase in [¹¹C]NMS binding in drug naïve people with schizophrenia, drug naïve people with BPD and drug free people with BPD [18, 19]. However, both studies suggested that levels of the binding of that radioligand was not altered in people with BPD who did not have psychotic symptoms, suggesting the increase in DADR2 is associated with a psychotic state rather than a specific diagnoses. These data must be interpreted with caution as the number of non-psychotic people with BPD was very small (*n* = 7) and interpreting the meaning of changes in [¹¹C]NMS is not straight forward.

In what are now extensive studies of DADR2 in the human CNS, it is significant that fewer females have been included (Table 1). However, no study has identified differences in binding with gender, a notion that was confirmed by a study specifically designed to address that question [30]. By contrast, some studies have reported that levels of dopamine DA-D2 receptor decreased with age in the frontal [24] and temporal cortices [24, 37] and striatum [19]. These data

add to findings from other neuroimaging studies using multiple ligands [19, 43, 44] and studies using postmortem tissue [45, 34] that have shown a loss of dopamine DA-D2 with aging in multiple CNS regions. Recent data has shown that changes in gene expression change with increasing duration of illness in the cortex of people with schizophrenia [46, 47] and that some of these may represent an accelerated aging process in people with the disorders [48]. This means that aging is an important confound that must be carefully controlled in all studies of DADR2 in the human CNS.

2.2. Findings on Dopamine-D1 Like Receptors

The DADR1 are the family of DADRs that do not have a high affinity for antipsychotic drugs but are critical in the physiological effects of dopamine in the CNS [49]. The DADR1 is the predominant family of dopamine receptors in the human cortex [50]. It is therefore significant that a study that failed to show a change in ligand binding to DADR2 in people with schizophrenia found that [¹¹C]SCH23390 binding to DADR1 was unchanged in the striatum but decreased by 15% and 20% in the prefrontal cortex of drug naïve and drug free people with the disorder, respectively [51] (Table 1). This study also reported that the decrease in DADR1 in the cortex of people with schizophrenia was inversely related to levels of negative symptomatology.

The notion of decreased DADR1 in the CNS from subjects with schizophrenia is supported by a study using [¹¹C]SCH23390 and [¹¹C]NNC 112, both of which bind to DADR1, which reported decreases in binding in frontal cortex (-29%, -32%), anterior cingulate (-25%, -28%), temporal cortex (-30%, -28%) and striatum (-21%, -22%) in people with the disorder [52]. However, it is notable that this study did not find changes in binding in the striatum and was carried out in people who had received antipsychotic drug treatment and had recently been switched to sulpiride. The effect of drug treatment could be significant given a recent study using drug naïve, drug free and treated people with schizophrenia suggested that ligand binding to DADR1 was restricted to, and increased in, the dorsolateral prefrontal cortex (32%), occipital frontal cortex (31%) and medial frontal cortex (22%) from the drug naïve subjects [53]. These data added to a previous study by this group that reported an increase in ligand binding to DADR1 in a mix of drug naïve and chronic drug-free people with schizophrenia [54]. Finally, the issue of the status of DADR1 levels in subjects with schizophrenia is further clouded by a study reporting no change in [¹¹C]SCH23390 binding to DADR1 in multiple cortical regions from people with schizophrenia [55].

The disparate results on DADR1 from people with schizophrenia reflect data obtained from postmortem studies that have reported unchanged (striatum [35, 56, 57]; cortex [40]) and increased (cortex [58, 59]) levels of that receptor in the CNS from subjects with schizophrenia. In addition, the potential for antipsychotic drugs to be a confounded is supported by reports that treating rats with such drugs causes changes in DADR1 which vary with drug, drug dose, treatment duration and CNS region [60-63]. It would therefore seem that more studies on DADR1 in drug naïve subjects with schizophrenia are needed to give a clearer view on the status of that family of receptors in the CNS of subjects with disorder.

2.3. Findings on the Dopamine Transporter

The dopamine transporter (DAT) is an important component of the dopaminergic system that is present on pre-synaptic dopaminergic neurons and acts to take up secreted dopamine back into the pre-synaptic neuron and has a critical role in regulating dopamine levels in the synapse [64]. Significantly, the great majority of neuroimaging studies suggest there is no change in the levels of DAT in the striatum from subjects with schizophrenia [65-72] (Table 1). However, one study found no changes in DAT in the striatum in a group of people with schizophrenia in the first episode [65] but did find a decrease (-11.5%) in levels of the transporter in the same CNS region from people in the chronic stage of the illness [73]. This raised the possibility that changes in DAT may appear with disease progression or because of treatment with antipsychotic drugs. However, another study has reported a small decrease (-9%) in levels of DAT in a group of drug naïve people with schizophrenia [74] and a subsequent study from this group showed that levels of DAT were significantly decreased in drug naïve subjects (-12%) and remained so after 4 weeks of antipsychotic drug treatment (-9%) [75]. This data were consistent with DAT been changed early after the onset of schizophrenia and that this change was not reversed by acute antipsychotic drug treatment. To cloud the issue further, another study reported a 50% increase in DAT in people with schizophrenia compared to controls and this compared to a 70% loss of DAT in a group of people with Parkinson's disease [76]. Finally, one study that failed to find a change in DAT in the striatum of drug naïve and drug free people with schizophrenia did report a 28% increase in the transporter in the thalamus from the same cohort. This latter finding could be indicating there may be region-specific changes in DAT, as well as dopamine receptors, in schizophrenia.

The majority of postmortem studies agree with results from neuroimaging that report levels of the dopamine transporter to be unchanged (striatum [35, 77, 78]; cortex [40]) in tissue from subjects with schizophrenia with only one study suggesting a decrease in the transporter in the striatum [79]. Similarly, studies on the effects of antipsychotic drug treatment have failed to show such treatments change the levels of DAT [80]. Therefore from both neuroimaging and post-mortem CNS studies it seems reasonable to conclude that there are not large changes in dopamine transporters in the striatum of people with schizophrenia and therefore changes in dopamine transporter levels are not likely be making a significant contribution to changes in extra-synaptic dopamine in people with the disorder.

2.4. The Dynamics of Dopamine Synthesis and Release

One aspect of neuroimaging studies that cannot be replicated using postmortem CNS is measuring parameters relating to the dynamics of neurotransmitter synthesis and release in the human CNS. In the case of dopamine, rates of neurotransmitter synthesis can be inferred by measuring [¹⁸F]fluorodopamine influx [81]. Rates of dopamine release have been estimated as the decrease in available ligand binding sited on the DADR2 due to the displacement by dopamine after a stimulus by a dopamine releasing agent such as amphetamine [82].

The outcome from studies on dopamine synthesis have been complex with the initial study reporting that the [18F]fluorodopamine influx constant (K_i) in putamen was 15% higher in people with schizophrenia compared to controls, with changes in caudate being smaller and lateralized to the left caudate [81] (Table 1). In a follow up study, this group confirmed that [18F]fluorodopamine uptake was increased in striatum in people with schizophrenia and that the K_i for [18F]fluorodopamine uptake was shown to have a negative correlation with depressive symptoms [83]. These findings were partly confirmed by a study which reported a significant decrease (-15%) in tracer uptake in ventral striatum with the same study reporting an increased (21%) in [18F]fluorodopamine uptake in posterior cingulate in people with the disorder [84]. Ongoing studies continue to suggest there are changes in dopamine synthesis in the CNS of subjects with schizophrenia. Hence, one study showed that the intrinsic clearance of [18F]fluorodopamine is 20–50% greater in the CNS of people with schizophrenia and there was also a 75–90% increase in the fractional rate constant for [18F]fluorodopamine elimination in people with the disorder [85]. Finally, the changes in [18F]fluorodopamine uptake have been used along with an Artificial Network Model to identify people with schizophrenia with 89% accuracy in a study where controls could be identified with a 94% [86]. If these data are correct they would suggest that, not only do people with schizophrenia have changes in dopamine synthesis but that these changes may be useful as a diagnostic biomarker.

The first study on amphetamine-induced dopamine release showed that the loss of [123I]iodobenzamide ([123I]IBZM) binding potential, a measure inversely related to levels of dopamine, was significantly greater in the striatum of people with schizophrenia ($-19.5 \pm 4.1\%$) compared to that in the control subjects ($-7.6 \pm 2.1\%$) [82] (Table 1). These data suggested there was an increased release of dopamine in response to amphetamine in people with the disorder. Further studies have shown the same outcome in drug naïve [87], drug free [88] and a mix of drug-free and treated [89] people with schizophrenia as well as people with schizotypal personality disorder [90].

The new insight into dynamic interactions of the dopaminergic system in the brain provided by neuroimaging seems to be pointing to problems in both the synthesis and release of dopamine in ~~at least~~ schizophrenia. Whilst there was postmortem CNS data that suggested such pre-synaptic problems may exist [8], having a direct confirmation that pre-synaptic processing of dopamine is an issue in schizophrenia is a significant step forward in understanding the pathophysiology of the disorder.

2.5. Interpreting Changes in Dopamine Pathways in Schizophrenia and Psychoses

Bringing together neuroimaging studies, that have mainly been carried out in people with schizophrenia, it would appear that there is an increased synthesis and release of dopamine in the striatum of people with the disorder which occurs in that absence of changes in levels of DADR2, DADR1 and DAT. This is a significantly different profile to that found in people who are methamphetamine users who have acute and chronic decreased levels of DADR2 [91] and DAT

[92]. Methamphetamine and other drugs of addiction act to increase release of dopamine in the brain [93] and therefore the changes in the CNS of people who use these drugs are likely to be compensatory mechanisms related to high levels of synaptic dopamine. This notion is partly supported by studies in acute Parkinson's disease, where there are decreased levels of synaptic dopamine [94] and where DADR2 are increased [95, 96]. Thus, current data would argue that, as well as changes in dopamine synthesis and release, there is a failure to down-regulate DADR2 in people with schizophrenia in the face of high levels of synaptic dopamine. This could suggest that mechanisms that are known to act to down-regulate DADR2 [97] may be affected by the pathophysiology of schizophrenia and / or the drive to a psychotic state.

3. NEUROIMAGING AND THE SEROTONIN HYPOTHESIS OF SCHIZOPHRENIA

The serotonin hypothesis of schizophrenia has its basis in the observation that people who have taken lysergic acid show a propensity to experience florid hallucinations [98]. This observation implicates the serotonergic system because lysergic acid binds to a number of serotonin receptors [99] and hence suggests the serotonergic system might be involved in the pathophysiology of psychotic disorders [100].

3.1. Findings on the Serotonin 2A Receptor

The first serotonergic marker to be studied in people with psychoses was the serotonin 2A receptor (5HT2AR). This was probably driven by the fact that a suitable ligand was available, the receptor was recognized as a target for second generation antipsychotic drugs [101] and levels of that receptor had been shown to be decreased in postmortem CNS from people with schizophrenia [102].

The first studies on 5HT2AR were in mixed cohorts of drug naïve and drug free people with schizophrenia and showed no differences in the level of receptor in the CNS of people with the disorder [103, 104, 105, 106] (Table 2; Fig. 1). By contrast, the first report of decreased 5HT2AR (-16%) in the CNS from subjects with schizophrenia was study of a cohort of purely drug naïve people with the disorder [107]. Since this finding, regional selective decreases in levels of 5HT2AR have been reported in people at high risk of developing schizophrenia [108], those in early and late prodromal stages of the disorder [109] and in a relatively large drug naïve cohort of people with the disorder [110]. Contrary to these reports is a study that reported a 40% increase in levels of 5HT2AR in a cohort of people in their first episode of schizophrenia [111]. Despite this later study, ~~overall~~ current data raises the intriguing possibility that levels of 5HT2AR may be affected early in the progression to frank schizophrenia and the differences present in the CNS in the early stages of the disorder either disappear as part of the pathophysiology of the disorder or due to drug treatment. The change in 5HT2AR early in the progression toward schizophrenia is interesting as it raises the possibility that abnormal levels of 5HT2AR may be present early in life and could therefore be affecting fetal development. This is significant because neurotransmitters systems are critical for normal maturation of the CNS [112] and therefore derangements of molecules such as the 5HT2AR early in life could

Table 1. Neuroimaging Studies on Dopaminergic Markers in the CNS of People with Psychiatric Disorders Using Positron Emission Tomography and Single Photon Emission Computer Tomography.

Target: Dopamine D2-like Receptors								
Technique	Diagnoses	CNS Region(s)	Radioligand	Treatment Groups	n	M : F	Outcome	Ref.
PET	Sz	Caudate Nucleus	NMS	Drug naïve Treated Controls	10 5 11	8 : 2 5 : 0 11	↑ 151 % ↑ 161 %	[13]
	Sz	Right and Left Putamen	RAC	Drug naïve Controls	15 14	9 : 6 10 : 4	No Difference	[14]
	Sz	Putamen	RAC	Drug naïve Controls	18 20	10 : 8 10 : 10	No Difference	[23]
	Sz	Striatum	BROMO	Drug naïve Briefly treated Controls	9 3 12	M M M	No Difference	[196]
	Sz	Striatum	BROMO	Drug naïve Briefly treated Controls	10 9 14	Na Na 14 : 0	No Difference	[25]
	Sz	Striatum	NMS	Chronic drug naïve Chronic drug free Controls	18 7 17	Na Na 13 : 4	↑ 106 %	[16]
	Sz	Striatum	NMS	Late onset Controls	13 17	3 / 10 13 / 4	↑ 10%	[20]
	Sz	Striatum	RAC	Drug naïve Controls	13 10	9 : 4 6 : 4	No Difference	[21]
	Sz	Striatum	NMS	Drug naïve Controls	7 7	5 : 2 7	No Difference	[22]
	Sz	Striatum	NMS	Drug naïve Drug free Controls	9 5 15	4 : 5 3 : 2 13 : 2	↑ 63%	[17]
	Sz	Anterior cingulate	FLB	Drug naïve Controls	11 18	11 : 0 18 : 0	↓ 12.5 Sz.	[36]
	Sz	Thalamus, anterior cingulate, frontal and temporal cortices	FLB	Drug naïve Controls	9 8	3 : 6 4 : 4	↓ in right medial thalamus.	[24]
	Sz	Caudate, putamen and thalamus	RAC	Drug naïve Controls	18 17	9 : 9 13 : 4	↓ in right thalamus	[42]
	Sz + SzAff + SzForm	Thalamus	FALL	Drug naïve + Drug Free Controls	12 3 15	10 : 5 9 : 6	No change across entire thalamus but ↓ 18% in medial dorsolateral nucleus and pulvinar.	[41]
	Sz and BPD	Striatum	NMS	Sz drug naïve BPD drug naïve BPD drug free Controls	10 11 3 12	8 : 2 6 : 5 3 : 0 9 : 3	↑ 147% Sz ↑ 82 % BPD with psychoses	[18]
	Sz and BPD	Striatum	NMS	Drug naïve Sz Psychotic BPD Non-psychotic BPD Controls	22 7 7 24	13 : 9 4 : 3 5 : 2 19 : 5	↑ 35% Sz ↑ 36% BPD with psychoses.	[19]

(Table 1) Contd....

Target: Dopamine D2-like Receptors								
Technique	Diagnoses	CNS Region(s)	Radioligand	Treatment Groups	n	M : F	Outcome	Ref.
SPECT	Sz	Striatum	IBMZ	Drug naïve Drug free Controls	17 3 20	Na Na 11 : 9	No Difference	[26]
	Sz and Sz-Aff	Basal Ganglia	IBMZ	Sz drug free Sz-affect drug free Controls	19 2 16	16 : 3 2 : 0 11 : 5	No Difference	[27]
	Sz	Basal Ganglia	IBMZ	Drug naïve Controls	23 20	11 : 12 8 : 10	No Difference	[28]
	Sz	Temporal cortices	EPI	Drug naïve Controls	7 7	3 : 4 4 : 3	↓ 29% temporal cortex	[37]
	Sz	Basal Ganglia / Frontal cortex	IBMZ	Drug naïve Drug free Controls	12 16 0	5 : 7 13 : 3	No Difference	[29]
	Sz + SzForm	Basal Ganglia / Frontal cortex	IBMZ	Drug naïve Controls	15 0	7 : 8	No Difference	[30]
	Sz		IBMZ	Drug naïve Controls	23 10	19 / 4 5 / 5	↓ 15% striatum	[197]
			IBMZ	Ultra High Risk Controls	14 15	12 / 4 13 / 2	No difference	[31]
Target: Dopamine D2-like Receptors and Dopamine Transporter								
	Sz	Striatum	IBMZ TROD	Drug naïve Controls	11 12	6 : 5 9 : 3	No difference	[68]
	Sz	Striatum	IBMZ TROD	First episode Controls	20 12	18 / 2 9 / 3	No difference	[71]
Target: Dopamine D2-like Receptors and Dopamine D1 Receptor								
PET	Sz	Striatum Prefrontal cortex Anterior Cingulate Temporal cortex	SCH23390 NMS	Drug naïve Drug free Controls	10 7 18	10 : 0 7 : 0 18 : 0	Striatum: No change DA-D1, No change DA-D2 Prefrontal cortex: drug naïve -15%, drug free -20%.	[51]
Target: Dopamine D1-like Receptors								
PET	Sz	Multiple cortical regions Striatum Thalamus	NNC	Drug naïve Chronic drug free Controls	7 9 16	3 / 13 5 / 11	↑ 28% dorsolateral prefrontal cortex	[54]
	Sz + SzForm	Multiple cortical and sub-cortical regions	SCH23390	Drug naïve Controls	10 10	8 / 2 8 / 2	No differences	[55]
								[198]
	Sz		SCH23390 NNC	Treated but switched to sulpride Controls	6 12	5 / 1 6 / 6	SCH23390 ↓ 29% frontal cortex, 25% anterior cingulate, 30% temporal cortex and 21% striatum. NNC ↓ 32% frontal cortex, 28% anterior cingulate, 28% temporal cortex and 22% striatum.	[52]

(Table 1) Contd....

Target: Dopamine D1-like Receptors								
Technique	Diagnoses	CNS Region(s)	Radioligand	Treatment Groups	n	M : F	Outcome	Ref.
	Sz	Multiple cortical regions Striatum	NNC	Drug naïve Chronic drug free Controls drug naïve Controls drug free	12 15 24 24	5 / 7 11 / 2 12 / 12 20 / 4	Drug naïve: ↑ 32% dorsolateral prefrontal cortex, 31% occipital frontal cortex and 22% medial frontal cortex. Others: No differences	[53]
Target: Dopamine Transporter								
PET	Sz	Caudate Putamen	PE	First episode, drug naïve Controls	9 9	6 / 3 6 / 3	No differences	[65]
	Sz	Caudate Putamen	PE	Chronic Control	8 8		↓ 11.5%	[73]
	Sz + SzForm	Caudate Putamen Thalamus Substantia Nigra	PE	Drug naïve Drug free Controls	6 2 12	6 / 2 10 / 2	28 % increase in thalamus	[72]
SPECT	Sz	Striatum	TROD	Drug naïve Controls	10 12	10 / 2	No differences	[67]
	Sz	Striatum	CIT	Chronic Treated Parkinson's Controls	6 10 5	6 / 0 5 / 0	50% increase in Sz and a 70% loss in PD	[76]
	Sz	Striatum	CIT	First episode developed Parkinson's First episode no Parkinson's Controls	10 10 10	6 / 4 8 / 2 6 / 4	↓ 9 % ↓ 9 %	[74]
	Sz	Striatum	TROD	First episode drug naïve Controls	10 10	6 / 4 6 / 4	No differences	[69]
	Sz	Striatum	TROD	First episode drug naïve Controls	28 12	23 / 5 10 / 2	No differences	[70]
	Sz	Striatum	CIT	Drug naïve with Treatment Follow Controls	20 15	14 / 6	↓ 12%	[75]
Target: Dopamine Turnover								
PET	Sz	Striatum	DOPA	Drug naïve Controls	7 8	4 / 3 6 / 2	↑ fluorodopa influx.	[81]
	Sz	Striatum	DOPA	Drug naïve Controls	10 13	4 / 6 8 / 5	↑ fluorodopa uptake in	[83]
	Sz	Eight cortical and sub-cortical regions	DOPA	Drug free Treated Controls	9 10 13	7 / 2 8 / 2 8 / 5	Drug free patients had a significant decrease (-15%) in tracer uptake in ventral striatum and an increased (21%) uptake in posterior cingulate.	[84]

(Table 1) Contd....

Target: Dopamine Turnover								
Technique	Diagnoses	CNS Region(s)	Radioligand	Treatment Groups	n	M : F	Outcome	Ref.
	Sz	Caudate, putamen, mid-brain, ventral striatum	DOPA	Drug Naïve Controls	8 15	8 / 0	↑ Intrinsic fluoro-dopa clearance 20–50%	[85]
	Sz	Striatum	DOPA	Paranoid Sz Drug Naïve Medication Free Treated Controls	19 4 3 12 31		Use an Artificial Network Model to classify people with Sz vs. controls. Claim 94% accuracy for controls and 89% for those with Sz.	[86]
Target: Amphetamine-induced dopamine release								
SPECT	Sz	Striatum	IBZM	Drug naïve = 1 Drug Free = 8 Treated = 6 Controls	15 15	14 / 1 14 / 1	↑ DA release	[82]
	Sz	Striatum	IBZM	Mixed treated and drug free Controls	11 12		↑ DA release	[89]
	Sz	Striatum	IBZM	Drug Free Controls	15 15	12 / 3 12 / 3	↑ DA release	[88]
	Sz-Typ	Striatum	IBZM	Unmedicated Controls	13 13	10 / 3 9 / 4	↑ DA release	[90]
	Sz	Striatum	IBZM	Drug Naïve Controls	6 8	4 / 2 2 / 6	↑ DA release	[87]

Abbreviations: BPD = bipolar disorders, BROMO = [⁷⁶Br]bromospiperone, DOPA = [18F]fluorodopamine, CIT = [¹²³I]FP-CIT, EPI = [¹²³I]epidepride, FALL = [18F]Fallypride, FLP = [¹¹C]FLB 457, IBMZ = [¹²³I]iodobenzamide, NMS = [¹¹C]methylnspiperone, NNC = [¹¹C]NNC112, PD = Parkinson's disease, PE = [¹¹C]PE2I, RAC = [¹¹C]raclopride, SCH23390 = [¹¹C]SCH23390, Sz = Schizophrenia, SzAff = schizoaffective disorder, SzForm = schizophreniform, Sz-Typ = schizotypal personality disorder, TROD = [^{99m}Tc]TRODAT.

result in abnormal CNS development. It is therefore intriguing to consider whether some of the structural and functional abnormalities that are being detected in specifically in people at high-risk of developing schizophrenia [113-115] may have resulted from alterations in levels of molecules such as the 5HT2AR in their CNS. Such outcomes may gain credence as we get a better understanding of the impact of changes in 5HT2AR on CNS development from genetically modified mice [116].

The majority of postmortem studies using postmortem tissue have also found decreased 5HT2AR in the cortex of subjects with schizophrenia [40, 117-125]. However, in studies using membrane based assays, rather than autoradiography, levels of 5HT2AR have been reported as either unchanged [126] or increased [127] in schizophrenia. It has been suggested that the discrepancies between these findings could be due to separating an endogenous regulator of 5HT2AR binding from the receptor when membranes are washed prior to binding assays being completed [128]. Finally, an autoradiography study of the caudate-putamen suggested that there was an increase in 5HT2R in tissue from subjects with schizophrenia [129]. Taking into account the majority of postmortem studies, there seems to be a growing consensus that 5HT2AR are decreased in the cortex of sub-

jects with schizophrenia and, for reasons yet to be explained, this is only detectable early in the progression to frank schizophrenia when using neuroimaging.

Neuroimaging data could also be interpreted as suggesting that decreases in 5HT2AR may disappear after treatment in subjects with schizophrenia. Significantly, studies in rats suggest that acute treatment with antipsychotic drugs that do not directly target the 5HT2AR do not affect CNS levels of the receptor [130-132] whereas treatment with antipsychotic drugs that target the receptor reduce its levels in the rat CNS [130-134]. These data would not support the notion that the apparent decrease in 5HT2AR in drug naïve people with schizophrenia disappears later in the disorder because of antipsychotic drug treatment. This leaves the intriguing possibility that decreased 5HT2AR early in people at high-risk for schizophrenia, when measured by neuroimaging, may provide an indication of a propensity to develop the frank disorder.

3.2. Findings on other Serotonergic Markers

There have been fewer studies using neuroimaging to measure levels of other serotonergic markers in the CNS of subjects with psychoses. Thus, three studies have reported levels of the 5HT1AR are not altered in the CNS of people

Table 2. Neuroimaging Studies on Non-Dopamine Markers Using Positron Emission Tomography and Single Photon Emission Computer Tomography in Subjects with Psychotic Subjects

Target: Serotonin 2A Receptor								
Technique	Diagnoses	CNS Region(s)	Radioligand	Treatment Groups	n	M : F	Significant Differences	Ref.
PET	Sz	4 cortical regions	SEPTO	Neuroleptic naïve + neuroleptic free Controls	14 15	10 / 4 8 / 7	No differences.	[103]
PET	Sz		SEPTO	Neuroleptic naïve Neuroleptic free Controls	10 3 26	10 / 3 11 / 15	No differences	[104]
PET	Sz	Frontal cortex	SEPTO	Neuroleptic naïve Controls	6 7	5 / 1 4 / 3	See Figure 1	[107]
PET	Sz	4 cortical regions	NMS	Neuroleptic naïve = 10 Neuroleptic free = 7	17 12		No difference.	[105]
PET	Sz		SEPTO	Drug Free Controls	13 35	11 / 2 15 / 20	No differences.	[106]
PET	Sz	5 CNS regions	ALTA	High Risk Controls	6 7	5 / 1 5 / 2	See Figure 1	[109]
PET	Sz	15 CNS Regions	ALTA	First Episode Controls	15 15	11 / 4 11 / 4	See Figure 1	[111]
PET	Sz	9 CNS regions measured in both hemispheres	ALTA	Early Prodromal Late Prodromal Controls	6 8 21	4 / 2 6 / 2 13 / 8	See Figure 1	[108]
PET	Sz	18 CNS Regions	ALTA	Drug naïve Control	30 30		See Figure 1	[110]
Target: Serotonin 1A Receptor								
PET	Sz	9 CNS regions	WAY	Drug naïve Controls	14 14	8 / 6 8 / 6	No differences	[135]
PET	Sz	8 CNS Regions	WAY	Drug naïve Drug free Controls	8 3 22	9 / 2 18 / 4	↓ 19% amygdala. No change prefrontal, temporal, occipital, parietal cortices or anterior cingulate, hip- pocampus or raphe	[138]
PET	Sz	5 CNS regions	WAY	Treated Clozapine treated Controls	11 11 11	11 / 0 11 / 0 11 / 0	No difference	[136]
PET	Sz + Sz-Aff	11 CNS Regions	WAY	Drug free Controls	22 18	16 / 6 15 / 3	No difference	[137]
Target: GABA _A Receptor								
SPECT	Sz + Sz-Aff	3 CNS regions	IOM	Drug free and first treatment Controls	15 12	14 / 1 11 / 1	No differences	[147]
SPECT	Sz	11 CNS regions	IOM	Neuroleptic free Treated Controls	5 11 16	16 / 0 16 / 0	No differences	[148]
SPECT	Sz		IOM	Treated Controls	25 24	25 / 0 24 / 0	No differences	[149]

(Table 2) Contd....

Target: GABA _A Receptor								
Technique	Diagnoses	CNS Region(s)	Radioligand	Treatment Groups	n	M : F	Significant Differences	Ref.
SPECT	Sz	10 CNS regions	RO	Neuroleptic naïve Drug Free Controls	6 5 12	6 / 5 12 / 0	No differences	[199]
Target: Peripheral Benzodiazepine Receptor								
PET	Sz	9 CNS regions	PK	Treated Controls	7 7	4 / 3 6 / 1	⬆51% hippocampus ⬇24% basal ganglia. No change in frontal, occipital, temporal, parietal lobes, thalamus, midbrain, pons or cerebellum.	[156]
PET	Sz	8 CNS Regions	DAA	Treated Controls	14 14	8 / 6 9 / 5	No Change	[155]
Target: NMDA Receptor								
SPECT	Sz	Thalamus and striatum	CNS	Drug Free Treated Controls	5 7 10		No differences	[159]
SPECT	Sz	Not stated	CNS	Drug Free Typical treatment Clozapine Treated Controls	5 7 9 13		⬇-93% binding in left hippocampus in drug free subjects. No change right hippocampus.	[160]
Target: Muscarinic Receptors								
SPECT	Sz	8 CNS Regions	QNB	Drug free Controls	12 12	8 / 4 8 / 4	Caudate = 37%, Putamen = -29%, Thalamus = -30%, Medial frontal = 27%, Lateral frontal = 25%, Temporal = -33%, Occipital = -20%.	[170]
Target: Cannabinoid 1 Receptor								
PET	Sz	19 CNS regions	OMAR	Treated Controls	10 10	10 / 0 10 / 0	Overall increase across regions with a within region increase in PONS	[187]
Target: Histamine H1 Receptor								
PET	Sz	10 cortical regions	DOX	Treated Controls	10 10	10 / 0	⬇-62% prefrontal cortex and -58% cingulate gyrus	[193]

Abbreviations: ALTA = [¹⁸F]altanserin, CNS = [¹²³I]CNS 1261, DAA = [¹¹C]DAA1106, DOX = [¹¹C]doxepin, IOM = [¹²³I]iomazenil, NMS = [¹¹C]methylspiperone, OMAR = [¹¹C]OMAR, PK = [¹¹C]-(R)-PK11195, QNB = [¹²³I]QNB, RO = [¹¹C]Ro15-4513, SEPTO = [¹⁸SF]setoperone, Sz = Schizophrenia, SzAff = schizoaffective disorder, WAY = [¹¹C]WAY100635

with schizophrenia [135-137] whilst one study has reported a 19% decrease in the 5HT_{1A}R in the amygdala but not seven other CNS regions from subjects with the disorder [138]. These findings are therefore in general agreement with studies using postmortem CNS that have failed to show changes in 5HT_{1A}R in the cortex of subjects with schizophrenia [139, 140] rather than the majority of studies which report increased levels of those receptors in subjects with the disorder

[119, 141-144]. At this point it is unclear as to why, in the case of the 5HT_{1A}R, there are discrepancies in findings between postmortem studies and neuroimaging. This is particularly the case given antipsychotic treatment in rats does not appear to affect levels of that receptor [119].

In addition to studies on serotonin receptors, there has been a limited number of studies using neuroimaging that

Fig. (1). Region-specific changes in levels of ligand binding to the serotonin 2A receptor as measured in neuroimaging studies in people at high-risk of developing schizophrenia or in the prodromal phase, first episode or established phase of the disorder. Individuals with frank schizophrenia are in drug naïve or drug free states during CNS neuroimaging.

suggest levels of the serotonin transporter are not altered in the CNS of subjects with schizophrenia [66, 145] which is in line with postmortem studies [146].

4. NEUROIMAGING STUDIES ON OTHER NEUROTRANSMITTER SYSTEMS IN SCHIZOPHRENIA

There have been few other neuroimaging studies on other neurotransmitter systems in the CNS of subjects with schizophrenia. A number of studies have reported there is no change in levels of the benzodiazepine binding site on the GABA_A receptor in the CNS of subjects with the disorder [147-149]. These findings agree with the majority of findings on that binding site in postmortem tissue from subjects with the schizophrenia [150-154]. One neuroimaging study has shown that the peripheral benzodiazepine receptor is unchanged in 8 CNS regions from drug treated people with schizophrenia [155] which compares to a second study that reported levels of the receptor to be increased (51%) in the hippocampus, decreased in the basal ganglia (-24%) but unaltered in 7 other CNS regions from a cohort of treated people with the disorder [156]. These data are different to a postmortem study that found decreased levels of peripheral benzodiazepine receptor in the superior parietal cortex, primary visual area and putamen from people with schizophrenia [157]. Thus, further studies on the peripheral benzodiazepine receptor in schizophrenia are required to understand what may be occurring with this binding site, which is predominantly present on astrocytes and microglia and may be a marker of inflammatory activity [158].

Neuroimaging studies of glutamatergic markers have focused on the NMDA receptor with one study reporting no change in [¹²³I]CNS 1261 binding to that receptor in the thalamus and striatum from people with schizophrenia [159]. Subsequently, the same group has reported a decrease in levels of the NMDA receptor in the left, but not right, hippocampus from people with the disorder [160]. Significantly, a number of postmortem studies have failed to show any changes in NMDA receptors in the hippocampus [161-164] and striatum [165, 166] from people with schizophrenia. In the thalamus, levels NMDA receptors have been reported as increased [167], unchanged [168] or lower [169] in tissue from people with the disorder. Hence, there is a clear need for more studies to try and harmonize data on possible changes in the NMDA receptor in schizophrenia.

One study has reported widespread decreases in [¹²³I]iodoquinclidinyl benzilate ([¹²³I]IQNB) to muscarinic receptors in the CNS from drug free people with schizophrenia [170]. Significantly, there are now many postmortem studies suggesting muscarinic receptors are decreased in the cortex of people with schizophrenia [171-183]. Moreover, a recent study has confirmed the widespread decreases in muscarinic receptors reported in the neuroimaging study using postmortem CNS [183]. In addition, postmortem studies suggest it is the muscarinic M1 receptor that is altered in the cortex of people with schizophrenia [175, 184] whereas it is possible that other muscarinic receptors are altered in the hippocampus [179], striatum [185] and thalamus [186] of people with the disorder.

One study has also measured [^{11}C] OMAR binding to the CB1 receptor and has reported an all of CNS increase in ligand binding with a significant within region increase (23%) in binding detected in the Pons [187]. These data tend to support previous postmortem studies that have suggested levels of CB1 receptors are increased in the CNS of subjects with schizophrenia [188, 189] rather than those suggesting the levels of that receptor are unchanged [190] or decreased [191] in the CNS of people with the disorder. Further study of the CB1 receptor in the CNS of subjects with schizophrenia would therefore be worthwhile as they may give a better understanding as to why cannabis use may precipitate or worsen the symptoms of the disorder [192].

Finally, one neuroimaging study has reported marked decreases in [^{11}C]doxepin binding to the histamine H1 receptor in the frontal and prefrontal (-62 %) cortices and the cingulate gyrus (-58%) in people with schizophrenia [193]. These data partially support a postmortem finding of decreases in the same receptor in the prefrontal cortex from people with the disorder [194].

5. CONCLUDING REMARKS

Findings from molecular neuroimaging studies are now clearly impacting on our understanding of the neurochemistry of schizophrenia. As with other methodologies, such studies have methodological confounds which include limitations on the number of available ligands limiting the number of molecules that can be studied, limitations on the number of scans per individual because of cumulative radioactive load and the practical aspects of the methodologies limiting diagnostic cohort sizes. The latter issue is of growing significance with the increasing acknowledgement that schizophrenia is a syndrome and that not being able to dissect the syndrome into individual diagnostically homogenous groups is limiting the progression of our understanding of the causes of the schizophrenias [195]. On the other hand, neuroimaging could be a front line tool in measuring CNS biomarkers that allow the separation of schizophrenia into sub-groups, such as the sub-group that has a marked loss of cortical muscarinic receptors [181]. Therefore the ongoing development of ligands to be used with molecular imaging technology is critical, as is the capacity to increase the cohort sizes studied.

At a pragmatic level, neuroimaging studies of some markers in the CNS of subjects with people with schizophrenia are confirming findings from studies using postmortem CNS but in drug naïve and drug free people. Such findings decrease concerns that such postmortem studies are reflecting some postmortem artifact or a simple drug effect. However, neuroimaging studies are producing exciting novel findings in their own right. Thus, molecular imaging has revealed abnormalities in the synthesis and release of dopamine in the CNS from subjects with schizophrenia; an effect that may be compounded by a failure to appropriately down-regulate DADR2 in the caudate nucleus. In addition, data suggests that decreased levels of 5HT2AR occur early in the progression towards schizophrenia raising the intriguing possibility that decreased 5HT2AR may be a marker for those at risk or in the prodromal phase that are likely to progress to frank illness. Such findings cannot be made using any other technology yet available and contribute a significant increase in our knowledge on the pathophysiology of schizophrenia.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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