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Review

Advances in synaptic PET imaging and intervention with synapse-targeted small-molecular drugs for dementia diagnosis and therapy

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ABSTRACT

Dementia is characterized by synaptic and neuronal dysfunction in disease-specific brain regions. Repeated failure of dementia clinical trials with therapeutic drugs targeting abnormal protein aggregates has caused researchers to shift their focus to synaptic functions and increased the importance of clinically available imaging for synaptic density and the development of synapse-targeted intervention. Synaptic density imaging with positron emission tomography (PET) tracer enables non-invasive detection of synaptic loss and hence investigates the association with other neuropathological events exemplified by disease-specific abnormal protein accumulation. Many studies have reviewed the progress of synaptic density imaging; however, to our knowledge, there is no article yet that summarizes the research progress of multimodal imaging of synaptic density tracers combined with other dementia biomarkers. Moreover, synaptic function intervention for dementia therapy has not yet been summarized. In this review, first we detail the progress of synaptic density imaging including tracer development and preclinical/clinical application, followed by a discussion of multimodal imaging of synaptic density tracers combined with classic dementia biomarkers in the clinical research stage. Finally, we briefly summarize the synapse-targeted drugs for dementia therapy.

1. Introduction

Dementia is defined as the loss of cognitive functioning to such an extent that it interferes with an individual's daily living and activities. Patients with cognitive disorder require around-the-clock care, which is associated with heavy familial, economic, and social burdens. Various disorders and factors contribute to the development of dementia. Alzheimer's disease (AD) is the most common form of dementia with accumulation of abnormal protein aggregates known as amyloid plaques and tau tangles. Based on updated calculations, an estimated 6.7 million Americans aged ≥ 65 years were living with AD in 2023 [1]. Lewy body dementia (LBD) is a form of dementia caused by abnormal aggregation of the protein alpha-synuclein, called Lewy bodies [2]. Frontotemporal dementia (FTD) is the third-most prevalent form of dementia, following AD and LBD. FTD stands out as a primary subtype of early-onset dementia [3]. Vascular dementia is caused by different conditions that interrupt the flow of blood and oxygen supply to the brain [4]. Dementia is usually accompanied by a progressive and irreversible loss of neurons and brain function. Synapses are highly specialized contacts between nerve cells that transmit signals from the pre-synaptic to the postsynaptic neurons. Synapses are crucial for cognitive function, and synaptic loss is a key and common pathology in brains with dementia [5].

Imaging with positron emission tomography (PET) for disease-specific abnormal protein aggregates is a powerful tool for early diagnosis based on the fact that these protein aggregations begin in the very early stage of the disease as noted in AD, where cerebral amyloid plaques appear decades before actual disease onset [6]. However, the disease severity is usually not consistent with the level of amyloid plaques accumulated in the AD brain [6]. Given that neurotoxic oligomer species of amyloid rather than the fibrillary form may induce degeneration of synapses and consequently, impairment of cognitive function in AD [7], synaptic function is crucial for the maintenance of neuronal activity and cognitive function. Therefore, quantitative assessment of synaptic density has increasingly caught the attention of clinicians and researchers [8,9].

The acetylcholine esterase inhibitors (AChEIs) donepezil, galantamine, and rivastigmine, and the low-to-moderate affinity, noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist memantine are

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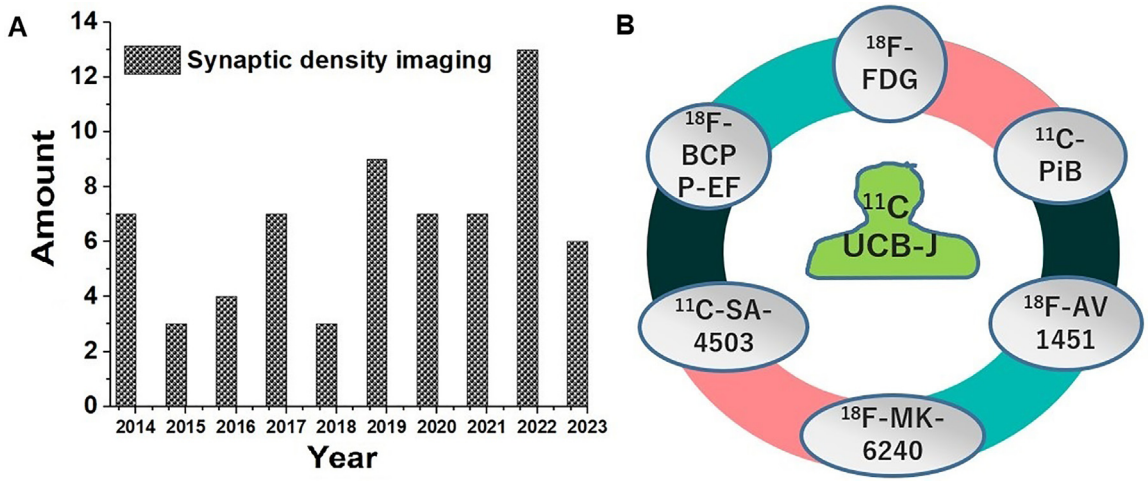

Fig. 1. (A) Statistical chart for annual published reviews, returned from a search for "Synaptic density imaging" through the Web of Science. (B) Representative PET probes name used for multimodal imaging combined with ^{11}C-UCB-J.

the FDA-approved medications for AD [10]. These drugs only target and improve the clinical symptoms without modifying the pathological steps leading to AD. The FDA granted an accelerated approval to anti-amyloid antibody Aducanumab in 2021 and to Lecanemab in 2023, which acts on the evolution of the AD treatment. However, a high incidence of amyloid protein-related imaging abnormalities (ARIA) has raised doubts regarding this therapeutic approach [11]. In contrast, synaptic loss is an interevent between abnormal protein aggregation and neuronal degeneration. A mixture of direct effects of protein aggregates as well as indirect effects such as inflammation and neuronal energetics are likely to affect synaptic integrity [12]. Focusing on the synapse for therapeutic and diagnostic opportunities raises some important conceptual and strategic issues regarding translational research, and sheds light on how preclinical research can inform clinical studies.

Thus far, several review papers with a focus on synaptic density imaging have been published. As shown in Fig. 1A, 82 published articles have focused on synapses imaging in the past decade. For example, the authors outlined *in vivo* imaging of synaptic density and its utility for the diagnosis and treatment monitoring of neurodegenerative and psychiatric diseases [13,14]. Other review papers have focused on the discovery and development of tracers for imaging of synaptic density [15,16]. However, there is a lack of reviews that comprehensively summarize the recent advances in translational imaging for synaptic density including multimodal imaging development (Fig. 1B) and preclinical/clinical applications. Given that recently multi-tracer imaging to understand the relationship between neuropathological events such as accumulation of amyloid/tau or energy metabolism have provided an insightful understanding of the pathogenesis of dementia. The limitation of synaptic density imaging with single tracer is becoming increasingly obvious. Moreover, a rare review paper mentioned the potential contribution of synaptic density imaging to synapse-targeted intervention development for dementia therapy. To address the limitations of current review papers, we have summarized recent advances in the translational imaging of synaptic density including tracer development, preclinical/clinical application, multi-tracer imaging combined with classic dementia biomarkers, and synapse-targeted intervention for dementia therapy.

2. Synaptic imaging for dementia diagnosis and functional evaluation

2.1. Imaging biomarkers for synaptic density

Synaptic vesicles (SV) are neurotransmitter-containing storage units located in the axon terminals. The total number of synaptic vesicle glycoprotein 2 (SV2) is highly consistent across vesicles at presynaptic terminals, with 2–5 copies per synaptic vesicle [17,18]. Therefore, SV2 is a suitable biomarker for synaptic density. SV2 has three isoforms (SV2A, SV2B, and SV2C). SV2A is a 12-transmembrane domain glycoprotein expressed in synaptic vesicles in the whole brain, apart from trigeminal and facial nerve nuclei, and is especially abundant in subcortical areas such as the thalamus and basal ganglia. SV2B is mainly expressed in the cortical and hippocampal regions. SV2C is present only in the striatum, pallidum, midbrain, brainstem, substantia nigra, and olfactory bulb [19]. Therefore, SV2A is a more suitable imaging biomarker for whole-brain mapping of synaptic density than SV2B and SVC.

2.2. PET tracers for SV2A imaging

2.2.1. The first SV2A-PET ligands

[^{11}C]-levetiracetam is the first SV2A-PET ligand to be developed (Fig. 2). However, multistep labeling reactions and low labeling yield hamper its clinical application [20]. [^{99m}Tc]-levetiracetam is an easily developed SPECT ligand for SV2A imaging. It showed easy labeling reaction and high brain permeability with a brain/blood ratio up to 28.5 at 5 min post intranasal administration [21]. However, this radioactive tracer is not widely used likely because of comparatively low resolution and sensibility of the SPECT ligand.

2.2.2. UCB series SV2A-PET ligands

In 2014, based on the analysis of the relationship between pharmacological activities and chemical structures of existing compounds such as levetiracetam, brivaracetam, and indolone acetamide, UCB Pharm and the University of Liege (Belgium) developed a series of SV2A ligands through computer-aided drug design. After comprehensively evaluating ligand properties such as pharmacological activity and metabolic stability, UCB-H, UCB-A, and UCB-J were selected to be the potential SV2A ligands [22].

2.2.2.1. [^{18}F]-UCB-H

In vivo quantification of SV2A with [^{18}F]-UCB-H was first reported in the 2012 meeting of the World Molecular Imaging Conference. PET imaging revealed a high uptake of [^{18}F]-UCB-H in the rat brain before a rapid decline. Pretreatment the rat with the SV2A ligand brivaracetam, which has a 20-fold higher affinity for SV2A than levetiracetam, showed a significant decrease in the brain uptake, indicating highly specific binding of [^{18}F]-UCB-H *in vivo* [23]. Bretin et al. reported that this radiotracer meets the standard regulations regarding radiation dose for use in human clinical trials [24]. A significant decrease of [^{18}F]-UCB-H uptake was observed in the hippocampi of AD patients compared to

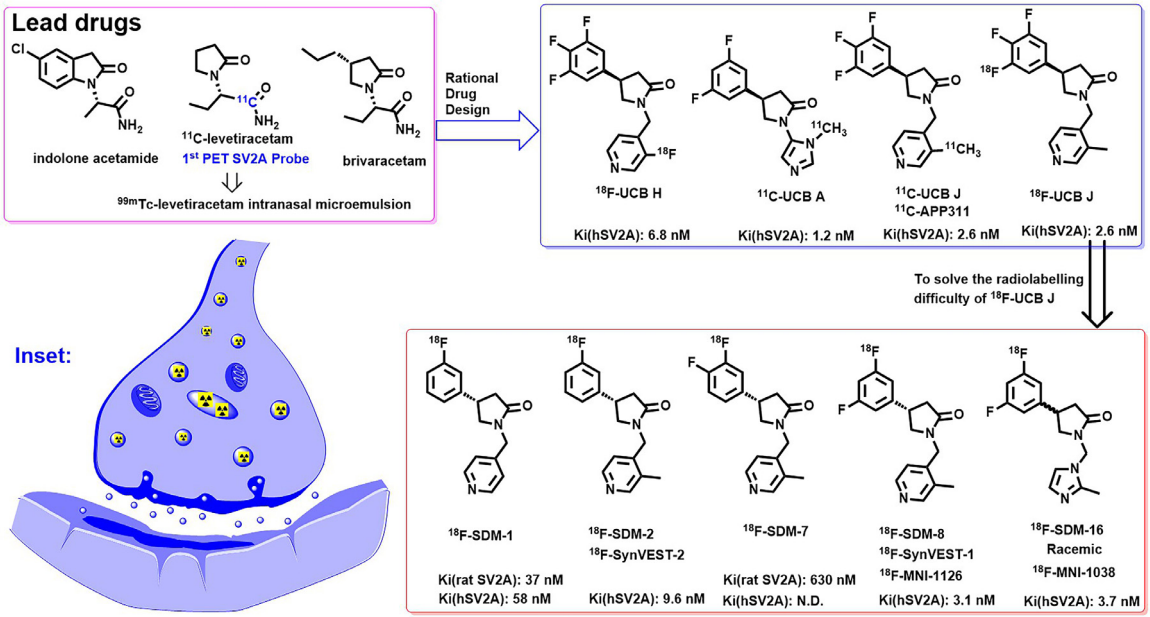

Fig. 2. The chemical structures of SV2A PET imaging tracers. IC_{50}: the half maximal inhibitory concentration, Ki: The inhibitory constant for human SV2A, pIC_{50} = -log (IC_{50}). Inset: Schematic diagram of SV2A pet probe labeling synaptic vesicles.

healthy control subjects, and was related to patients' cognitive decline [25,26]. Unfortunately, the total distribution volume (*Vt*) value of [^{18}F]-UCB-H (3–10 mL/cc) is not ideal. By contrast, the *Vt* value of [^{11}C]-UCB-J is up to 25–55 mL/cc [27].

2.2.2.2. [^{11}C]-UCB-A

The binding affinity of UCB-A to human SV2A protein is 1.2 nM, which is the highest among the three aforementioned ligands. The ^{11}C radiolabeling of UCB-A is easier than that of [^{11}C]-levetiracetam, with a two-step reaction and high radiochemical purity of > 98%. However, kinetic analysis showed slow brain kinetics, with peak activity at 70–80 min after injection, and poor metabolic stability in humans [28], indicating its unsuitability for clinical application.

2.2.2.3. [^{11}C]- and [^{18}F]-UCB-J

^{11}C-labeled UCB-J ([^{11}C]-UCB-J; also known as [^{11}C]-APP311) is the most widely used PET ligand for SV2A imaging, owing to its easy radiosynthesis, high radiochemical yield, and excellent ligand properties. [^{11}C]-UCB-J was produced from 1 mg of precursor in a radiochemical yield of 11% ± 4% (based on trapped ^{11}C-methyliodide radioactivity), with a radiochemical purity of 99% ± 0.5% and a chemical purity of 99.8% ± 2.4% [27]. It exhibited specific and selective binding affinities for human and rodent SV2, high brain permeability, rapid washout, low *in vivo* non-specific binding and favorable metabolic profile in mini pig or non-human primates [27,29]. There is an excellent linear correlation across all gray matter regions between *in vivo* [^{11}C]-UCB-J binding and synaptic density, examined by immunochemical analysis, for a gold standard biomarker of synaptophysin, indicating the utility of SV2A-PET imaging for non-invasive quantification of synaptic density [30,31]. Similar brain permeability, kinetics, and distribution cross experimental models including rodent, minipig and non-human primates are convenient for preclinical applications (Fig. 3) [27,29,32].

In clinical studies, [^{11}C]-UCB-J exhibited excellent PET tracer characteristics and sufficient safety in adolescents [33] or for multiple PET examinations in the same individual [34,35]. Acquisition and quantitative methods for dynamic [^{11}C]-UCB-J have also been validated by different groups. A simplified reference tissue model (SRTM2) is the preferred method for a voxel-wise analysis of using white matter (centrum semi-ovale–SO) as the reference tissue [36]. The images of either standardized uptake value ratio (SUVR) with a time span from 60 to 90 min ($SUVR_{60\text{-}90\ min}$) or from 50 to 80 min ($SUVR_{50\text{-}80\ min}$) are suitable for establishing parametric maps of [^{11}C]-UCB-J binding potential, allowing non-invasive quantification for SV2A in humans [37,38]. However, the halftime of ^{11}C is 20.4 min, which is a significant limitation for a drug with a metabolism time of 60–90 min. Hence, ^{18}F-labeled UCB-J ([^{18}F]-UCB-J) has been developed for longer half-life time ($T_{1/2}$ of ^{18}F: 109.8 min). Unfortunately, the radiochemical yield of [^{18}F]-UCB-J was only 1%–2% [39], likely owing to low reaction activity of three adjacent fluorine atoms that belonged to a benzene ring. Owing to the electron withdraw effect of double fluorine atoms on the benzene ring, it is difficult to fluorinate the third fluorine atom onto the benzene ring through electrophilic fluorine, which is the main fluorine source produced by a conventional cyclotron [40]. Poor radiochemical yield greatly limits its application in preclinical and clinical studies. These results are presented in Table 1.

2.2.3. New development SV2A-PET probes from [^{11}C]-UCB-J optimization

The low [^{18}F] radiolabeling yield of UCB-J is attributed to the multi-fluorine substitution in benzene. Removal of one or two fluorine atoms on the phenyl moiety of the UCB-J structure led to the discovery of SDM-1, SDM-2, SDM-7, and SDM-8 [41]. Imidazole-substituted pyridine in SDM-8 yielded SDM-16 [42]. [^{18}F]-SDM-8 (also known as [^{18}F]-SynVEST-1 and [^{18}F]-MNI-1126) and [^{18}F]-SDM-16 (also known as [^{18}F]-MNI-1038) are two well-evaluated tracers, which were classified as the third-generation SV2A ligands (Chemical structures of representative ligands; Fig. 2). These two PET tracers showed high V_T (~30 mL/cm^3) and the cerebral distribution was highly correlated with that of [^{11}C]-UCB-J in all sub-regions of the gray matter. Radiochemical yields of [^{18}F]-SDM-8 and [^{18}F]-SDM-16 (approximately 24% and 20%, respectively) are also adequate for clinical research purposes [43,44]. [^{18}F]-SDM-8 has been applied to clinical studies in many synaptic-related diseases such as AD [45], PD [46,47], amyotrophic lateral sclerosis [48], spinocerebellar ataxia type 3 [49], gaming disorder [50], focal cortical dysplasia type II [51,52], neuroendocrine differentiation in prostate cancer [53], and hypothalamic hamartoma [54]. The preclinical evaluation of [^{18}F]-SDM-16 seemed to suggest that it could be a promising synaptic density tracer [55,56]. However, so far, only one study has reported an autoradiography to assess synaptic density in the human cerebellar cortex and dentate nucleus in three essential tremor patients [57]. No clinical study yet reports the application of this drug.

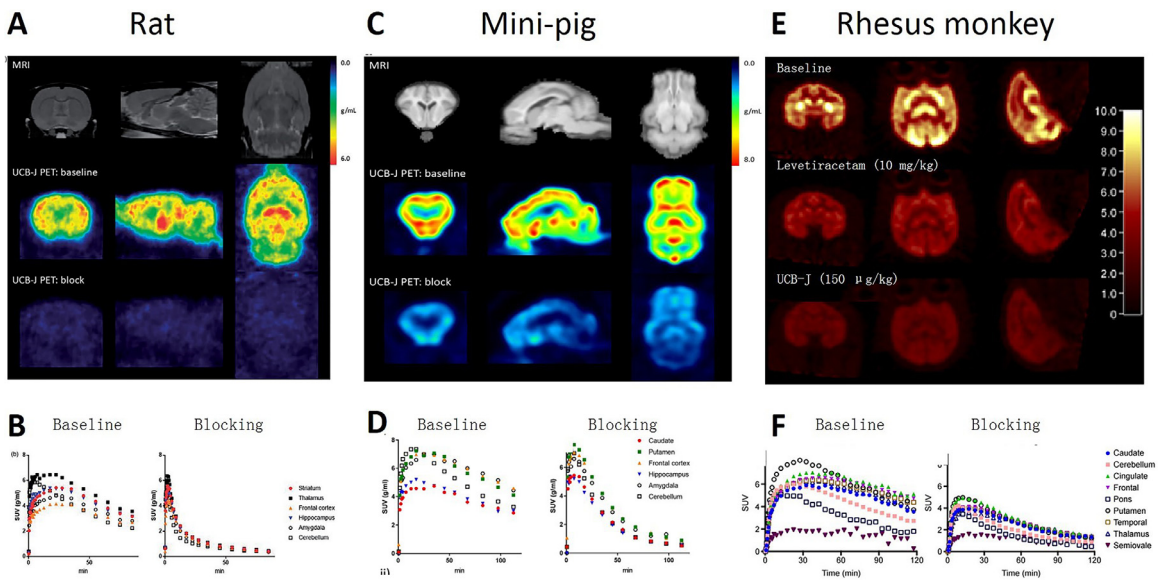

Fig. 3. [^{11}C]-UCB-J imaging in various experimental animals. (A, B) Template magnetic resonance imaging (MRI) (top row in panel A) and representative [^{11}C]-UCB-J images summed SUV images (30–90 min) under baseline conditions (middle row in panel A) and after blocking with 100 mg/kg levetiracetam (lower row in panel A) in coronal (left), sagittal (middle), and transverse (right) views. Representative time-activity curves without (baseline) and with blocking (blocking) in the same rat (B). Data from Thomsen et al. [32]. (C, D): Template MRI (top row in panel C) and summed SUV images (30–120 min) under baseline conditions (middle row in panel C) and after blocking with 30 mg/kg levetiracetam (lower row in panel C) in coronal (left), sagittal (middle), and transverse (right) views. Representative time-activity curves without (baseline) and with blocking (blocking) in the same minipig are shown in panel D. Data from Thomsen et al. [29]. (E, F): Representative [^{11}C]-UCB-J PET images of baseline (upper in panel E), after pretreatment with levetiracetam (10 mg/kg) (middle in panel E), and after co-injection with unlabeled UCBJ (150 ug/kg) (lower in panel E) summed from 30 to 45 min in normal rhesus monkey brain. Time-activity curves without (baseline) and with blocking (10 mg/kg levetiracetam, blocking) in the same rhesus monkey are shown in panel F. This research was originally published in JNM. Nabulsi et al. Synthesis and Preclinical Evaluation of 11C-UCB-J as a PET Tracer for Imaging the Synaptic Vesicle Glycoprotein 2A in the Brain. J Nucl Med. 2016;57:777-784. © SNMMI. [27].

Table 1
Summary of the medical application of [^{11}C]-UCB-J-PET for dementia diagnosis.

Imaging subject	Important results	Institution	Ref.
Rhesus monkey	Detection of high regional-specific binding and a favorable metabolic profile in the living brains.	Yale School of Medicine	[27]
Mini pig	Proved UCB-J to be a valid *in vivo* marker of synaptic density in the minipig brain	Aarhus University	[29]
4 healthy volunteers	Ensured the safety of PET scan for adolescents.	Yale School of Medicine	[33]
5 healthy volunteers	Excellent PET tracer characteristics were exhibited.	Yale School of Medicine	[34]
3 healthy volunteers	It was safe and showed mixed renal and hepatobiliary clearance.	KU Leuven	[35]
10 healthy volunteers	Identified a method for a voxel-wise analysis of dynamic [^{11}C] UCB-J PET	KU Leuven	[36]
10 healthy volunteers	Blocking study validated semi-ovale (SO) as a suitable reference tissue for quantification.	KU Leuven	[37]
80 healthy volunteers	No significant impact of age and sex on synaptic loss.	KU Leuven	[59]
3 dementia, 1 FTD, 19 controls	Pre-symptomatic C9orf72 carriers showed reduced synaptic density.	University of Cambridge	[60]
10 AD, 11 controls	Participants with AD exhibited a notable decrease (41%) in hippocampal SV2A-specific binding compared to cognitively normal participants.	Yale School of Medicine	[61]
34 AD, 19 controls	Reductions of SV2A binding in medial temporal and neocortical brain regions in early AD.	Yale School of Medicine	[62]
12 PD, 12 controls	Participants with AD exhibited a notable decrease (41%) in hippocampal SV2A specific binding compared to cognitively normal participants.	Yale School of Medicine	[63]
21 nPD, 13 DLB or PDD, 15 controls	Widespread synaptic loss in the cortical areas in DLB/PDD cohorts.	Aarhus University Hospital	[64]
11 behavioral variant FTD, 25 controls	Patients with behavioral variant FTD showed severe synaptic loss compared to controls	University of Cambridge	[67]
32 PSP, 16 CBD, 33 controls	Rapid progressive synaptic loss, correlating with clinical progression in primary tauopathies.	University of Cambridge	[68]
58 healthy older adults (≥ 50 years)	Mild Motor Signs in healthy aging are associated with lower synaptic density throughout the brain.	KU Leuven	[69]
45 AD (amyloid+), 19 controls	Synaptic density can serve as a robust biomarker of disease presence and severity in the early stages of AD.	Yale University School of Medicine	[70]

In future, [^{18}F]-SDM-8 will likely play an important role in synaptic density imaging and multimodal clinical studies with sufficient accuracy and precision, owing to its advantages in higher radiolabeling yield and longer halftime [58].

2.3. Medical application of synaptic density imaging

Given the excellent ligand properties of [^{11}C]-UCB-J for synaptic density imaging in rodents and non-human primates, most clinical studies have used [^{11}C]-UCB-J-PET for non-invasive measurement of synaptic density. A clinical PET study with 80 healthy volunteers demonstrated that synaptic density is not influenced by age or sex [59]. Until now, it remains unclear whether aging has an impact on synaptic density. Reduction of synaptic density was also detected in the disease-specific brain regions of patients, including pre-symptomatic C9orf72 mutation carriers [60], AD patients [61,62], PD [63] and PD dementia (PDD) or DLB) patients [64]. More importantly, researchers found significantly positive correlations between synaptic density and global

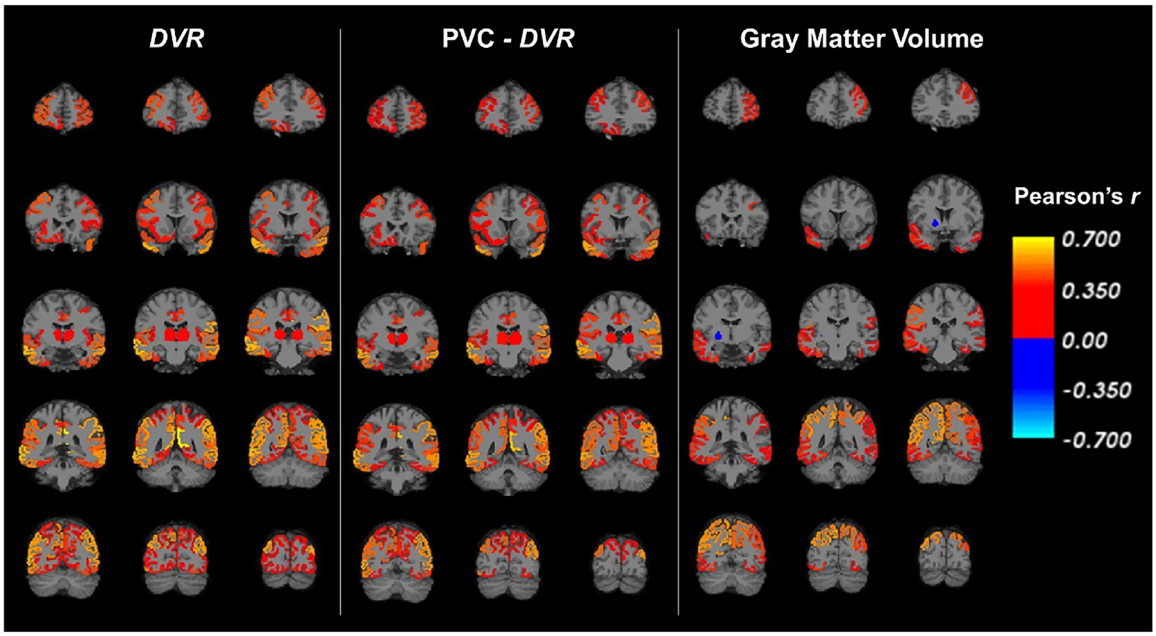

Fig. 4. The correlation of synaptic density with cognitive function in AD patients. Correlation maps of synaptic density (DVR) and global cognition in all regions for participants with AD. (left) Pearson's correlation coefficient (r) was calculated for the correlation between synaptic density ([^{11}C]-UCB-J DVR) and global cognition in all FreeSurfer regions. A similar analysis was conducted (middle) after PVC of [^{11}C]-UCB-J PET images, and (right) with gray matter volume. DVR, distribution volume ratio of [^{11}C]-UCB-J calculated with a whole cerebellum reference region; PET, positron emission tomography; PVC, partial volume correction. Data and images were modified from Mecca et al. [62].

cognitive function in AD patients (Fig. 4), indicating that synaptic density was a stronger predictor of cognitive performance [60,61]. However, non-dementia patients such as those with major depressive disorder (MDD) and/or post-traumatic stress disorder (PTSD) also showed significant loss of synapses [65,66], indicating that synaptic loss is not a dementia-specific pathological change. Thus, synaptic density imaging may be unsuitable for early or differential diagnosis of dementia [67–70]. The collated items were listed in Table 1.

2.4. Multi-tracer imaging for SV2A-relevant neuropathological events

Multi-tracer imaging enables the assessment of multiple pathologies [71]. In combination with other PET tracers, synaptic density imaging enables the investigation of the relationship between synaptic loss and other neurogenerative events such as amyloid or tau deposition. It is important to understand the disease-specific pathological or physiological processes. Researchers have found an age-dependent mitochondrial dysfunction and synaptic loss in the caudate of healthy volunteers in a clinical multi-tracer study, where *in vivo* imaging with [^{11}C]-UCB-J, [^{18}F]-BCPP-EF (mitochondrial complex 1 ligand), and [^{11}C]-SA-4503 (σ-1 receptor ligand) was performed to measure synaptic density, mitochondrial function, and neuronal stress, respectively [72]. Aided by imaging with [^{11}C]-UCB-J [^{11}C]-PiB (amyloid-PET tracer) and [^{18}F]-AV-1451 (tau-PET tracer), researchers found that both Aβ and tau deposition were inversely associated with hippocampal synaptic density in amnestic mild cognitive impairment (aMCI) and mild AD dementia [73,74]. These imaging combination scans also showed that synaptic density was markedly decreased in two well-characterized patients with DLB, and there were no significant regional correlations between [^{11}C]-UCB-J binding and either amyloid (^{11}C-PiB) or tau (^{18}F-AV-1451) in the grey matter tissues from either patient [75]. Interestingly, a similar examination demonstrated an obvious synaptic loss and negative correlation of synaptic density with tau accumulation in subcortical areas (caudate nucleus, putamen) of patients with progressive supranuclear palsy (PSP) (Richardson's syndrome) and amyloid-negative corticobasal degeneration (CBD) [76,77]. Similarly, the close relationship between tau deposition and synaptic density loss was detected in the medial temporal lobe of aMCI patients without amyloid accumulation, by using multi-tracer imaging with [^{11}C]-UCB-J, [^{11}C]-PiB, and [^{18}F]-MK 6240, a tau-PET tracer [78]. Collectively, these studies suggested a stronger involvement of tau accumulation in synaptic loss than amyloid accumulation.

Glucose metabolism, which is usually assessed by [^{18}F]-FDG-PET, is a widely used index for neuronal activity in clinical studies. Combined examinations with [^{11}C]-UCB-J and [^{18}F]-FDG showed that inter-tracer correlations were higher between synaptic density and glucose metabolism in the medial temporal regions, with lower correlations in the neocortical regions in AD patients [79]. The relationship was strongly modulated by regional differences in healthy subjects [80], indicating a close brain region- or pathology-dependent relationship between synaptic density and glucose metabolism. Other neuropathological events such as neuroinflammation, which is well known to affect glucose metabolism [81,82], may result in such brain region- or pathology-dependent inconsistency mentioned above. Further investigation is required to clarify whether imaging of synaptic density enables a more accurate assessment of neuronal activity than glucose metabolism. These results are summarized in Table 2.

2.5. Multimodal imaging study with magnetic resonance imaging (MRI) and SV2A PET

Independent component analyses were performed on resting-state functional MRI (fMRI) and [^{11}C]-UCB-J PET data from 34 healthy adult participants. Initial evidence of a neurophysiological link between the resting state network activity and local synaptic density was found, which provides a new perspective to neurodegenerative and psychiatric disorders [83]. Another multimodal imaging research used diffusion tensor imaging (DTI) technology via MRI and [^{11}C]-UCB-J PET to investigate the relationship between gray matter microstructure and synaptic density in 33 amyloid-positive participants with AD and 17 amyloid-negative cognitively normal participants (age range of cohort: 50–83 years). The results showed that higher gray matter mean diffusivity

Table 2
Summary of multi-tracer imaging researches.

Imaging subject	Imaging probes	Important results	Institution	Ref.
12 healthy volunteers	[^{11}C]-UCB-J, [^{18}F]-BCPP-EF, [^{11}C]-SA-4503	Age-dependent decrease in mitochondrial function and synaptic density	Invicro LLC	[72]
14 aMCI, 24 dementia, 19 controls	[^{11}C]-UCB-J, [^{11}C]-PiB	A significant inverse association between global Aβ deposition and hippocampal SV2A expression in participants with aMCI.	Yale School of Medicine	[73]
5 MCI, 5 dementia, 10 controls	[^{11}C]-UCB-J, [^{18}F]-AV-1451	Tau accumulation was inversely associated with hippocampal synaptic density	Yale School of Medicine	[74]
2 DLB, 10 controls	[^{11}C]-UCB-J, [^{11}C]-PiB, [^{18}F]-AV-1451	Synaptic density was markedly decreased in two well-characterized DLB patients	University of Cambridge	[75]
15 CBS, 14 PSP, 15 controls	[^{11}C]-UCB-J, [^{11}C]-PiB	Significant synaptic loss in amyloid-negative tauopathies.	University of Cambridge	[76]
12 CBS, 23 PSP, 19 controls	[^{11}C]-UCB-J, [^{18}F]-AV-1451	Negative correlation between tau accumulation and synaptic density	University of Cambridge	[77]
10 aMCI, 10 controls	[^{11}C]-UCB-J, [^{18}F]-MK 6240, [^{11}C]-PiB	Simultaneous occurrence of tau deposition and synaptic loss in patients with aMCI	KU Leuven	[78]
14 AD, 11 controls	[^{11}C]-UCB-J, [^{18}F]-FDG	Region-dependent relationship between synaptic density and glucose metabolism in AD patients and healthy controls.	Yale School of Medicine	[79]
20 healthy volunteers	[^{11}C]-UCB-J, [^{18}F]-FDG	Regional synaptic density and glucose consumption were indeed highly significantly correlated	KU Leuven	[80]
21 nPD, 13 DLB/PDD, 15 controls	[^{11}C]-UCB-J, [^{18}F]-FDG	The magnitude of reduced glucose uptake exceeded the magnitude of reduced cortical synaptic density in DLB	Aarhus University Hospital	[81]
18 HD, 15 controls	[^{11}C]-UCB-J, [^{18}F]-FDG	HD shows longitudinal loss of putaminal SV2A binding and putaminal glucose metabolism	KU Leuven	[82]

Table 3
Summary of synaptic interventions using small molecular drugs for dementia therapy.

Agent	NCT number	Sponsor	Phase	Start date	Conditions
Levetiracetam (AGB101)	NCT02002819	University of Minnesota	2	June 2014	AD
	NCT03489044	University of Oxford	2	October 28, 2018	AD Epilepsy
CT-1812 (Elayta)	NCT02570997	Cognition Therapeutics	1	September 2015	Cognitive Impairment
	NCT03716427		1	November 10, 2016	Healthy Volunteers
	NCT03522129		1	May 30, 2018	AD
	NCT02907567		1 and 2	September 2016	AD
	NCT03493282		1 and 2	March 28, 2018	AD
	NCT04735536		2	August 15, 2020	AD
	NCT03507790		2	October 2, 2018	Mild-to-moderate AD
SDI-118	NCT05199142	Syndesi Therapeutics	1	September 23, 2021	Cognitive Decline
UCB-0255	None	UCB	Pre-		AD

is significantly associated with lower synaptic density in participants with AD, which can be found across many brain regions that are commonly affected in AD [84]. Additional studies that integrate structural and tracer imaging are necessary to ascertain whether imaging synaptic density offers supplementary information to differentiate neurodegenerative diseases.

3. Synaptic function intervention for dementia therapy

Recent studies have shown an association of decreased synaptic function with symptom severity in numerous CNS disorders, suggesting that synaptic dysfunction is the common element across these disorders [85]. Therefore, interventions that target synaptic function may be a promising therapeutical strategy for dementia. However, unlike synaptic imaging, there are limited clinical studies on synaptic intervention for dementia therapy. Relevant examples are listed in Table 3.

3.1. Drug candidates targeting synaptic functions

3.1.1. Levetiracetam

Many studies have suggested that AD and epilepsy possibly share some underlying pathophysiologic mechanisms or one is an epiphenomenon of the other [86]. Epileptic seizures or other asymptomatic neuroexcitatory events contribute to the loss of cognitive function [87]. SV2A was identified as the specific binding site for levetiracetam, an FDA-approved second-generation antiepileptic drug [88]. Levetiracetam prevented seizures, reduced neuronal over-excitation, and improved cognition in animal models of AD. Devi et al. reported that levetiracetam can ameliorate memory impairments of aged C57BL/6 mice (17–20 months of age) in the contextual fear conditioning paradigm, and acute administration of levetiracetam after modeling was also efficacious in rescuing contextual memory decline in aged mice [89]. A clinical finding showed that treatment with levetiracetam may improve cognitive and general functions in older epileptic patients [90]. Based on current evidence, the investigators are promoting a comprehensive clinical project called Hope 4 MCI which includes two trials (NCT02002819 and NCT03489044) to determine the therapeutic effect of levetiracetam on AD [91]. In the phase 2a randomized NCT02002819 clinical trial, a total of 34 adults (21 women [61.8%]; mean [SD] age, 62.3 [7.7] years) with AD were enrolled. This trial showed that treatment with low-dose levetiracetam (125 mg/bid, 4 weeks) was well tolerated in patients with AD, and although levetiracetam treatment did not improve the primary outcome in recruits, it improved cognitive function in those with epileptiform activity in the prespecified exploratory analysis. Levetiracetam treatment improved accuracy in spatial memory and executive functioning tasks among participants with epileptiform activity and had a good safety profile [92]. The results of trial NCT03489044 have not yet been published. The study investigators hope to find an anti-seizure medication, not necessarily levetiracetam, with a positive influence on memory function in AD in the future [93].

3.1.2. SDI-118

SDI-118 is a SV2A-positive modulator, designed for improving cognition in cognitively impaired patients. A phase 1 clinical study (NCT05486195) initiated by Syndesi Therapeutics in ongoing to identify the safety and tolerability of this candidate. Single oral doses of SDI-118 up to 80 mg were very well tolerated in healthy male subjects, and the adverse effects mainly occurred in higher dose ranges. These data support further clinical exploration of SDI-118 in patients with cognitive disorders [94].

3.1.3. UCB-0255

UCB-0255 is a selective negative modulator with high affinity for SV2A. It increased the recognition index of phencyclidine (PCP)-treated rats by 30% and thereby normalized the cognitive function to the level of normal rats. This drug also alleviated forgetting of long-term memory for familiar objects by increasing the recognition index by 20%. At the pharmacologically active dose, UCB0255 was found to occupy 5%–70% of the binding sites of SV2A, as evaluated by *in vivo* binding experiments. No pro-seizure activities were observed in the dose range associated with pro-cognitive effects [95]. These preclinical data support UCB0255 as a promising candidate for further research and development.

3.1.4. CT1812

CT1812 is a small-molecule antagonist of progesterone-receptor membrane component 1 (PGRMC1/Sigma-2 receptor). Its binding to the PGRMC1/Sigma-2 receptor can allosterically decrease the affinity of oligomeric Aβ for this receptor on the synapse and thereby interfere with Aβ-induced synaptic toxicity [96]. The antagonists of PGRMC1 can not only prevent a range of different Aβ species from binding to target molecules on neuronal terminals but also release bound Aβ from binding sites, hence reversing Aβ oligomers-induced cognitive deficits in AD mouse models [97]. Counter-screening of a proprietary library of CNS drug-like small molecules which block the binding of Aβ oligomers to receptors revealed that compounds CT0109 and CT0093 were highly potent and specific ligands of the PGRMC1/Sigma-2 receptor [98]. As a representative of the Sigma-2 receptor inhibitors, CT1812 was optimized from CT0109 and found that it facilitated brain clearance of Aβ oligomers, likely owing to increased free Aβ oligomers (based on the above-mechanism mentioned), and improved cognitive behaviors [99]. Phase I clinical trials have identified the safety and tolerance of this drug in healthy older volunteers. CT1812 was well tolerated at a single-dose administration up to 1120 mg and a multiple-dose administration up to 840 mg and 560 mg in healthy young and healthy older subjects, respectively [100]. The cognitive functional improvement conferred by CT1812 was verified in AD model and wild-type mice, and the effect of releasing Aβ oligomers was detectable in an *in vitro* experimental system using postmortem AD brain tissue [99]. Furthermore, CT1812 significantly increased the Aβ oligomers, reduced synaptic harmful proteins and phosphorylated tau fragments, and amended the dysregulation of AD-related proteins in the cerebrospinal fluid fraction of AD patients (NCT02907567) [100]. The completed and going clinical trials with CT1812 are listed in Table 3.

3.2. Utility of SV2A imaging for drug development

It is believed that the synapse is the main target for neurotoxic amyloid or tau oligomers [101]. Synaptic density imaging is considered valuable for monitoring the effect of synapse-protective drugs. SV2A imaging with [^{11}C]-UCB-J has captured a significant decrease in synaptic density in amyloid-enriched hippocampi of APP/PS1 mice, compared to age-matched normal mice. Moreover, researchers have found that administration with saracatinib (a Fyn kinase inhibitor currently in clinical development for AD treatment) rescued amyloid-associated synaptic loss in APP/PS1 mice by using [^{11}C]-UCB-J-PET, indicating the utility of SV2A imaging for monitoring the therapeutic effect of medical intervention [102]. However, there are still few studies using SV2A imaging for preclinical development of anti-dementia medications. One of reason may be less impairment of synapses in AD models with amyloid pathologies. A slight decrease of $< 4\%$ in the binding potential of [^{11}C]-UCB-J was detected in the hippocampal region of APP/PS1 mice compared to control mice (SUVR values with whole brain as the reference tissue were 1.11 ± 0.04 and 1.15 ± 0.02 for APP/PS1 and wild-type mice, respectively) [99], likely because of the lack of tau pathology in this AD model. Further investigation is required to identify its utility in anti-dementia medication development by using AD models with more severe synaptic loss such as tauopathy models [103].

4. Discussion and perspectives

The development of SV2A-PET tracers represented by [^{11}C]-UCB-J has enabled the non-invasive assessment of synaptic density, which is a potential index for neuronal function. [^{18}F]-SDM-8 and [^{18}F]-SDM-16 are two promising ^{18}F-labeled SV2A-PET tracers that were developed to overcome the limitations of the short half-life of the ^{11}C-labeled tracer. However, more solid evidence is required to ascertain the clinical availability of these ^{18}F-labeled PET tracers in the future.

SV2A imaging with [^{11}C]-UCB-J has detected synaptic loss in a series of dementia patients including AD, DLB, and other tauopathies, identifying synaptic loss as a common pathology of dementia. However, non-dementia cases such as MDD are also associated with a significant decrease in synaptic density, indicating the uncertainty of SV2A imaging as a diagnostic tool for dementia. Multi-tracer examinations for synaptic density and other neuropathologies such as amyloid and tau accumulation enable us to investigate the tempo-spatial relationship between neuropathological events to clarify the pathological processes of neurodegenerative disorders. SV2A imaging can reflect brain pathology, while energy metabolism imaging (^{18}F-FDG PET) reflects neuronal activity. Therefore, the combination of SV2A imaging and energy metabolism imaging provides a fusion of both the physical and chemical states of the brain and offers a deeper understanding of brain condition. However, it is still unclear what regulates the brain region- and pathology-dependent relationship between synaptic density and glucose metabolism.

Repeated unsuccessful clinical trials with anti-amyloid or anti-tau therapies have caused researchers to expand their focus from abnormal protein aggregates to a broader range of targets for dementia therapies. Synaptic loss is more closely associated with neuronal dysfunction than disease-specific abnormal protein accumulation. Therefore, intervention targeting synaptic function recovery has become a more promising therapeutic strategy for dementia. The latest clinical trials with the above-described drug candidates are still at the phase II stage and on a small scale, with considerable uncertainties regarding their further development and application. SV2A imaging has been used for the decision of clinical dose by calculating the receptor occupancy of drug candidates. Further research should focus on the effect evaluation of therapeutic drugs by using synaptic density imaging.

Author contributions

Lu Xiuhong: Original draft preparation. Ji Bin: Writing- Reviewing and Editing. Huang Gang: Conceptualization. Ding Hong: Supervision. All authors have made a substantial contribution to this work and approved it for publication.

Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

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References

[1] Alzheimer's Association, 2023 Alzheimer's disease facts and figures, Alzheimers Dement. 19 (4) (2023) 1598–1695.
[2] L. Barb, S. Abu-Rumeileh, S. Halbgebauer, et al., CSF synaptic biomarkers in AT(N)-Based Subgroups of Lewy Body Disease, Neurology 101 (1) (2023) e50–e62.
[3] J. Bang, S. Spina, B.L. Miller, Frontotemporal dementia, Lancet 386 (10004) (2015) 1672–1682.
[4] L. Gu, H. Shu, Y. Wang, et al., Blood neurofilament light chain in different types of dementia, Curr. Alzheimer. Res. 20 (3) (2023) 149–160.

[5] M. Tzioras, R.I. McGeachan, C.S. Durrant, et al., Synaptic degeneration in Alzheimer disease, Nat. Rev. Neurol. 19 (1) (2023) 19–38.
[6] S.E. Lesné, M.A. Sherman, M. Grant, et al., Brain amyloid-β oligomers in ageing and Alzheimer's disease, Brain 136 (Pt 5) (2013) 1383–1398.
[7] X.T. Fang, G. Hultqvist, S.R. Meier, et al., High detection sensitivity with antibody-based PET radioligand for amyloid beta in brain, Neuroimage 184 (2019) 881–888.
[8] S.M. Bajjalieh, K. Peterson, R. Shinghal, et al., SV2, a brain synaptic vesicle protein, Science 257 (5074) (1992) 1271–1273.
[9] D.J. Selkoe, Alzheimer's disease is a synaptic failure, Science 298 (5594) (2002) 789.
[10] K.G. Yiannopoulou, S.G. Papageorgiou, Current and future treatments in Alzheimer disease: An update, J. Cent. Nerv. Syst. Dis. 12 (2002) 1179573520907397.
[11] H. Fillit, A. Green, Aducanumab and the FDA-where are we now? Nat. Rev. Neurol. 17 (3) (2021) 129–130.
[12] T. Arendt, Synaptic degeneration in Alzheimer's disease, Acta. Neuropathol. 118 (2009) 167–179.
[13] Y. Kong, S. Zhang, L. Huang, Positron emission computed tomography imaging of synaptic vesicle glycoprotein 2A in Alzheimer's disease, Front. Aging Neurosci. 13 (2021) 731114.
[14] Z. Cai, S. Li, D. Matuskey, et al., PET imaging of synaptic density: A new tool for investigation of neuropsychiatric diseases, Neurosci. Lett. 691 (2019) 44–50.
[15] M.E. Serrano, E. Kim, M.M. Petrinovic, et al., Imaging synaptic density: The next holy grail of neuroscience? Front. Neurosci. 16 (2022) 796129.
[16] R.E. Carson, M. Naganawa, T. Toyonaga, et al., Imaging of synaptic density in neurodegenerative disorders, J. Nucl. Med. 63 (Suppl 1) (2022) 60S–67S.
[17] S.A. Mutch, P. Kensel-Hammes, J.C. Gadd, et al., Protein quantification at the single vesicle level reveals that a subset of synaptic vesicle proteins are trafficked with high precision, J. Neurosci. 31 (4) (2011) 1461–1470.
[18] S. Takamori, M. Hol, K. Stenius, et al., Molecular anatomy of a trafficking organelle, Cell 127 (4) (2006) 831–846.
[19] S.M. Bajjalieh, G.D. Frantz, J.M. Weimann, et al., Differential expression of synaptic vesicle protein 2 (SV2) isoforms, J. Neurosci. 14 (9) (1994) 5223.
[20] H. Cai, T.J. Mangner, O. Muzik, et al., Radiosynthesis of ^{11}C-levetiracetam: A potential marker for PET imaging of SV2A expression, ACS Med. Chem. Lett. 5 (10) (2014) 1152–1155.
[21] H.M. Rashed, R.B. Shamma, H.A. El-Sabagh, Preparation of 99mTc-levetiracetam intranasal microemulsion as the first radiotracer for SPECT imaging of the synaptic vesicle protein SV2A, Eur. J. Pharm. Sci. 121 (2018) 29–33.
[22] J. Mercier, L. Archen, V. Bollu, et al., Discovery of heterocyclic nonacetamide synaptic vesicle protein 2A (SV2A) ligands with single-digit nanomolar potency: Opening avenues towards the first SV2A positron emission tomography (PET) ligands, ChemMedChem 9 (4) (2014) 693–698.
[23] G.I. Warnock, J. Aerts, M.A. Bahri, et al., Evaluation of ^{18}F-UCB-H as a novel PET tracer for synaptic vesicle protein 2A in the brain, J. Nucl. Med. 55 (8) (2014) 1336–1341.
[24] F Bretin, G Warnock, MA Bahri, et al., Preclinical radiation dosimetry for the novel SV2A radiotracer [18F] UCB-H, EJNMMI Res. 3 (1) (2013) 35.
[25] M.A. Bahri, A. Plenevaux, J. Aerts, et al., Measuring brain synaptic vesicle protein 2A with positron emission tomography and [^{18}F]-UCB-H. Alzheimer's dementia, Transl. Res. Clin. Interv. 3 (4) (2017) 481–486.
[26] C. Bastin, M.A. Bahri, F. Meyer, et al., In vivo imaging of synaptic loss in Alzheimer's disease with [^{18}F]-UCB-H positron emission tomography, Eur. J. Nucl. Med. Mol. Imaging 47 (2) (2019) 390–402.
[27] N.B. Nabulsi, J. Mercier, D. Holden, et al., Synthesis and preclinical evaluation of 11C-UCB-J as a PET tracer for imaging the synaptic vesicle glycoprotein 2A in the brain, J. Nucl. Med. 57 (5) (2016) 777–784.
[28] S. Estrada, M. Lubberink, A. Thibblin, et al., [(11)C]UCB-A, a novel PET tracer for synaptic vesicle protein 2A, Nucl. Med. Biol. 43 (6) (2016) 325–332.
[29] M.B. Thomsen, A.C. Schacht, A.K.O. Alstrup, et al., Preclinical pet studies of [^{11}C] UCB-J binding in minipig brain, Mol. Imaging Biol. 22 (5) (2020) 1290–1300.
[30] K. Buckley, R.B. Kelly, Identification of a transmembrane glycoprotein specific for secretory vesicles of neural and endocrine cells, J. Cell Biol. 100 (4) (1985) 1284–1294.
[31] S.J. Finnema, N.B. Nabulsi, T. Eid, et al., Imaging synaptic density in the living human brain, Sci. Transl. Med. 8 (348) (2016) 348ra96.
[32] M.B. Thomsen, J. Jacobsen, T.P. Lillethorup, et al., In vivo imaging of synaptic SV2A protein density in healthy and striatal-lesioned rats with [11C] UCB-J PET, J. Cereb. Blood Flow Metab. 41 (4) (2021) 819–830.
[33] J. Bini, D. Holden, K. Fontaine, et al., Human adult and adolescent biodistribution and dosimetry of the synaptic vesicle glycoprotein 2A radioligand ^{11}C-UCB-J, EJNMMI Res. 10 (1) (2020) 83.
[34] S.J. Finnema, N.B. Nabulsi, J. Mercier, et al., Kinetic evaluation and test–retest reproducibility of [^{11}C] UCB-J, a novel radioligand for positron emissiontomography imaging of synaptic vesicle glycoprotein 2A in humans, J. Cereb. Blood Flow Metab. 38 (11) (2018) 2041–2052.
[35] C. Cawthorne, P. Maguire, J. Mercier, et al., Human biodistribution and dosimetry of [^{11}C]-UCB-J, a PET radiotracer for imaging synaptic density, EJNMMI. Phys. 8 (1) (2021) 37.
[36] N. Mertens, R.P. Maguire, K. Serdons, et al., Validation of parametric methods for [^{11}C]UCB-J PET imaging using subcortical white matter as reference tissue, Mol. Imaging Biol. 22 (2) (2020) 444–452.
[37] M. Koole, J.V. Aalst, M. Devrome, et al., Quantifying SV2A density and drug occupancy in the human brain using [^{11}C] UCB-J PET imaging and subcortical white matter as reference tissue, Eur. J. Nucl. Med. Mol. Imaging 46 (2) (2018) 396–406.
[38] S. Rossano, T. Toyonaga, S.J. Finnema, et al., Assessment of a white matter reference region for 11C-UCB-J PET quantification, J. Cereb. Blood Flow. Metab. 40 (9) (2020) 1890–1901.
[39] S. Li, Z. Cai, W. Zhang, et al., Synthesis and in vivo evaluation of [^{18}F] UCB-J for PET imaging of synaptic vesicle glycoprotein 2A (SV2A), Eur. J. Nucl. Med. Mol. Imaging 46 (9) (2019) 1952–1965.
[40] R. Chirakal, R.M. Adams, G. Firnau, et al., Electrophilic 18F from a Siemens 11 MeV proton-only cyclotron, Nucl. Med. Biol. 22 (1) (1995) 111–116.
[41] C.C. Constantinescu, C. Tresse, M.Q. Zheng, et al., Development and in vivo preclinical imaging of fluorine-18-labeled synaptic vesicle protein 2A (SV2A) PET tracers, Mol. Imaging Biol. 21 (3) (2019) 509–518.
[42] C. Zheng, D. Holden, M.Q. Zheng, et al., A metabolically stable PET tracer for imaging synaptic vesicle protein 2A: Synthesis and preclinical characterization of [^{18}F] SDM-16, Eur. J. Nucl. Med. Mol. Imaging 49 (5) (2021) 1482–1496.
[43] S. Li, Z. Cai, X. Wu, et al., Synthesis and in vivo evaluation of a novel PET radiotracer for imaging of synaptic vesicle glycoprotein 2A (SV2A) in nonhuman primates, ACS Chem. Neurosci. 10 (3) (2019) 1544–1554.
[44] S. Patel, A. Knight, S. Krause, et al., Preclinical in vitro and in vivo characterization of synaptic vesicle 2A-targeting compounds amenable to F-18 labeling as potential PET radioligands for imaging of synapse integrity, Mol. Imaging Biol. 22 (4) (2020) 832–841.
[45] J. Zhang, J. Wang, X. Xu, et al., In vivo synaptic density loss correlates with impaired functional and related structural connectivity in Alzheimer's disease, J. Cereb. Blood Flow Metab. 43 (6) (2023) 977–988.
[46] S.L. Martin, C. Uribe, A.P. Strafella, PET imaging of synaptic density in Parkinsonian disorders, J. Neurosci. Res. (2023). https://doi.org/10.1002/jnr.25253.
[47] K. Smart, C. Uribe, K.L. Desmond, et al., Preliminary assessment of reference region quantification and reduced scanning times for [^{18}F]SynVesT-1 PET in Parkinson's disease, Mol. Imaging. (2023) 1855985.
[48] Y. Tang, P. Liu, W. Li, et al., Detection of changes in synaptic density in amyotrophic lateral sclerosis patients using 18 F-SynVesT-1 positron emission tomography, Eur. J. Neurol. 29 (10) (2022) 2934–2943.
[49] Z. Chen, G. Liao, N. Wan, et al., Synaptic loss in spinocerebellar ataxia type 3 revealed by SV2A positron emission tomography, Mov. Disord. 38 (6) (2023) 978–989.
[50] J. Hou, Q. Xiao, M. Zhou, et al., Lower synaptic density associated with gaming disorder: An ^{18}F-SynVesT-1 PET imaging study, Gen. Psychiatr. 236 (5) (2023) e101112.
[51] Y. Tang, J. Yu, M. Zhou, et al., Cortical abnormalities of synaptic vesicle protein 2A in focal cortical dysplasia type II identified in vivo with ^{18}F-SynVesT-1 positron emission tomography imaging, Eur. J. Nucl. Med. Mol. Imaging 49 (10) (2022) 3482–3491.
[52] Y. Tang, J. Yu, M. Zhou, et al., 18 F-SynVesT-1 PET in focal cortical dysplasia type II with thickening cortex, Clin. Nucl. Med. 47 (8) (2022) 741–743.
[53] B. Guan, N. Zhou, C.Y. Wu, et al., Validation of SV2A-targeted PET imaging for noninvasive assessment of neuroendocrine differentiation in prostate cancer, Int. J. Mol. Sci. 22 (23) (2021) 13085.
[54] L. Xiao, M. Zhou, Y. Tang, et al., 18 F-SynVesT-1 positron emission tomography in a hypothalamic hamartoma with abnormal uptake, Epilepsia 64 (4) (2023) e43–e47.
[55] C. Zheng, T.B. Toyonaga, Chen, et al., Decreased synaptic vesicle glycoprotein 2A binding in a rodent model of familial Alzheimer's disease detected by [^{18}F]SDM-16, Front. Neurol. 14 (2023) 1045644.
[56] T. Toyonaga, A. Fesharaki-Zadeh, S.M. Strittmatter, et al., PET imaging of synaptic density: Challenges and opportunities of synaptic vesicle glycoprotein 2A PET in small animal imaging, Front. Neurosci. 16 (2022) 787404.
[57] Y. Yang, C. Zheng, B. Chen, et al., Decreased synaptic vesicle glycoprotein 2A binding in the human postmortem essential tremor cerebellum: Evidence of reduction in synaptic density, Cerebellum (2023). https://doi.org/10.1007/s12311-023-01611-8.
[58] R.H. Asch, M. Naganawa, N. Nabulsi, et al., Evaluating infusion methods and simplified quantification of synaptic density in vivo with [11C]UCB-J and [18F]SynVesT-1 PET, J. Cereb. Blood Flow Metab. 43 (12) (2023) 2120–2129.
[59] L. Michiels, A. Delva, J. van Aalst, et al., Synaptic density in healthy human aging is not influenced by age or sex: A 11C-UCB-J PET study, Neuroimage 232 (2021) 117877.
[60] M. Malpetti, N. Holland, P.S. Jones, et al., Synaptic density in carriers of C9orf72 mutations: A [^{11}C] UCB-J PET study, Ann. Clin. Transl. Neurol. 8 (7) (2021) 1515–1523.
[61] M.K. Chen, A.P. Mecca, M. Naganawa, et al., Assessing synaptic density in Alzheimer disease with synaptic vesicle glycoprotein 2A positron emission tomographic imaging, JAMA Neurol. 75 (10) (2018) 1215–1224.
[62] A.P. Mecca, R.S. O'Dell, E.S. Sharp, et al., Synaptic density and cognitive performance in Alzheimer's disease: A PET imaging study with [11 C]UCB-J, Alzheimers Dement. 18 (12) (2022) 2527–2536.
[63] D. Matuskey, S. Tinaz, K.C. Wilcox, et al., Synaptic changes in parkinson disease assessed with in vivo imaging, Ann. Neurol. 87 (3) (2020) 329–338.
[64] K.B. Andersen, A.K. Hansen, M.F. Damholdt, et al., Reduced synaptic density in patients with Lewy body dementia: An [^{11}C] UCB-J PET imaging study, Mov. Disord. 36 (9) (2021) 2057–2065.
[65] H.J. Kang, B. Voleti, T. Hajszan, et al., Decreased expression of synapse-related genes and loss of synapses in major depressive disorder, Nat. Med. 18 (9) (2012) 1413–1417.
[66] J.H. Krystal, C.G. Abdallah, L.A. Averill, et al., Synaptic loss and the pathophysiology of PTSD: Implications for ketamine as a prototype novel therapeutic, Curr. Psychiatry Rep. 19 (10) (2017) 74.

[67] M. Malpetti, P.S. Jones, T.E. Cope, et al., Synaptic loss in frontotemporal dementia revealed by [11C]UCB-J positron emission tomography, Ann. Neurol. 93 (1) (2023) 142–154.
[68] N. Holland, P.S. Jones, G. Savulich, et al., Longitudinal synaptic loss in primary tauopathies: An in vivo [11 C]UCB-J positron emission tomography study, Mov. Disord. 38 (7) (2023) 1316–1326.
[69] M.V. Cauwenberge, A. Delva, T.V. Casteele, Mild motor signs in healthy aging are associated with lower synaptic density in the brain, Mov. Disord. 38 (10) (2023) 1786–1794.
[70] J.D. Mikkelsen, S. Kaad, S.S. Aripaka, et al., Synaptic vesicle glycoprotein 2A (SV2A) levels in the cerebral cortex in patients with Alzheimer's disease: A radioligand binding study in postmortem brains, Neurobiol. Aging 129 (2023) 50–57.
[71] D.J. Kadrmas, J.M. Hoffman, Methodology for quantitative rapid multi-tracer PET tumor characterizations, Theranostics 3 (10) (2013) 757–773.
[72] A. Mansur, E.A. Rabiner, R.A. Comley, et al., Characterization of 3 PET tracers for quantification of mitochondrial and synaptic function in healthy human brain: 18F-BCPP-EF, 11C-SA-4503, and 11C-UCB-J, J. Nucl. Med. 61 (1) (2020) 96–103.
[73] R.S. O'Dell, A.P. Mecca, M.K. Chen, et al., Association of Aβ deposition and regional synaptic density in early Alzheimer's disease: A PET imaging study with [11C] UCB-J, Alzheimers Res. Ther. 13 (1) (2021) 11.
[74] A.P. Meccaa, M.K. Chen, R.S. O'Dell, et al., Association of entorhinal cortical tau deposition and hippocampal synaptic density in older individuals with normal cognition and early Alzheimer's disease, Neurobiol. Aging 111 (2022) 44–53.
[75] N. Nicastro, N. Holland, G. Savulich, et al., 11C-UCB-J synaptic PET and multimodal imaging in dementia with Lewy bodies, Eur. J. Hybrid Imaging 4 (1) (2020) 25.
[76] N. Holland, P. Simon-Jones, G. Savulich, et al., Synaptic loss in primary tauopathies revealed by [11C] UCB-J positron emission tomography, Mov. Disord. 35 (10) (2020) 1834–1842.
[77] N. Holland, M. Malpetti, T. Rittman, et al., Molecular pathology and synaptic loss in primary tauopathies: An 18F-AV-1451 and 11C-UCB-J PET study, Brain 145 (1) (2021) 340–348.
[78] H. Vanhaute, J. Ceccarini, L. Michiels, et al., In vivo synaptic density loss is related to tau deposition in amnestic mild cognitive impairment, Neurology 95 (5) (2020) e545–e553.
[79] M.K. Chen, A.P. Mecca, M. Naganawa, et al., Comparison of [11C] UCB-J and [18F] FDG PET in Alzheimer's disease: A tracer kinetic modeling study, J. Cereb. Blood Flow Metab. 41 (9) (2021) 2395–2409.
[80] J. van-Aalst, J. Ceccarini, S. Sunaert, et al., In vivo synaptic density relates to glucose metabolism at rest in healthy subjects, but is strongly modulated by regional differences, J. Cereb. Blood Flow Metab. 41 (8) (2021) 1978–1987.
[81] K.B. Andersen, A.K. Hansen, A.C. Schacht, et al., Synaptic density and glucose consumption in patients with Lewy body diseases: An [11C]UCB-J and [18F]FDG PET study, Mov. Disord. 38 (5) (2023) 796–805.
[82] A. Delva, K.V. Laere, W. Vandenberghe, Longitudinal imaging of regional brain volumes, SV2A, and glucose metabolism in Huntington's disease, Mov. Disord. 38 (8) (2023) 1515–1526.
[83] X.T. Fang, T. Volpi, S.E. Holmes, et al., Linking resting-state network fluctuations with systems of coherent synaptic density: A multimodal fMRI and 11C-UCB-J PET study, Front. Hum. Neurosci. 17 (2023) 1124254.
[84] J.A. Silva-Rudberg, E. Salardini, R.S. O'Dell, et al., Assessment of gray matter microstructure and synaptic density in Alzheimer's disease: A multimodal imaging study with DTI and SV2A PET, Am. J. Geriatr. Psychiatry 32 (1) (2024) 17–28.
[85] S. Tu, S. Okamoto, S.A. Lipton, et al., Oligomeric Aβ-induced synaptic dysfunction in Alzheimer's disease, Mol. Neurodegener. 9 (2014) 48.
[86] D. Pandis, N. Scarmeas, Seizures in Alzheimer disease: Clinical and epidemiological data, Epilepsy Curr. 12 (5) (2012) 184–187.
[87] J.J. Palop, L. Mucke, Epilepsy and cognitive impairments in Alzheimer disease, Arch. Neurol. 66 (4) (2009) 435–440.
[88] M. Madeo, A.D. Kovács, D.A. Pearce, The human synaptic vesicle protein, SV2A, functions as a galactose transporter in Saccharomyces cerevisiae, J. Biol. Chem. 289 (48) (2014) 33066–33071.
[89] L. Devi, M. Ohno, Effects of levetiracetam, an antiepileptic drug, on memory impairments associated with aging and Alzheimer's disease in mice, Neurobiol. Learn. Mem. 102 (2014) 7–11.
[90] E. Cumbo, L.D. Ligori, Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease, Epilepsy Behav. 17 (4) (2010) 461–466.
[91] J. Liu, L.N. Wang, Treatment of epilepsy for people with Alzheimer's disease, Cochrane Database Syst. Rev. 5 (5) (2021) CD011922.
[92] K. Vossel, K.G. Ranasinghe, A.J. Beagle, et al., Share effect of levetiracetam on cognition in patients with alzheimer disease with and without epileptiform activity: A randomized clinical trial, JAMA Neurol. 78 (11) (2021) 1345–1354.
[93] A. Sen, M. Akinola, X.Y. Tai, et al., An investigation of levetiracetam in Alzheimer's disease (ILiAD): A double-blind, placebo-controlled, randomised crossover proof of concept study, Trials 22 (1) (2021) 508.
[94] W. Botermans, M. Koole, K.V. Laere, et al., SDI-118, a novel procognitive SV2A modulator: First-in-human randomized controlled trial including PET/fMRI assessment of target engagement, Front. Pharmacol. 13 (2023) 1066447.
[95] W. Löscher, M. Gillard, Z.A. Sands, et al., Synaptic vesicle glycoprotein 2A ligands in the treatment of epilepsy and beyond, CNS Drugs 30 (11) (2016) 1055–1077.
[96] G.M. Rishton, G.C. Look, Z.J. Ni ZJ, et al., Discovery of investigational drug CT1812, an antagonist of the sigma-2 receptor complex for Alzheimer's disease, ACS Med. Chem. Lett. 12 (9) (2021) 1389–1395.
[97] N.J. Izzo, J. Xu, C. Zeng, et al., Alzheimer's therapeutics targeting amyloid beta 1-42 oligomers II: Sigma-2/PGRMC1 receptors mediate Abeta 42 oligomer binding and synaptotoxicity, PLoS One 9 (11) (2014) e111899.
[98] N.J. Izzo, A. Staniszewski, L. To, et al., Alzheimer's therapeutics targeting amyloid beta 1-42 oligomers I: Abeta 42 oligomer binding to specific neuronal receptors is displaced by drug candidates that improve cognitive deficits, PLoS One 9 (11) (2014) e111898 9.
[99] M. Grundman, R. Morgan, J.D. Lickliter, et al., A phase 1 clinical trial of the sigma-2 receptor complex allosteric antagonist CT1812, a novel therapeutic candidate for Alzheimer's disease, Alzheimers Dement. 5 (2019) 20–26.
[100] N.J. Izzo, C.M. Yuede, K.M. LaBarbera, et al., Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification, Alzheimers Dement. 17 (8) (2021) 1365–1382.
[101] S.S. Shafiei, M.J. Guerrero-Muñoz, D.L. Castillo-Carranza, Tau oligomers: Cytotoxicity, propagation, and mitochondrial damage, Front. Aging Neurosci. 9 (2017) 83.
[102] T. Toyonaga, L.M. Smith, S.J. Finnema, et al., In vivo synaptic density imaging with 11C-UCB-J detects treatment effects of saracatinib in a mouse model of Alzheimer disease, J. Nucl. Med. 60 (12) (2019) 1780–1786.
[103] J.J. Götz, J. Götz, Experimental models of tauopathy-from mechanisms to therapies, Adv. Exp. Med. Biol. 1184 (2017) 381–391.

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