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Review article

PET imaging of synaptic density: A new tool for investigation of neuropsychiatric diseases

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ABSTRACT

Synaptic vesicle glycoprotein 2A (SV2A) is expressed ubiquitously in neurons of the central nervous system, and is the binding target of the anti-epileptic drug levetiracetam. Because of the availability of positron emission tomography (PET) ligands targeting SV2A, there is increasing enthusiasm on the use of SV2A PET to study a variety of neuropsychiatric diseases. This review discusses the recent development of radioligands for PET imaging of SV2A and their potential use in the research and diagnosis of CNS diseases.

1. Introduction

Synapses are essential for neurotransmission, and synaptic abnormality is associated with a variety of neuropsychiatric disorders, *e.g.*, Alzheimer's disease (AD), Parkinson's disease (PD), autism spectrum disorder (ASD), Down syndrome, epilepsy, Huntington's disease, and schizophrenia [51,52]. A healthy human brain contains hundreds of billions of neurons, linking to each other through synapses. A single neuron may have up to tens of thousands of synaptic contacts with other neurons. Therefore, hundreds of trillions of synapses exist in the human brain, with about 150–164 trillion synapses in the cerebral neocortex [68,86]. Regional synaptic density is traditionally estimated *via* stereology, immunohistochemistry, and electron microscopy [15]. As dysfunction or loss of synapses is related to a series of neuropsychiatric disorders, non-invasive *in vivo* imaging and quantification of synaptic density might allow early detection, staging, and prognosis of these diseases. Until recently, however, investigation of synapses and their dynamic changes in living subjects has been limited by the lack of a suitable *in vivo* imaging biomarker for synapses. Positron emission tomography (PET) imaging of synaptic vesicle glycoprotein 2A (SV2A) was developed as the first-in-class noninvasive method to measure synaptic density *in vivo* [29].

Synaptic vesicle glycoprotein 2 (SV2) is one type of synaptic vesicle (SV) proteins in the presynaptic compartment. SV2 comprises of three isoforms, SV2A, SV2B, and SV2C. They are highly conserved 12-transmembrane glycoproteins expressed on secretory vesicles of neurons and endocrine cells of vertebrates [12]. Of the three SV2 isoforms, only SV2A is expressed ubiquitously in glutamatergic and GABAergic neurons of the central nervous system, neuroendocrine cells, and ganglia in the peripheral nervous system [5,21,25,69]. SV2A is also the biological target of the anti-epileptic drugs levetiracetam (Keppra®) and brivaracetam [32,33,57].

Because SV2A is ubiquitously expressed in essentially all presynaptic vesicles [5], it can be used as a suitable biomarker for synaptic density among other proteins expressed in the presynaptic proteome and synaptic vesicles [7]. We have recently demonstrated that SV2A can be imaged and quantified by PET imaging with the novel SV2A-specific radioligand [^{11}C]UCB-J [30,66]. Further, we have demonstrated that SV2A PET signals correlated with SV2A expression levels measured *in vitro* in different regions of the nonhuman primate brain, and that brain regional SV2A levels closely correlated with those of synaptophysin, another commonly used marker for synaptic density [29]. Hence, *in vivo* imaging of synaptic density has now become possible with the use of SV2A PET. In this brief review, we illustrate recent developments in SV2A PET imaging agents, and discuss the potential applications of SV2A PET in the investigations of neuropsychiatric

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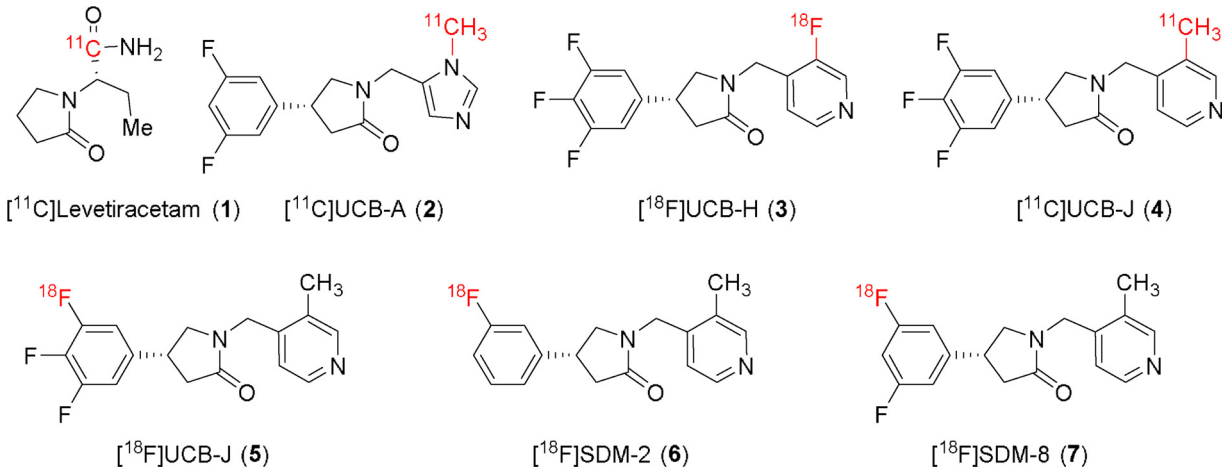

Fig. 1. Structures of SV2A PET ligands [^{11}C]levetiracetam (**1**), [^{11}C]UCB-A (**2**), [^{18}F]UCB-H (**3**), [^{11}C]UCB-J (**4**), [^{18}F]UCB-J (**5**), [^{18}F]SDM-2 (**6**), and [^{18}F]SDM-8 (**7**).

diseases [72].

2. Development of SV2A PET imaging agents to measure synaptic density *in vivo*

Because levetiracetam binds specifically to SV2A, it was labeled with carbon-11 (^{11}C) in an attempt to use [^{11}C]levetiracetam (**1**, Fig. 1) as an *in vivo* SV2A PET imaging agent [13]. However, the binding affinity of levetiracetam is rather low (K_i = 1.74 μM) [20], and thus the use of [^{11}C]levetiracetam is unlikely to provide meaningful PET signals. Based on the common pharmacophore of levetiracetam and brivaracetam, SV2A-specific ligands with improved binding affinities were discovered as potential candidates for SV2A PET imaging [63]. We and other labs have tested [^{11}C]UCB-A (**2**) [27], [^{18}F]UCB-H (**3**) [8,92,93], and [^{11}C]UCB-J (**4**) [65] (Fig. 1) in nonhuman primates, and found that [^{11}C]UCB-J has the best pharmacokinetic and imaging characteristics: high brain uptake, fast and reversible tissue binding kinetics, and high specific binding signals as measured by non-displaceable binding potential (BP_{ND}) values across different brain regions, as well as moderately fast metabolism and high free fraction in the plasma [66]. On the other hand, the uptake rate of [^{11}C]UCB-A in monkey brains was slow and did not reach equilibrium within hours, making the quantification analysis rather challenging [2]. With a lower SV2A binding affinity (pIC_{50} = 7.8 for [^{18}F]UCB-H, *vs*. 8.2 for [^{11}C]UCB-J) [63], [^{18}F]UCB-H provided low specific binding signals in the monkey brain [66]. When the three SV2A ligands were translated to human studies, the clinical data turned out to be consistent with preclinical results, with [^{11}C]UCB-J showing ideal imaging characteristics and high specific binding signals [29], while [^{11}C]UCB-A presenting slow binding kinetics in the human brain and challenges in quantitative analysis [56], and [^{18}F]UCB-H displaying rather low specific binding signals [4]. Therefore, [^{11}C]UCB-A and [^{18}F]UCB-H have significant limitations as PET radioligands for imaging and quantifying SV2A in human brains.

Although [^{11}C]UCB-J possesses ideal imaging and *in vivo* binding characteristics, the short radioactive half-life of carbon-11 (20.4 min) limits its production and use only to PET centers with onsite cyclotrons. Therefore, we set out to develop ^{18}F-labeled SV2A ligands to improve the accessibility, enable multicenter clinical trials, and accelerate their potential diagnostic applications in the clinic. Our early exploration resulted in [^{18}F]UCB-J (**5**) (Fig. 1) [54]. Evaluation of [^{18}F]UCB-J in nonhuman primates revealed that its pharmacokinetics (Fig. 2), regional distribution and BP_{ND} values were the same as those of [^{11}C]UCB-J (Table 1). Our ongoing evaluation of mono- and di-fluorinated analogs of UCB-J then led to the discovery of novel ^{18}F-labeled SV2A PET tracers, *e.g.*, [^{18}F]SDM-2 (**6**) [14] and [^{18}F]SDM-8 (**7**) [53] (Fig. 1). Pharmacokinetics of [^{18}F]SDM-2 in brain is faster than [^{11}C]UCB-J (Fig. 2), while regional BP_{ND} values are comparable (Table 1). On the other hand, [^{18}F]SDM-8 exhibits pharmacokinetics analogous to that of [^{11}C]UCB-J (Fig. 2), with regional BP_{ND} values higher than those of [^{11}C]UCB-J (Table 1) [1]. The availability of ^{18}F-labeled SV2A PET imaging probes thus opened the opportunity to validate SV2A PET clinically in a variety of neuropsychiatric diseases through multicenter clinical trials. Translations of these newly discovered ^{18}F-labeled SV2A PET tracers with superior imaging characteristics are underway at the Yale PET Center in a first-in-human study.

3. Applications of SV2A PET imaging in the investigation of neuropsychiatric disorders

3.1. PET imaging of SV2A in AD

AD affects more than 35 million people worldwide, and the number is estimated to quadruple in 40 years if there remains no cure [37]. AD is characterized by the accumulation of β-amyloid (aβ) plaques and hyperphosphorylated tau protein aggregates, with significant loss of neurons and atrophy at late stage, and can only be definitively diagnosed with postmortem histology staining of brain tissues [22,83,95]. Early symptoms of AD are marked by the impairment of declarative memories, and accumulating evidence suggests that this occurs as the hippocampal synapses are compromised by soluble β-amyloid protein oligomers during the earliest phases of AD [46–48]. Evidence also suggests that neuropathophysiological changes occur many years, if not decades, before clinical presentations start, with synapse loss preceding the accumulation of aβ plaques [80]. As one of the earliest and most consistent hallmarks of AD, regional synapse loss correlates with the severity of AD from a postmortem study of AD patients [77]. Regional synapse loss in the hippocampus and prefrontal cortex is also directly related to memory and cognitive dysfunction in prodromal AD [78]. This might happen before the extensive onset of aβ plaques and hyperphosphorylated tau tangles [81], with soluble oligomeric aβ as the main culprit for synaptic toxicity [38]. Based on this concept, interventions targeting to interrupt the toxic interactions between aβ oligomers and synapses/neurons, *e.g.*, metabotropic glutamate receptor-5 (mGluR5) antagonist, sigma-2 receptor antagonist, and α7 nicotinic acetylcholine receptor (α7 nAChR) agonist, *etc.* are under active pursuit [10,34,40,41,55,82]. SV2A PET, as a synapse marker, will be a suitable method for monitoring the therapeutic effects of these new interventions [88]. Longitudinal SV2A, aβ, and tau PET imaging covering the whole spectrum from preclinical AD to dementia could provide temporal information and hints on the relationship of these AD hallmarks.

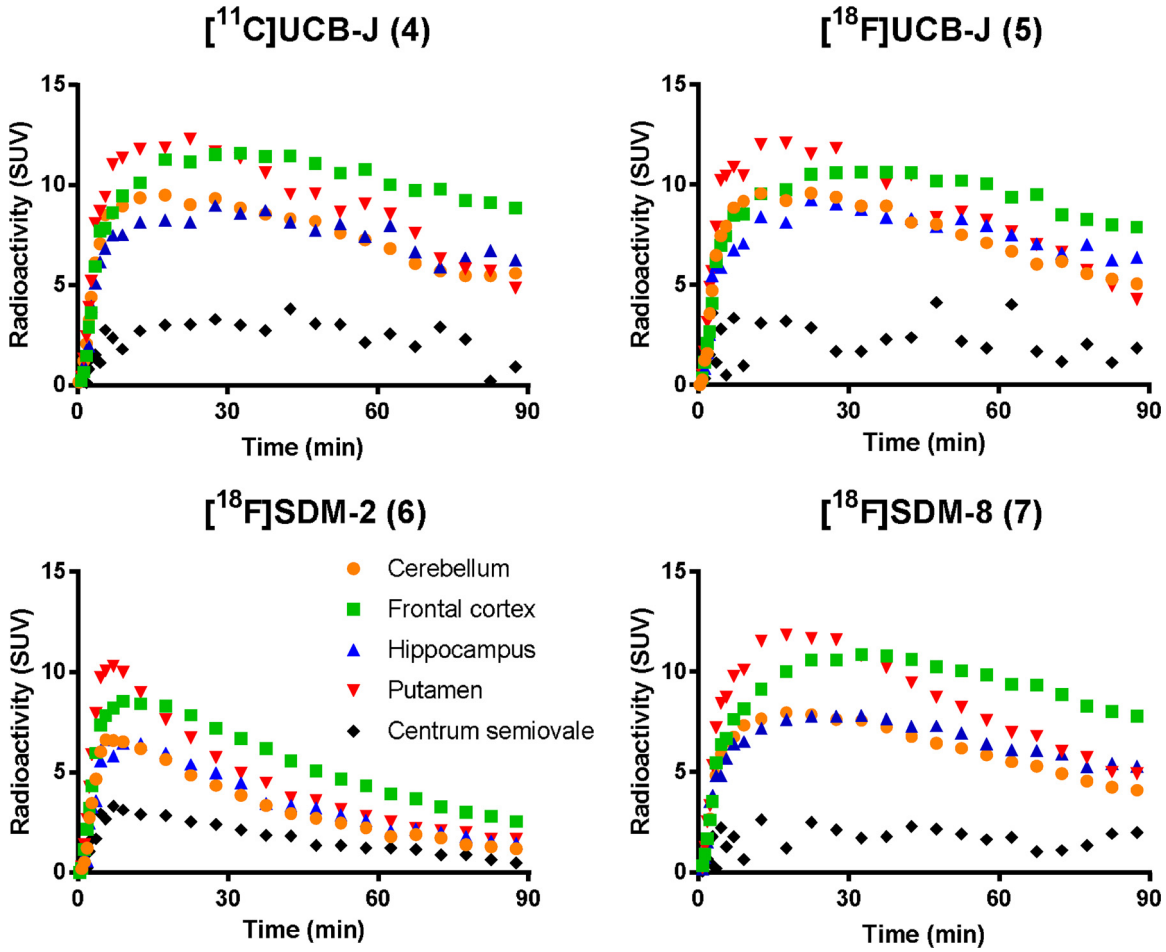

Fig. 2. Time-activity curves of SV2A PET ligands [^{11}C]UCB-J (**4**), [^{18}F]UCB-J (**5**), [^{18}F]SDM-2 (**6**), and [^{18}F]SDM-8 (**7**) in the same rhesus monkey brain.

Table 1
Regional BP_{ND} values[a] for SV2A PET ligands [^{18}F]UCB-J (**5**), [^{18}F]SDM-2 (**6**), [^{18}F]SDM-8 (**7**) in rhesus monkey brains, in comparison with those of [^{11}C]UCB-J (**4**).

Brain region	[^{18}F]UCB-J (n = 3)	[^{18}F]SDM-2 (n = 3)	[^{18}F]SDM-8 (n = 2)	[^{11}C]UCB-J (n = 6)
Frontal cortex	3.90	3.29	4.26	3.18
Occipital cortex	3.35	2.90	3.75	2.97
Temporal cortex	3.14	2.63	3.60	2.79
Putamen	2.62	2.21	3.03	2.42
Caudate nucleus	2.54	2.29	2.93	2.40
Thalamus	2.53	2.18	3.08	2.03
Hippocampus	1.99	1.58	2.36	1.59
Amygdala	1.65	1.05	1.70	0.85

[a] Values are the averages of n measurements.

A SV2A PET imaging study using [^{11}C]UCB-J in 10 MCI/AD patients and 11 age-matched cognitively normal subjects demonstrated significant synapse loss in the hippocampus of MCI/AD patients relative to controls (41% decrease in BP_{ND}, $p = 0.005$) (Fig. 3) [6,16,62], which is consistent with previous postmortem studies in MCI and AD [60,75,77,78]. Further evaluations of SV2A PET in AD will explore the differences in pattern of changes in the AD brain that may be revealed by SV2A, FDG metabolism, aβ, and tau PET, and the underlying mechanisms. Additional research will explore the etiology of synapse loss in AD, which may confirm or challenge the current aβ plaque hypothesis, or even lead to new hypothesis on AD pathogenesis. Further, recent preclinical evidence pointed to the contribution of immunoreaction to early synapse loss in rodent models of AD [38]. Hence, clinical PET imaging studies using SV2A and relevant immunoimaging agents will be able to probe the relationship between abnormal immune reactions and early synapse loss in MCI patients. This could potentially lead to identification of new therapeutic targets and accelerate the discovery of a cure for AD. Finally, in clinical trials of new generations of AD therapeutics, SV2A PET can be used as an objective tool for screening patients, endpoint measurement, and safety check. To this end, Cognition Therapeutics in collaboration with Yale School of Medicine has embarked on a pilot PET study using [^{11}C]UCB-J to evaluate the effect of treatment with the Sigma 2 receptor antagonist CT1812 on synaptic density in participants with mild to moderate AD (NCT03493282).

3.2. PET imaging of SV2A in PD

As the second most common neurodegenerative disease after AD, Parkinson's disease (PD) affects more than 10 million people worldwide, and causes enormous socioeconomic burden. There is evidence showing synaptic density changes in PD animal models and postmortem brain tissues of PD patients [70]. Though the loss of dopaminergic neurons in the striatum leads to the symptomatic disconnection of thought and action [3], synaptic loss has also been found outside of the nigrostriatal system and involves non-dopaminergic neurons in the cortex in PD [39]. Hence, synaptic dysfunction is centrally involved in PD and regional synaptic density changes are characteristic in its pathogenesis. SV2A PET imaging of synaptic density in the brains of PD patients may not only reveal disease progression, but also serve as a diagnosis or prognosis tool to facilitate the development of more effective disease-modifying interventions. A pilot SV2A PET imaging

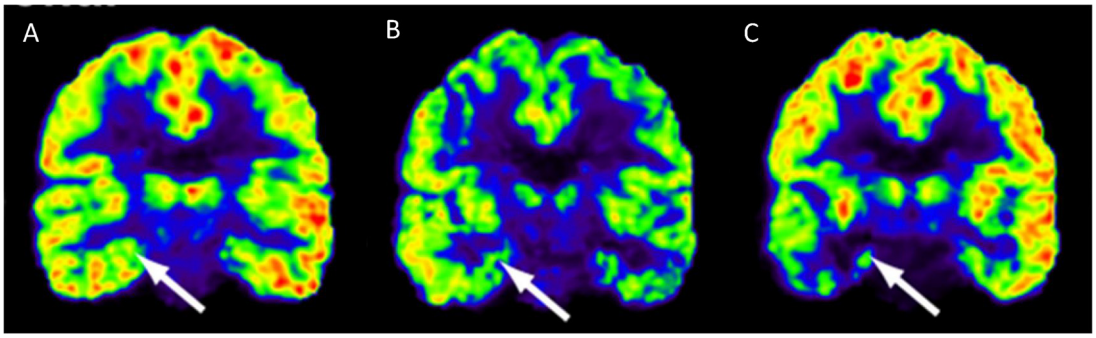

Fig. 3. Parametric SV2A PET V_T mapping of a healthy control (A), a PIB-positive MCI patient (B), and an AD patient (C) using [^{11}C]UCB-J (**4**). There is a discernable reduction of SV2A binding in the hippocampus of the MCI and AD patients (denoted by the arrows).

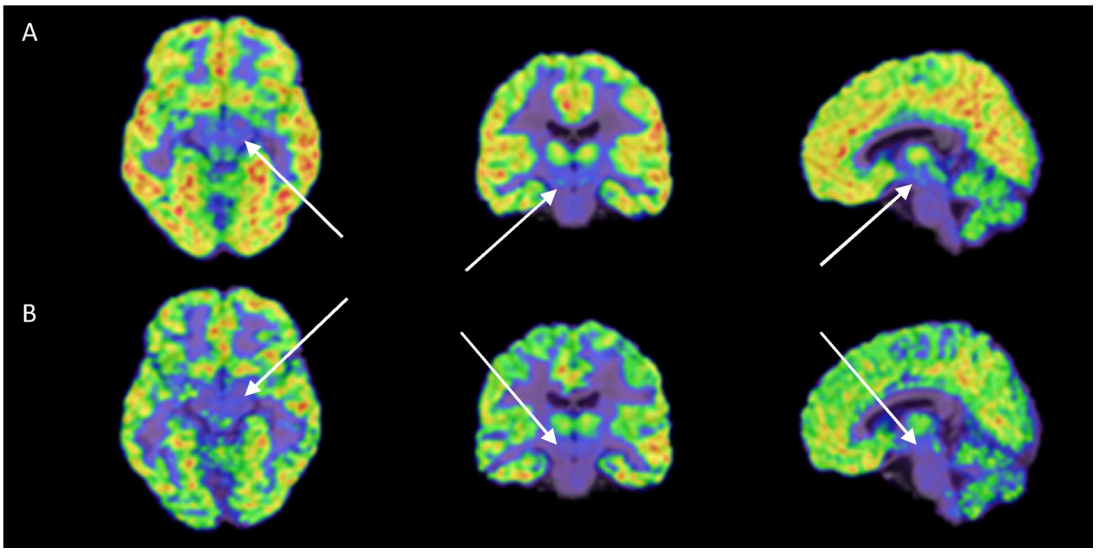

Fig. 4. Parametric SV2A PET V_T mapping of a representative healthy control (A) and a PD patient (B) using [^{11}C]UCB-J (**4**). There is a global reduction in SV2A binding across brain regions, with the most significant decrease (25%) in the substantia nigra (denoted by the arrows).

study in two PD subjects found the most significant synapse loss in the substantia nigra (25% lower uptake relative to healthy controls) (Fig. 4). Although larger cohort studies are currently underway to understand the usefulness and meaning of SV2A PET imaging in PD, these preliminary results have been very encouraging and constitute the first *in vivo* detection of synaptic changes in PD.

3.3. PET imaging of SV2A in epilepsy

Epilepsy is the fourth most common neurological disorder that affects people of all ages, with a prevalence rate of 0.5–1% [9,71]. Patients with glioma often develop epilepsy [45]. Epilepsy involves spontaneous and recurrent seizures spreading from the seizure onset zone (SOZ). Surgical resection of the epileptogenic tissue in the SOZ is a common practice in treating adult epilepsy patients, especially those with medically refractory epilepsy [43]. SOZ can be localized through video/EEG monitoring, magnetic resonance imaging, magnetoencephalography, and PET imaging [59]. ^{18}F-FDG is the standard radiotracer used in PET imaging and identification of SOZ in the clinic, although other radiotracers have also been tested for SOZ identification, *e.g.*, the $GABA_A$ receptor tracer [^{11}C]flumazenil, the serotonin 5-HT_{1A} receptor tracer [^{18}F]MPPF, and [^{11}C]alpha-methyltryptophan for serotonin synthesis [87].

SV2A is the binding site for the antiepileptic drugs (AEDs) levetiracetam and brivaracetam [32,33,57]. Therefore, SV2A may be an important biomarker in epilepsy. For example, mice with SV2A mutation develop severe seizure phenotype [19,42], and studies in rat models of epilepsy suggest the loss of SV2A as a contributing factor in epileptogenesis and pharmacoresistance [35,90,91]. In a post-mortem study, SV2A expression was found to be reduced by 30–50% in the anterior temporal neocortex of patients with temporal lobe epilepsy (TLE) [18,28,90]. Hence, PET imaging of SV2A might be useful for SOZ identification in epilepsy patients. Indeed, in a preliminary study, we demonstrated that [^{11}C]UCB-J (**4**) binding was asymmetric in the mesial temporal lobe in three subjects with TLE, consistent with SV2A loss in the ipsilateral mesial temporal lobe [29]. Thus, SV2A PET might provide a promising biomarker in the pre-surgery identification of SOZ in TLE patients.

3.4. PET imaging of SV2A in other neuropsychiatric disorders

Stroke is another devastating disease that has high mortality and morbidity rates. As the most commonly used clinical outcome measure for stroke in clinical trials, the modified ranking scale (mRS), which measures the degree of disability or dependence in the daily activities of the stroke patients, is subjective. On the other hand, one of the pathological features of stroke is synaptic deficits, with recovery of motor and memory functions after stroke accompanied by the increase in synaptic density. Studies in cortical stroke models have found a correlation between motor recovery and the expression level of synaptophysin, a biomarker of synaptic density [85]. Measurement of synaptic density by SV2A PET may provide an objective measure of disease progression and treatment efficacy.

Multiple sclerosis (MS) is a neurological disorder that can lead to

Table 2
Literature summary of SV2A PET studies using [^{11}C]UCB-J in neuropsychiatric disorders.

Year	Subjects	Key Findings
2018 [16,62]	10 AD patients and 11 healthy controls	Reduction of SV2A binding in hippocampus of AD patients
2017 [73]	6 schizophrenia patients and matched healthy controls	Global reduction of SV2A binding with greatest group difference in amygdala
2017 [26]	10 MDD patients and 7 healthy controls	15–17% reduction of SV2A in dorsolateral and ventromedial PFC in MDD patients
2016 [29]	Baboon, 10 healthy human subjects, 3 epilepsy patients	Correlation of SV2A PET with SV2A and synaptophysin protein expression; ~52% asymmetry in hippocampus of epilepsy patients

disability from cognitive dysfunction [17]. Cognitive deficits have been reported in 40–65% of MS patients at all stages and in all subtypes [50]. These cognitive deficits are related to demyelination associated with loss of synaptic density and brain atrophy [24]. Postmortem brain pathology showed hippocampal demyelination in MS as well as significant synaptic density loss (~50%) [24,64,94]. Significant reduction of cortical axonal density was observed only in demyelinated areas of cortical gray matter, but loss of synapses was present also in normal appearing gray matter [44]. Hence, as a synaptic density biomarker, SV2A PET imaging may be used to monitor the progression of MS in relation to cognitive dysfunction, and treatment effects of disease-modifying therapies. MS patients also often suffer from disabling tremors which are difficult to treat [84] and muscle spasticity[36]. Both of these conditions have been shown to improve by levetiracetam [36,84], leading to the possibility of SV2A PET imaging in these symptoms as well.

Huntington's disease (HD) is a neurodegenerative autosomal dominant disease caused by a CAG triplet expansion in the huntingtin gene [58]. Though the exact pathogenesis of HD is not well understood, previous work has shown a cascade of molecular and cellular changes, including neuronal dysfunction and death in brain regions such as the cerebral cortex and striatum [76]. Clinical characterizations of HD are progressive movement disorders, cognitive deficits and psychiatric symptoms [67]. Synaptic density changes have been implicated as a core feature of HD, with evidence of an increase in dendritic branching, spine density and size at mild stages of the disease and a decrease in later stages of the disease [31]. Both preclinical and clinical studies have shown reasonable consistency at molecular, physiological and structural levels that altered synapses are integral to the HD process. Because molecular changes in pre- and post-synaptic proteins precede structural abnormalities in dendrites and are correlated with specific cognitive and psychiatric deficits, such as learning and memory, imaging synaptic density in HD with SV2A PET could possibly be used as a biomarker to track presymptomatic HD progression, and to evaluate preclinical treatment effect.

Autism spectrum disorder (ASD) is a rather complex brain disease with strong genetic contributions. The majority of the genes implicated in ASD have a role in modulating synaptic plasticity through chromatin remodeling and transcription, protein synthesis, actin cytoskeleton dynamics or synaptic transmission [11]. Even though most cases of ASD remain idiopathic, the known etiologic contributors of ASD point to the central importance of synaptic alterations for the likely pathogenesis of the disease. SV2A PET thus would serve as a powerful tool to explore the relation of temporal and regional synaptic density changes with the phenotypes of ASD, and as a complementary modality to current diagnostic tools.

Given the lack of reliable biomarkers and the central convergence of synaptic dysfunction in psychiatric disorders such as depression [23,26], schizophrenia [61,73,74,79], anxiety [49], and addictive disorders [89], as well as in various movement disorders, (*e.g.*, dystonia, chorea, ataxia, essential tremor, tics and Tourette syndrome), detection of synaptic density changes with SV2A PET could be poised to make significant advances in understanding the etiology and effective treatments of these diseases. Current literature on SV2A PET imaging in neuropsychiatric disorders is summarized in Table 2.

4. Perspectives and future directions

SV2A has shown great promise as a biomarker for synaptic density, because of its ubiquitous expression in synapses. Although the clinical utility of SV2A imaging is largely speculative at this point, SV2A PET has the potential to be an important and valuable biomarker in the study, diagnosis, and staging of a variety of neurodegenerative and neuropsychiatric disorders, as well as in the evaluation of therapeutic effects. Clinical validation studies of this method are needed to pave the way for its uses in clinics. Nonetheless, with the emergence of more readily available ^{18}F-labeled SV2A imaging probes, SV2A PET is expected to lead to new insights into the etiology of, and treatment strategies for neuropsychiatric disorders, as abnormal synaptic changes have been indicated in the vast majority of these diseases. SV2A PET is also expected to contribute to the drug discovery process by facilitating patient stratification, monitoring therapeutic responses, and checking the efficacy of drugs in clinical trials.

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