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LEADING ARTICLE

Mapping the Synaptome in Neurodegeneration: Emerging Clinical Applications of SV2A PET Imaging

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Abstract

Synaptic loss is a core pathological feature of neurodegenerative disorders and closely relates to cognitive and functional decline. Positron emission tomography (PET) targeting synaptic vesicle glycoprotein 2A (SV2A) has recently emerged as a promising tool for the indirect assessment of presynaptic alterations in the living human brain. This leading article discusses the evolving clinical landscape of SV2A PET across the neurodegenerative spectrum, emphasizing its translational trajectory and emerging applications. Current evidence spans Alzheimer's disease (AD), other dementias, movement disorders, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). The literature is currently dominated by PET with [^{11}C]UCB-J, while [^{18}F]-labeled tracers, particularly [^{18}F]SynVesT-1, are expanding clinical feasibility through longer half-life and broader distribution potential. Across disorders, PET consistently detected SV2A reductions that frequently correlated with cognition, disease severity, and complementary biomarkers, including amyloid, tau, glucose metabolism, and dopaminergic imaging. Although the field remains limited by small cohorts, heterogeneous quantification strategies, and incomplete longitudinal validation, SV2A PET is rapidly evolving into a promising translational tool for studying synaptopathies and monitoring disease progression.

1 Introduction

Synaptic integrity is a fundamental determinant of normal brain function, underpinning processes ranging from sensory perception to cognition and behavior [1]. At the molecular level, synaptic vesicle proteins play a central role in neurotransmitter storage and release, ensuring efficient communication between neurons. Among these, synaptic vesicle glycoprotein 2A (SV2A) has emerged as a particularly compelling target owing to its expression across presynaptic terminals and its involvement in vesicle cycling and neurotransmission [2].

Historically, the study of synaptic alterations has relied heavily on postmortem analyses or indirect imaging markers, limiting our understanding of dynamic disease processes and treatment responses. This limitation has driven the search for in vivo biomarkers of presynaptic biology, leading to the development of positron emission tomography (PET) molecular imaging approaches targeting synaptic proteins such as SV2A [3]. However, the translation of synaptic biology into PET imaging required the identification of a molecular target that is both specific to synapses and amenable to radioligand development (Fig. 1). SV2A fulfilled these criteria, catalyzing a wave of research focused on the design and validation of selective PET tracers capable of crossing the blood–brain barrier, exhibiting high affinity and specificity, and demonstrating favorable kinetic properties. However, accumulating evidence indicates that SV2A expression is not uniform across all synapse types, and that SV2A PET should be interpreted primarily as a measure of SV2A availability rather than a direct quantification of total synapse density. Furthermore, changes in PET signal may reflect multiple biological processes, including loss of presynaptic terminals

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Key Points

Synaptic dysfunction is increasingly recognized as an important contributor to neurodegenerative disease pathophysiology and may precede overt neuronal loss or structural changes in several disorders. Consequently, in vivo assessment of synaptic integrity may provide biologically relevant information beyond conventional structural imaging.

PET imaging targeting synaptic vesicle glycoprotein 2A (SV2A) has emerged as a promising approach for investigating presynaptic integrity in living patients. Current evidence across disorders, including Alzheimer's disease, Parkinsonian syndromes, frontotemporal dementia, and Huntington's disease, suggests that PET can identify clinically meaningful patterns of SV2A reductions in neurodegenerative disorders.

The future clinical translation of SV2A PET will depend on methodological standardization, longitudinal validation, and integration with complementary imaging biomarkers, together with advances in fluorine-labeled radiotracers, acquisition strategies, and quantitative approaches.

and alterations in SV2A protein expression [4]. Given that synaptic degeneration is a hallmark of numerous neurological disorders, the ability to assess presynaptic alterations in vivo represents a major unmet need in both research and clinical practice [5].

The progressive failure of neural networks across the spectrum of neurodegenerative diseases is increasingly recognized as a process that begins well before the appearance of macroscopic structural changes. In this context, the concept of the "synaptome," originally introduced by Grant's group as the comprehensive molecular organization of synapse populations across the brain, emerges as a critical framework for understanding disease topography [6]. While traditional neuroimaging focuses on late-stage atrophy, the advent of SV2A-targeted PET imaging holds the promise to move the study of the human synaptome forward. In this regard, the development of SV2A-targeting radiotracers represents a paradigmatic example of translational neuroscience. Initial efforts were guided by the pharmacological properties of antiepileptic drugs such as levetiracetam, which binds selectively to SV2A [7]. This provided a crucial starting point for medicinal chemistry programs aimed at generating radiolabeled analogs suitable for PET imaging. Over time, several candidate tracers were synthesized and evaluated through iterative preclinical studies, including in vitro binding assays, autoradiography, and in vivo imaging in animal models [8, 9]. These investigations were essential for optimizing tracer characteristics such as binding potential, metabolic stability, and signal-to-noise ratio, ultimately enabling the selection of compounds with the highest likelihood of success in human studies.

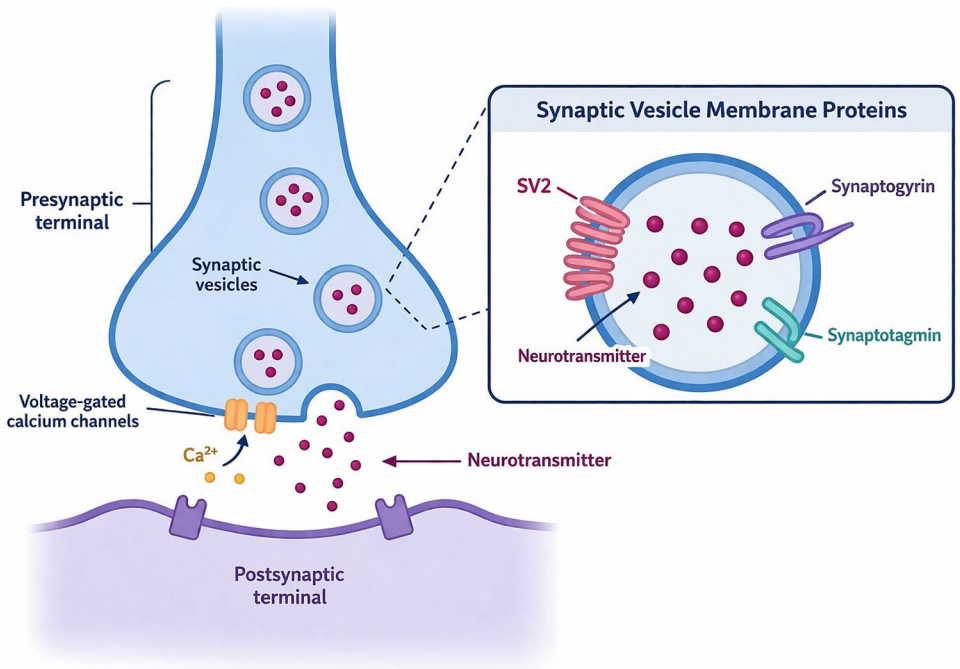

Fig. 1 Schematic representation: on the left, the postsynaptic terminal and synaptic vesicles are shown; on the right, the localization of the target (SV2A, a protein with ~ 12 transmembrane domains) and other vesicular targets (synaptogyrin and synaptotagmin) are illustrated (adapted from [26])

In preclinical and preliminary clinical studies, [^{11}C]UCB-J provided high-resolution imaging of SV2A presynaptic availability, but the short half-life of about 20 min limited its widespread clinical use, requiring on-site cyclotron production [9]. Accordingly, the development of SV2A PET radiotracers has recently shifted from [^{11}C]-labeled compounds to [^{18}F]-analogs such as SynVesT, motivated by their longer half-life and broader clinical applicability [10, 11]. This transition is expected to facilitate translational applications, including longitudinal studies of presynaptic integrity in neurodegenerative diseases and the evaluation of SV2A-targeting therapies [12, 13].

This article discusses the emerging clinical applications of SV2A PET imaging, highlighting its translational trajectory, current evidence, and future role as a biomarker of presynaptic integrity in neurodegeneration. Table 1 summarizes the key characteristics of PET imaging studies targeting SV2A alterations across several neurodegenerative disorders.

2 Alzheimer's Disease and Other Dementias

Mecca et al. used [^{11}C]UCB-J PET imaging targeting SV2A to quantify in vivo presynaptic alterations in individuals with early Alzheimer's disease (AD) [14]. They reported that global SV2A binding (i.e., distribution volume ratio [DVR]) was strongly associated with global cognition and performance across five cognitive domains (Fig. 2). Notably, PET-measured SV2A signal outperformed gray matter volume as a predictor of cognitive impairment, and these associations remained significant after partial volume correction. Regional analyses showed widespread cortical correlations, particularly in prefrontal, temporal, and parietal areas, whereas medial temporal regions exhibited weaker relationships. In a more recent study from the same group [15], the relationship between presynaptic integrity and cerebrospinal fluid (CSF) biomarkers in AD was investigated using SV2A PET imaging. The study evaluated participants aged 50–85 years, including individuals with AD, mild cognitive impairment (MCI), and cognitively normal (CN) controls, who underwent [^{11}C]UCB-J PET scans to quantify SV2A binding, as measured by DVR, and [^{11}C]Pittsburgh compound B ([^{11}C]PiB) PET scans to assess amyloid-β accumulation. CSF levels of SV2A, along with other synaptic and axonal proteins, such as SNAP25, neurogranin, GAP-43, and synaptotagmin-1, were measured to examine correlations with PET-derived SV2A signal. Results demonstrated that CSF SV2A was significantly reduced in participants with AD and strongly correlated with global SV2A PET binding, whereas other CSF markers showed weak or nonsignificant associations. These findings were largely consistent with another study conducted by the same research group [16], which demonstrated that PET-measured SV2A binding with [^{11}C]UCB-J was positively associated with CSF markers in patients with AD, but not in cognitively normal controls. Specifically, correlations were observed with AP2B1, neurogranin, γ-synuclein, GDI-1, PEBP-1, syntaxin-1B, and syntaxin-7, whereas no significant associations were found with neuronal pentraxins or 14-3-3 zeta/delta, highlighting the selective relationship between PET-derived SV2A signal and certain presynaptic and postsynaptic protein markers in AD.

O'Dell et al. used [^{11}C]UCB-J PET imaging targeting SV2A combined with principal component analysis (PCA) to characterize spatial covariance patterns of presynaptic integrity in 45 amyloid-positive individuals with AD and 19 cognitively normal controls [17]. PCA identified three principal components explaining approximately 70% of the variance in SV2A PET-derived DVR across 42 brain regions. Within the AD group, the first component, reflecting global SV2A binding, was positively associated with global cognition and all cognitive domains. Additional components captured regionally specific patterns, showing associations with age and disease severity. No significant relationships were observed in controls, highlighting disease-specific network alterations. These findings suggested that multivariate SV2A PET approaches could reveal spatially distributed presynaptic networks linked to clinical features in early AD.

More recently, Luan et al. used [^{18}F]SynVesT-1 PET imaging to investigate the propagation of PET-derived SV2A reductions across the AD spectrum in a large cohort including cognitively unimpaired and amyloid-beta (Aβ)-positive individuals [18]. Participants were retrospectively selected on the basis of availability of multimodal imaging data (magnetic resonance imaging [MRI], amyloid PET, and SV2A PET) acquired at the same visit. They reported that PET-measured SV2A binding, quantified as w-scores on the basis of standardized uptake value ratio (SUVR), progressively decreased from preclinical to dementia stages, with prominent involvement of lateral temporal, frontal, and posterior cortical regions. Connectivity analyses demonstrated that synaptic loss covaries across functionally and structurally connected regions, suggesting network-driven propagation mechanisms. Furthermore, synaptic alterations were associated with amyloid burden and plasma p-tau181, with evidence supporting a mediating role of tau pathology. These findings suggest that [^{18}F]SynVesT-1 PET might be employed to capture network-level presynaptic SV2A alterations linked to core AD pathophysiological processes.

Technical issues need to be considered in SV2A-targeted imaging. In this regard, the effect of partial volume correction (PVC), potentially affecting the reliability of PET imaging with [^{11}C]UCB-J, was investigated [19]. To disentangle

Table 1 Key characteristics of PET imaging studies targeting SV2A reductions and related pathways in neurodegenerative diseases

Study (author, year, country)	Disorder	Type of study	Sample (*n*)	SV2A tracer	Admin. activity	Imaging modality	Main quantitative measures	Co-administered tracers	Key findings
Lu et al., 2021, USA [19]	Alzheimer's disease	Methodological cross-sectional study	17 AD (+11 CN for reference)	[^{11}C]UCB-J	550 ± 208 MBq	Dynamic scans (60-min duration)	Distribution volume (V_t), rate constant (K_1), and BPND	[^{11}C]PiB (A)	Partial volume correction (PVC) significantly influenced PET outcomes, with iterative Yang correction providing good sensitivity to hippocampal SV2A reductions in Alzheimer's disease
Mecca et al., 2022, USA [14]	Alzheimer's disease (early AD, MCI + mild dementia)	Prospective, cross-sectional observational study	45 AD (+19 CN for reference)	[^{11}C]UCB-J	740 MBq	Dynamic scans performed for either 60 or 90 min following the injection of a bolus	DVR (global and regional), cognitive scores	[^{11}C]PiB (A)	SV2A binding strongly correlates with global cognition and all domains; stronger predictor than GM volume; widespread cortical associations
O'Dell et al., 2023, USA [17]	Alzheimer's disease	Observational cross-sectional study with a case-control comparison	45 AD (+19 CN)	[^{11}C]UCB-J	740 MBq	Dynamic [^{11}C]UCB-J scans acquired up to 90 min following the injection of a bolus	DVR + PCA components	[^{11}C]PiB (A)	PCA identified SV2A-related networks; global component correlates with cognition; other components linked to age and disease severity; effects specific to AD

Table 1 (continued)

Study (author, year, country)	Disorder	Type of study	Sample (*n*)	SV2A tracer	Admin. activity	Imaging modality	Main quantitative measures	Co-administered tracers	Key findings
Van Dyck et al., 2024, USA [20]	Alzheimer's disease	Phase 1/2 pilot trial	23 AD (7 placebo, 8 in the 100 mg group, 8 in the 300 mg group)	[^{11}C]UCB-J	740 MBq	90 min dynamic PET acquisition	DVR and BPND	[^{18}F]FDG (N)	The study found no significant 24-week changes in SV2A binding or glucose consumption, though volumetric MRI indicated potential tissue preservation
Li et al., 2024, China [21]	Alzheimer's disease spectrum	Cross-sectional observational study	CI: 64, CU: 33	[^{18}F]SynVesT-1	~ 3.7 MBq/kg body weight	Static PET (30 min, starting 60 min post-injection), PET/MRI	Regional SUVRs in hippocampus and PHG; global cortical [^{18}F]florbetapir SUVR	[^{18}F]florbetapir (A) [^{18}F]MK-6240 (T) [^{18}F]FDG (N)	[^{18}F]SynVesT-1 detected marked SV2A reductions, strongest in hippocampus/PHG, and SV2A binding correlated with A/T/N biomarkers, especially in amyloid-positive cognitively impaired subjects
Luan et al., 2025, China [18]	Alzheimer's disease spectrum (CU, MCI, dementia; Aβ stratified)	Observational study	~ 145 (54 CU Aβ−, 9 CU Aβ+, 28 MCI Aβ+, 54 dementia Aβ+)	[^{18}F]SynVesT-1	n.a.	30 min dynamic starting 60 min after injection, PET/MR	SUVR w-scores, connectivity analyses	[^{18}F]florbetapir (A)	SV2A reduction propagates along functional networks; progressive decline across AD stages; associations with Aβ and p-tau; tau partially mediates synaptic degeneration

Table 1 (continued)

Study (author, year, country)	Disorder	Type of study	Sample (*n*)	SV2A tracer	Admin. activity	Imaging modality	Main quantitative measures	Co-administered tracers	Key findings
Mecca et al., 2025, USA [15]	Alzheimer's disease	Cross-sectional observational study	AD: 21, CN: 7	[^{11}C]UCB-J	Up to 740 MBq	Dynamic PET scans: 60–90 min post-injection	DVR generated using reframed images from 0 to 60 min and whole cerebellum as the reference region	[^{11}C]PiB (A)	CSF SV2A was significantly lower in participants with AD and strongly correlated with PET SV2A binding, suggesting its potential utility as a biomarker of presynaptic integrity.
Nilsson et al., 2025, USA [16]	Alzheimer's disease	Observational study	AD: 21, CN: 7	[^{11}C]UCB-J	Up to 740 MBq	Dynamic PET scans: 60–90 min post-injection	DVR generated using reframed images from 0 to 60 min and whole cerebellum as the reference region	[^{11}C]PiB (A)	PET-measured SV2A signal in AD, but not controls, correlated with select CSF synaptic activity markers
Malpetti et al., 2023, USA [22]	Frontotemporal dementia	Prospective cross-sectional observational study	bvFTD: 11, HC: 25	[^{11}C]UCB-J	n.a.	Dynamic PET (90 min), PET/MR	BPND (voxel-wise and ROI-based), partial volume-corrected BPND, gray matter volume	SV2A only	Marked frontotemporal SV2A reduction, greater than atrophy, with strong association with worse cognition.
Holmes et al., 2024, USA [24]	Parkinson's disease	Prospective cross-sectional observational study	PD: 30, HC: 30	[^{11}C]UCB-J	577 ± 163 MBq	Dynamic PET (up to 90 min)	SV2A BPND (centrum semiovale reference); R1 as relative perfusion	SV2A only	PD showed reduced SV2A binding in early Braak regions, with nigral BPND linked to motor severity; longer-duration PD showed broader SV2A reduction, and R1 suggested concurrent perfusion alterations

Table 1 (continued)

Study (author, year, country)	Disorder	Type of study	Sample (*n*)	SV2A tracer	Admin. activity	Imaging modality	Main quantitative measures	Co-administered tracers	Key findings
Sabadad et al., 2025, USA [25]	Parkinson's disease	Prospective, cross-sectional observational dual-tracer PET study	PD:30, HC: 15	[^{11}C]UCB-J	549.2 ± 145.3 MBq	Dynamic PET ≥ 60 min	ROI BPND (caudate, putamen, VS, SN); intertracer Pearson partial correlations; %ΔBPND versus HC	[^{18}F]FE-PE2I(DAT)	DAT-SV2A coupling was present in controls but altered in PD; SN showed the best tracer concordance, while striatal DAT loss exceeded SV2A loss, particularly with longer disease duration
Martin et al., 2025, Canada [26]	Parkinson's disease	Prospective observational (case–control) study	PD: 10, HC: 12	[^{18}F]SynVesT-1	~ 192 ± 10 MBq	Dynamic PET (90–120 min)	BPND (reference region: centrum semiovale), voxel-wise + VOI analyses	SV2A only	Reduced SV2A binding in PD (notably substantia nigra and caudate), supporting synaptic loss
Andersen et al., 2023, Denmark [27]	Dementia with Lewy bodies	Prospective observational cross-sectional study	nPD: 21, DLB/PDD: 13, HC: 15	[^{11}C]UCB-J	500 ± 10% MBq	Dynamic 30 min PET starting 60 min post-injection	Normalized SUVR-1, VOI-based analysis in 14 composite regions, PVC, voxel-wise SPM comparisons	[^{18}F]FDG (N)	Abnormalities in glucose consumption were broader and larger than UCB-J binding loss, suggesting that hypometabolism in Lewy body disease is not explained by synaptic loss alone
Holland et al., 2023, UK [29]	Progressive supranuclear palsy and corticobasal degeneration	Longitudinal observational study (prospective)	PSP: 32, CBD: 16, HC: 33	[^{11}C]UCB-J	300 MBq (range 262–334)	Dynamic (90 min) PET/MRI	BPND via SRTM using centrum semiovale reference	[^{11}C]PiB (A)	Annualized SV2A reductions in the frontal lobe and caudate correlate with clinical and cognitive deterioration

Table 1 (continued)

Study (author, year, country)	Disorder	Type of study	Sample (*n*)	SV2A tracer	Admin. activity	Imaging modality	Main quantitative measures	Co-administered tracers	Key findings
Holland et al., 2024, UK [30]	Corticobasal syndrome	Prospective observational study	CBS: 25 (Aβ+: 8, Aβ–: 17); HC: 32	[^{11}C]UCB-J	n.s.	Dynamic (90 min) PET/MRI	BPND via SRTM using centrum semiovale reference	[^{18}F]AV-1451 (T) [^{11}C]PiB (A)	SV2A reduction was more severe and widespread in amyloid-negative CBS than in amyloid-positive CBS
Hao et al., 2026, China [31]	Progressive supranuclear palsy	Prospective observational (cross-sectional) study	PSP: 13, HC: 11	[^{18}F]SynVesT-1	3.7 MBq/kg	Static PET (scan at ~ 60 min post-injection, 10-min duration)	SUVR (ROI-based), voxel-wise analysis, ROC (AUC), correlation analyses (Spearman)	SV2A only	Significant regional SV2A reduction with high diagnostic performance (AUC up to 0.94) and correlation with disease severity markers
Delva et al., 2023, Belgium [33]	Huntington's disease (pre-manifest + early manifest)	Prospective longitudinal observational study	HD: 17, HC: 13	[^{11}C]UCB-J	182 ± 62 MBq	Static	SV2A SUVR-1 (centrum semiovale reference, PVC); longitudinal % change	[^{18}F]FDG (N)	PET detected widespread and progressive SV2A reduction (subcortical → cortical), but showed limited sensitivity to short-term longitudinal change versus MRI, likely due to higher variability
Tang et al., 2022, China [35]	Amyotrophic lateral sclerosis	Prospective cross-sectional observational study	ALS: 21, HC: 25	[18F]SynVesT-1	3.7 MBq/kg	Static PET (scan at ~ 60 min post-injection)	SUV and SUVR	SV2A only	SV2A PET allowed for identifying significantly reduced tracer uptake in patients with ALS relative to HC

Table 1 (continued)

Study (author, year, country)	Disorder	Type of study	Sample (*n*)	SV2A tracer	Admin. activity	Imaging modality	Main quantitative measures	Co-administered tracers	Key findings
de Natale et al., 2025, UK [36]	Amyotrophic lateral sclerosis	Cross-sectional (baseline of longitudinal cohort) study	ALS: 16, HC: 16	[^{11}C]UCB-J	n.s.	Dynamic (90 min, arterial sampling)	VT (primary, PVC-corrected); DVR-1 (secondary for UCB-J)	[^{18}F]BCPP-EF (MIT) [^{11}C]SA4503 (SIG)	Mitochondrial and sigma-1 receptor dysfunctions resulted in more sensitive biomarkers of ALS progression than SV2A reduction

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; Aβ, amyloid-β; A, amyloid burden; AUC, area under the curve; BPND, nondisplaceable binding potential; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CI, cognitively impaired; CN, cognitively normal; CSF, cerebrospinal fluid; CU, cognitively unimpaired; DAT, dopamine transporter; DLB, dementia with Lewy bodies; DVR, distribution volume ratio; FDG, 2-[18F]fluoro-2-deoxy-D-glucose; FTD, frontotemporal dementia; GM, gray matter; HC, healthy controls; HD, Huntington's disease; K_1, influx rate constant; MBq, megabecquerels; MCI, mild cognitive impairment; MIT, mitochondrial complex I; MRI, magnetic resonance imaging; n.a., not available; n.s., not significant; nPD, Parkinson's disease without dementia; PDD, Parkinson's disease with dementia; PD, Parkinson's disease; PET, positron emission tomography; PET/CT, positron emission tomography/computed tomography; PET/MR, positron emission tomography/magnetic resonance imaging; PHG, parahippocampal gyrus; PiB, Pittsburgh compound B; PCA, principal component analysis; PVC, partial volume correction; R1, relative tracer delivery/perfusion index; ROC, receiver operating characteristic; ROI, region of interest; SIG, sigma-1 receptors; SPM, statistical parametric mapping; SRTM, simplified reference tissue model; SN, substantia nigra; SUVR, standardized uptake value ratio; SUVR-1, standardized uptake value ratio normalized to reference region 1; SV2A, synaptic vesicle glycoprotein 2A; T, tau pathology; VT, total distribution volume; VOI, volume of interest; VS, ventral striatum; w-scores, weighted scores

the impact of gray matter atrophy from true synaptic loss in [^{11}C]UCB-J PET imaging, two PVC algorithms (Müller–Gärtner and iterative Yang) were applied. Quantitative measures, including distribution volume (VT), rate constant (K_1), and nondisplaceable binding potential (BPND), were compared between patients with AD and cognitively normal (CN) subjects. A significant reduction in SV2A binding, measured as both VT and BPND, in the hippocampus of patients with AD was observed. PVC was found to influence between-group differences, with the iterative Yang method increasing sensitivity in the hippocampus, whereas Müller–Gärtner generally reduced such differences. Overall, PET-derived measures, particularly after correction, were more sensitive to group differences than volumetric MRI. The findings suggested that algorithmic assumptions critically affected PVC outcomes, with the less restrictive assumptions of the iterative Yang method supporting its preferential use.

Of note, SV2A PET has been investigated as a potential tool for assessing the response to targeted therapies in patients with AD. A recent phase 1/2 pilot trial examined the impact of CT1812, a sigma-2 receptor ligand that allosterically displaces amyloid-β oligomers, on PET-derived SV2A binding, quantified as DVR, and glucose metabolism, quantified as SUVR, in patients with mild-to-moderate AD [20]. Using longitudinal PET imaging with [^{11}C]UCB-J to target SV2A (three time points: baseline, 12 weeks, and 24 weeks) and [^{18}F]FDG for metabolic monitoring, the study evaluated pharmacodynamic changes over 24 weeks. Results showed no statistically significant differences in PET biomarkers, clinical cognitive scales, or CSF measures between the treatment and placebo groups. In contrast, exploratory volumetric MRI analysis revealed a trend toward brain tissue preservation, with nominally significant findings in the prefrontal and hippocampal cortices. These findings suggest that any potential CT1812 neuroprotective effects might be better identified through MRI monitoring over time rather than by PET quantification of presynaptic integrity, given that current synaptic and metabolic PET measures did not immediately capture these changes.

Li et al. framed their study within the biomarker-based A/T/N classification of AD, in which tau pathology (T) was assessed using the second-generation tau PET tracer [^{18}F]MK-6240 targeting neurofibrillary tangles, amyloid burden (A) was gauged by employing [^{18}F]florbetapir, and presynaptic alterations (as a marker of neurodegeneration, [N]) were evaluated with [^{18}F]SynVesT-1 PET/magnetic resonance (MR) [21]. Contextually, glucose metabolism was determined with [^{18}F]FDG. In a cohort of 97 participants, the authors showed that SV2A reduction (quantified by SUVR) was most pronounced in the hippocampus and parahippocampal gyrus, especially in cognitively impaired, amyloid-positive subjects, while

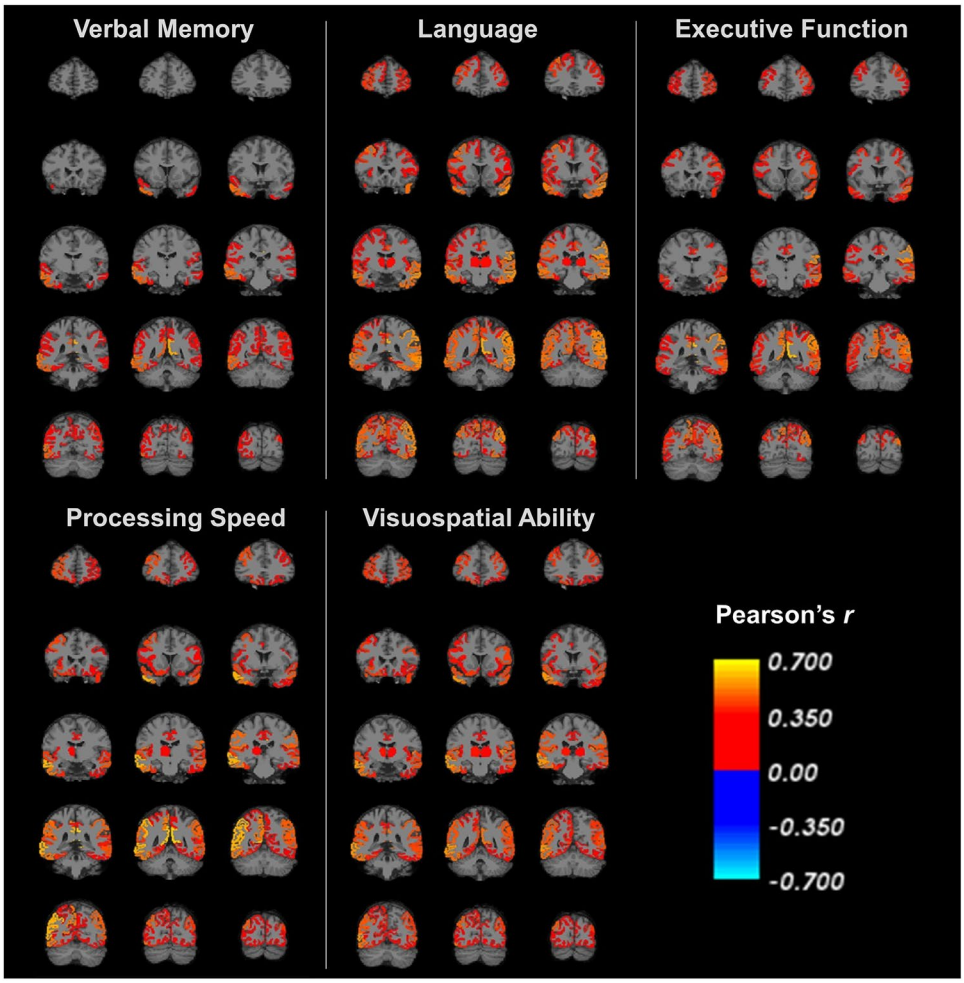

Fig. 2 Regional correlation maps between SV2A availability (DVR) and domain-specific cognitive performance in participants with Alzheimer's disease. Pearson's correlation coefficients (r) were computed between SV2A signal ([^{11}C]UCB-J DVR) and scores in **A** verbal memory, **B** language, **C** executive function, **D** processing speed, and **E** visuospatial abilities. For visualization purposes, each region was assigned a uniform r value and projected onto a standard T1-weighted MRI brain template. The color scale reflects correlation strength and is shown only for regions reaching an uncorrected significance threshold ($p < 0.05$). SV2A signal was quantified as DVR using the whole cerebellum as reference. Reprinted from [14] under a creative commons attribution 4.0 international license (http://creativecommons.Org/licenses/by/4.0/). No changes were made

amyloid-negative impairment showed a more limited pattern. Across the cohort, reduced SV2A binding was associated with higher amyloid and tau burden, while higher PET-derived SV2A signal paralleled preserved glucose metabolism ([^{18}F]FDG) and hippocampal volume. Plasma Aβ42/40 and p-tau181 also mirrored the imaging findings, with stronger correlations in the amyloid-positive cognitive impairment subgroup, which suggested that blood biomarkers may have reflected the same synaptic vulnerability. Overall, the authors concluded that [^{18}F]SynVesT-1 PET had complemented amyloid and tau imaging by offering a distinct, biologically meaningful readout of synaptic dysfunction across the AD continuum.

Frontotemporal dementia (FTD) represents another major cause of early onset cognitive decline, characterized by prominent behavioral and executive dysfunction and marked frontotemporal neurodegeneration. In this context, presynaptic alterations are thought to play a central role in disease pathophysiology and may precede overt structural atrophy. In this framework, Malpetti and coworkers investigated presynaptic integrity in vivo using SV2A PET imaging with [^{11}C]UCB-J in patients with behavioral variant FTD (bvFTD) compared to healthy controls [22]. In their cross-sectional study integrating dynamic PET acquisition and MRI, SV2A signal was quantified including voxel-wise and region of interest (ROI)-based BPND analyses, together with partial-volume-corrected BPND and gray matter volume comparisons. The authors demonstrated widespread bilateral reductions in SV2A binding across frontal, temporal, and limbic regions, consistent with a diffuse synaptic deficit. Notably, these alterations exceeded the degree of gray matter atrophy and significantly correlated with cognitive impairment, supporting the potential role of SV2A PET as a sensitive in vivo marker of synaptic dysfunction and a promising tool for disease characterization and monitoring in FTD.

3 Parkinson's Disease and Atypical Extrapyramidal Syndromes

Parkinson's Disease (PD) is increasingly conceptualized as a heterogeneous disorder with distinct pathogenic trajectories, including the "body-first" and "brain-first" subtypes, which may differ in the spatial and temporal progression

of neurodegeneration [23]. Within this framework, synaptic loss is thought to represent an early and clinically relevant hallmark of disease progression, potentially preceding overt neuronal death and structural changes detectable with conventional imaging. In a recent cross-sectional PET study, Holmes and coworkers used the SV2A tracer [^{11}C]UCB-J to probe presynaptic alterations in PD versus age- and sex-matched healthy controls, aiming to link synaptic loss with clinical severity [24]. The authors enrolled 30 patients with PD and 30 controls, showing lower SV2A BPND in PD, especially in the substantia nigra, brainstem, and caudate, with additional involvement of olfactory and frontal regions in exploratory analyses. Lower nigral PET-measured SV2A binding correlated with worse motor impairment (MDS-UPDRS part III), supporting SV2A PET as a clinically relevant biomarker of PD pathology rather than a purely anatomical readout. In the subgroup with longer disease duration (> 6 years), SV2A reduction was broader and more pronounced, extending beyond early Braak-stage regions to cortical and subcortical territories, in line with progressive disease spread. The same scan also yielded an R1-derived perfusion signal, which showed reduced relative perfusion in PD and additional associations with symptom burden, suggesting that [^{11}C]UCB-J PET may provide complementary information on synaptic integrity and regional perfusion.

The combined use of dopamine transporter (DAT) tracers and SV2A-targeting radioligands enables a multilevel in vivo assessment of nigrostriatal degeneration, capturing both dopaminergic terminal integrity and global presynaptic biology, thus providing complementary readouts of neurodegeneration. Sadabad and colleagues compared [^{18}F]FE-PE2I (targeting DAT) and [^{11}C]UCB-J PET in 30 patients with PD and 13 healthy controls scanned on separate days [25]. Using BPND in the caudate, putamen, ventral striatum, and substantia nigra, they found that DAT and SV2A covaried in controls, but this physiological coupling was largely disrupted in PD. In PD, the striatal DAT loss was more pronounced than SV2A loss, especially in earlier disease, whereas the substantia nigra showed the closest overlap between the two tracers. Overall, these findings support a stage-dependent decoupling between dopaminergic degeneration and SV2A reduction, highlighting the complementary role of the two imaging modalities.

Recently, Martin and coworkers investigated presynaptic integrity in PD using the SV2A radiotracer [^{18}F]SynVesT-1 PET in a cohort of patients with PD and healthy controls [26], as shown in Fig. 3. Dynamic PET acquisition with kinetic modeling revealed significantly reduced BPND in key PD-related regions, including the substantia nigra and caudate nucleus, with voxel-wise confirmation in the putamen and cerebellum. Exploratory analyses suggested more widespread cortical and subcortical reductions, although these did not survive multiple comparison correction. No significant correlations were observed between SV2A binding and clinical measures of disease severity or cognition. Overall, the study confirmed reduced SV2A binding in PD and supported the comparability of [^{18}F]SynVesT-1 with previous SV2A tracers, supporting its utility for future clinical and longitudinal applications.

In the context of synaptic imaging in Lewy body disorders, Andersen and coworkers investigated the relationship between PET-measured SV2A signal and cerebral metabolism by combining PET with [^{11}C]UCB-J and glucose metabolism imaging with [^{18}F]FDG in a cohort including patients with PD with dementia (PDD) and without dementia (nPD), dementia with Lewy bodies (DLB), and healthy controls [27]. The primary outcome measure consisted of normalized SUVR-1 values, assessed using both volume of interest (VOI)-based and voxel-wise analyses to quantify SV2A PET signal and [^{18}F]FDG uptake. The authors reported that patients with DLB/PDD exhibited widespread cortical reductions in both SV2A binding and glucose uptake, whereas nPD individuals showed only limited alterations. Notably, the extent and magnitude of hypometabolism consistently exceeded the corresponding reductions in PET-measured SV2A signal across multiple cortical regions. These findings suggested that the metabolic deficits characterizing Lewy body diseases cannot be fully explained by reductions in SV2A PET binding alone, pointing toward additional network-level or subcortical mechanisms contributing to the observed phenotype.

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are primary four-repeat (4R) tauopathies that represent the most common forms of atypical parkinsonian syndromes. These disorders are histopathologically defined by the abnormal accumulation of hyperphosphorylated tau protein with four microtubule-binding repeats, leading to severe neuroinflammation and precocious synaptic loss. Clinically, they manifest with overlapping features of motor impairment, cognitive decline, and gaze abnormalities, often posing a diagnostic challenge [28]. Since presynaptic integrity is expected to represent a more sensitive marker of functional impairment than gross atrophy, in vivo quantification of the SV2A might emerge as an essential tool to track disease progression and evaluate neuroprotective strategies in these specific parkinsonian variants. Holland and coworkers conducted a longitudinal [^{11}C]UCB-J PET study to quantify the rate of presynaptic alterations, as measured by BPND, in patients with PSP and CBD [29]. The authors identified significant annualized binding potential reductions in the frontal lobe (− 3.5%) and right caudate (− 3.9%). These longitudinal decreases in SV2A availability were associated with worsening clinical scores on the PSP Rating Scale and Addenbrooke's Cognitive Examination. The study suggested that SV2A PET might be a sensitive biomarker for monitoring

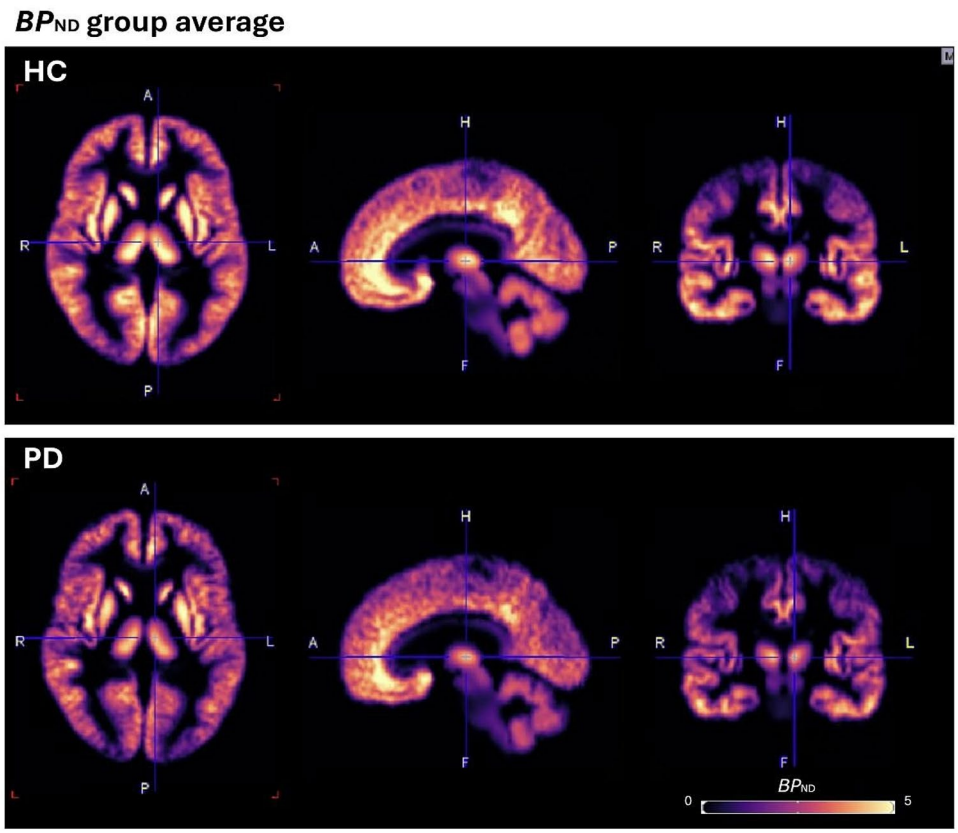

Fig. 3 Group-averaged maps of binding potential (BPND) in healthy controls (HC, $n = 12$) and participants with Parkinson's disease (PD, $n = 10$). Images are displayed with the color scale indicating BPND values. Visual comparison suggests a reduction in BPND across the PD group relative to healthy controls. Reprinted from [26] under a creative commons attribution 4.0 international license (http://creativecommons.Org/licenses/by/4.0/). No changes were made

disease progression and evaluating the efficacy of potential disease-modifying therapies. Subsequently, the same research group investigated the relationship between SV2A availability, tau burden, and b-amyloid status in 25 patients with corticobasal syndrome using [^{11}C]UCB-J, [^{11}C]PiB, and [^{18}F]AV-1451 PET imaging [30]. The study demonstrated that while both reduced [^{11}C]UCB-J binding (i.e., BPND) and increased [^{18}F]AV-1451 uptake significantly correlated with clinical severity, SV2A reduction was notably more severe and widespread in amyloid-negative cases compared to amyloid-positive individuals. These findings indicate that the reduction of PET-derived SV2A binding represents a core feature of primary 4R-tauopathies, often exceeding the spatial distribution of tau aggregates. Furthermore, the dissociation between synaptic loss and amyloid status suggested that SV2A imaging may provide a more sensitive and specific metric for neurodegeneration in CBD than traditional protein-based biomarkers.

On the same path, a recently published paper by Hao et al. reported the first application of [^{18}F]SynVesT-1 PET in PSP, demonstrating widespread reductions in SV2A binding across midbrain, basal ganglia, thalamus, and frontal regions compared to healthy controls [31]. The study employed both voxel-wise and ROI-based analyses, showing significantly decreased SUVR values, with the left caudate providing high diagnostic accuracy (AUC = 0.94). Notably, PET-derived SV2A binding correlated positively with the midbrain-to-pons ratio, suggesting a link with disease severity. The use of a static acquisition protocol and SUVR quantification supported clinical feasibility, highlighting SV2A PET as a promising biomarker for early diagnosis and disease monitoring in PSP.

4 Other Neurodegenerative Disorders

Huntington's disease (HD) is a progressive neurodegenerative disorder in which synaptic dysfunction is thought to occur early and may precede overt neuronal loss, making SV2A PET a promising biomarker of disease progression [32]. However, longitudinal evidence comparing synaptic imaging to established modalities such as volumetric MRI and [^{18}F]FDG PET has been lacking, particularly in early disease stages relevant for disease-modifying trials. Delva and coworkers performed a longitudinal multimodal imaging study combining [^{11}C]UCB-J PET, [^{18}F]FDG PET, and volumetric MRI in premanifest and early manifest HD mutation carriers versus healthy controls [33]. Their principal outcome measures included longitudinal changes in partial-volume-corrected SUVR-1 and regional percentage changes over time. They enrolled 17 HD subjects and 13 controls submitted to PET imaging at baseline and after ~ 21 months,

showing widespread baseline SV2A reductions in striatal and cortical regions, with progressive spatial extension from subcortical to cortical areas, particularly in premanifest individuals. Longitudinally, only modest declines in SV2A binding (e.g., putaminal − 6.4%) were observed and did not survive multiple comparison correction, whereas MRI detected significant volume loss in several regions. Despite lower longitudinal sensitivity, [^{11}C]UCB-J PET remained more sensitive than [^{18}F]FDG PET and MRI for cross-sectional detection of widespread synaptic alterations. Overall, these findings suggested that SV2A PET might be capable of identifying early and spatially extensive synaptic pathology, while MRI may be more robust for tracking short-term disease progression due to lower variability.

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder characterized by selective degeneration of upper and lower motor neurons, leading to muscle weakness, paralysis, and ultimately respiratory failure [34]. In exploratory research on this topic, Tang et al. utilized [^{18}F]SynVesT-1 PET imaging to evaluate in vivo presynaptic changes in patients with ALS [35]. The authors identified significant reductions in tracer uptake, expressed as SUV and SUVR, within the temporal lobe, inferior frontal gyrus, anterior cingulate, and hippocampus-insula regions, mapping the neuroanatomical correlates of cognitive and behavioral dysfunction. By comparing clinical subtypes, the researchers found distinct profiles of PET-derived SV2A binding for bulbar and spinal onset, suggesting that SV2A PET is a sensitive biomarker for extra-motor cortical involvement and disease stratification. More recently, De Natale et al. performed a cross-sectional PET study combining three different tracers: [^{11}C]UCB-J, targeting SV2A; [^{18}F]BCPP-EF, selectively binding to mitochondrial complex I; and [^{11}C]SA4503, directed toward the sigma-1 receptor [36]. The authors enrolled cognitively normal patients, patients with limb-onset ALS, and matched healthy controls. Using dynamic acquisitions with arterial input and kinetic modeling (i.e., VT as the primary endpoint), they observed no significant global reduction in SV2A binding across the whole ALS cohort, with only a localized increase in the posterior cingulate in slow progressors. Conversely, mitochondrial and sigma-1 receptor deficits were prominent, particularly in moderate-to-fast progressors, involving limbic and cortical regions and correlating with clinical severity. These findings suggest that PET-measured SV2A reduction may be subtle or stage-dependent in ALS, whereas mitochondrial and endoplasmic reticulum-related dysfunction appear to be more sensitive markers of disease progression.

Overall, PET can provide a sensitive readout of early and widespread SV2A reduction in Huntington's disease, but its role in ALS appears limited, suggesting that synaptic loss may be less prominent or biologically distinct compared to other disease mechanisms.

5 Methodological Considerations for PET SV2A Imaging

Although the biological rationale underlying SV2A PET is now well-established, several methodological issues continue to influence the interpretation, reproducibility, and eventual clinical translation of this imaging approach. As with all quantitative brain PET techniques, partial volume effects represent a major source of bias, particularly in neurodegenerative diseases characterized by progressive cortical atrophy. In this setting, spillover between gray matter, white matter, and cerebrospinal fluid may lead to underestimation of tracer uptake, making PVC an important component of quantitative analysis [37]. However, different PVC algorithms rely on distinct mathematical assumptions and may produce substantially different quantitative estimates. Among the approaches currently applied to SV2A PET, the iterative Yang algorithm has generally demonstrated greater sensitivity for detecting regional SV2A reductions than the Müller–Gärtner method, particularly within severely atrophic structures such as the hippocampus [19]. This difference likely reflects the less restrictive assumptions of the iterative Yang method regarding tissue homogeneity and spillover correction, although no universally accepted correction strategy has yet emerged. Consequently, PVC methodology should be carefully considered when comparing results across studies, especially when subtle disease-related differences are investigated.

An equally important source of variability concerns tracer quantification. Current studies have employed a range of outcome measures (i.e., VT, BPND, DVR, SUVR, etc.), each reflecting different levels of methodological complexity and biological interpretation. VT, generally estimated from dynamic acquisitions combined with arterial blood sampling, remains the most comprehensive measure of tracer distribution but is operationally demanding and therefore difficult to implement outside specialized research centers [38]. Reference tissue approaches yielding BPND or DVR avoid arterial sampling and have therefore become the most widely adopted quantitative methods for [^{11}C]UCB-J studies, provided that an appropriate reference region can be identified. By contrast, recent investigations using [^{18}F]-labeled tracers, particularly [^{18}F]SynVesT-1, have increasingly explored static acquisition protocols with SUVR measurements, reflecting the need for clinically feasible imaging protocols suitable for larger cohorts and multicenter studies [39]. Although simplified approaches substantially improve clinical practicality, they remain dependent on assumptions regarding tracer kinetics and equilibrium conditions, and their equivalence to fully quantitative kinetic modeling continues to require further validation.

The selection of an appropriate reference region represents another unresolved methodological issue [40]. Unlike several receptor PET tracers, SV2A is widely expressed throughout the brain, making the identification of tissue devoid of specific binding inherently challenging. Consequently, different studies have adopted alternative reference regions or kinetic models, including cerebellar and white matter-based approaches, each associated with specific advantages and limitations. The absence of a universally accepted reference standard inevitably contributes to inter-study heterogeneity and complicates direct comparison of quantitative results. Likewise, acquisition protocols remain heterogeneous, ranging from fully dynamic imaging with compartmental modeling to simplified static acquisitions, reflecting the current balance between quantitative accuracy and clinical feasibility. While dynamic imaging remains the reference standard for biological validation and tracer characterization, simplified acquisition strategies are likely to play a pivotal role in the future dissemination of SV2A PET, provided that they demonstrate robust agreement with kinetic modeling across different tracers, disease populations, and imaging centers.

Overall, these methodological considerations should not be regarded simply as technical limitations but rather as critical determinants of biological interpretation. Harmonization of acquisition protocols, quantitative outcome measures, reference region selection, and image processing pipelines will be essential before SV2A PET can be fully integrated into multicenter studies, longitudinal therapeutic trials, and ultimately routine clinical practice. The recent transition from [^{11}C]- to [^{18}F]-labeled radioligands represents an important step toward broader clinical implementation, but methodological standardization remains equally necessary to ensure that quantitative differences across studies reflect true biological variation rather than analytical variability. Table 2 compares the principal quantitative approaches currently used for SV2A PET and their respective strengths and limitations.

6 Toward Clinical Implementation of SV2A PET

Current evidence supports SV2A PET as a sensitive in vivo biomarker of presynaptic SV2A availability and presynaptic alterations in neurodegenerative diseases (Table 3). Despite methodological heterogeneity, available studies demonstrate a remarkably consistent pattern of reduced SV2A PET binding across neurodegenerative disorders, with moderate-to-large effect sizes and robust clinical correlations, particularly in AD.

An important conceptual consideration is that current SV2A PET radiotracers quantify the in vivo availability of the SV2A protein rather than total synapse number [4]. Although reductions in SV2A PET binding are commonly interpreted as reflecting synaptic loss, recent experimental evidence suggests that SV2A is expressed in specific subsets of synapses rather than uniformly across the entire synaptome, and that PET signal changes may also arise from altered SV2A expression within surviving presynaptic terminals. In addition, experimental studies suggest that SV2A expression is heterogeneous across different synapse populations and may be differentially affected by disease-specific pathological processes [4]. Furthermore, because SV2A is the molecular target of antiepileptic agents such as levetiracetam, the potential influence of pharmacological modulation on tracer binding should be considered in future longitudinal and therapeutic studies, although current evidence in neurodegenerative populations remains limited. Consequently, SV2A PET should be regarded as a biologically informative biomarker of presynaptic SV2A availability, while its interpretation as a direct measure of global synapse density should be made cautiously and within the context of complementary pathological and imaging evidence.

A major challenge in the field is how to position SV2A PET relative to [^{18}F]FDG, because both are ultimately related to synaptic physiology, but they are not equivalent biomarkers since they capture distinct biological processes [41]. [^{18}F]FDG is best understood as an indirect marker of

Table 2 Common quantitative outcome measures used in SV2A PET

Metric	Requires dynamic scan	Arterial input	Advantages	Limitations
VT	Yes	Usually yes	Quantitative gold standard	Requires arterial sampling and complex kinetic modeling
BPND/DVR	Yes	No (reference model)	Widely validated, avoids arterial sampling	Depends on validity of the reference region assumption
SUVR	No (static)	No	Simple and clinically practical	Semi-quantitative; affected by uptake timing and flow

VT, distribution volume; BPND, nondisplaceable binding potential; DVR, distribution volume ratio; SUVR, standardized uptake value ratio

Table 3 Disease-level synthesis of SV2A PET findings across major neurodegenerative disorders

Macro-area disease		SV2A reduction	Predominant affected regions	Clinical correlations	Key pathophysiological insights
Alzheimer's disease and other dementias	Alzheimer's disease	Moderate–severe (~ 20–40%)	Temporal, parietal, posterior cortex	Strong (global cognition and domains)	Early, widespread SV2A reduction; closely linked to amyloid/tau pathology
	Frontotemporal dementia	Marked	Frontal, temporal, limbic regions	Strong (executive/behavioral impairment)	SV2A reduction > atrophy; prominent network involvement > atrophy
Parkinson's disease and atypical extrapyramidal syndromes	Parkinson's disease (PD)	Mild–moderate	Substantia nigra, caudate, brainstem	Moderate (motor severity)	Partial dissociation from dopaminergic (DAT) loss; progressive spread
	DLB/PD with dementia	Moderate	Cortex (diffuse)	Moderate (cognition)	Metabolic impairment exceeds SV2A reduction (SV2A < [^{18}F]FDG), suggesting additional network dysfunction
	PSP/CBD	Moderate (~ 3–4% annual decline)	Frontal cortex, basal ganglia, midbrain	Moderate–strong (clinical progression)	Early and progressive SV2A alterations; may exceed tau deposition; good diagnostic performance (AUC up to 0.94)
Other neurodegenerative disorders	Huntington's disease	Early, moderate	Striatum, cortical regions	Limited	Early widespread alterations; higher cross-sectional sensitivity than [^{18}F]FDG/MRI
	Amyotrophic lateral sclerosis	Variable (region- and stage-dependent)	Frontal, temporal, limbic regions,	Limited	SV2A reduction less prominent; mitochondrial and sigma-1 alterations may predominate

DLB, dementia with Lewy bodies; PD, Parkinson's disease; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; SV2A, synaptic vesicle glycoprotein 2A; DAT, dopamine transporter; [^{18}F]FDG, 2-[^{18}F]fluoro-2-deoxy-D-glucose; AUC, area under the curve

synaptic activity: cerebral glucose uptake largely reflects neuronal energy demand linked to synaptic transmission, yet the signal is also influenced by astrocytic metabolism, neurovascular coupling, cerebral blood flow, blood glucose levels, insulin sensitivity, patient preparation, medication effects, seizure activity, sedation, and partial volume effects [42]. In other words, [^{18}F]FDG does not measure synapses per se, rather it measures metabolic demand that is often, but not always, driven by synaptic function [43]. SV2A PET, by contrast, provides a more direct measure of presynaptic SV2A availability than metabolic imaging and therefore offers a biologically specific readout of presynaptic alterations. Nevertheless, its interpretation as a surrogate of overall synapse density requires caution, given the heterogeneous expression of SV2A across synapse populations. This specificity is its main strength, especially in disorders where early synaptic failure precedes overt atrophy or frank neuronal loss. At the same time, SV2A PET is not a perfect "gold standard": it remains vulnerable to partial volume effects, tracer-specific kinetic variability, uncertainty about the best reference region, and limited standardization across sites, scanners, and analysis pipelines [19]. Furthermore, whereas [^{18}F]FDG has decades of clinical validation and a very large evidence base, SV2A PET is still in the translational phase, so its incremental value over established metabolic imaging must be demonstrated in larger cohorts, with test–retest data, multicenter harmonization, and longitudinal outcome studies [44]. The real opportunity is not to frame [^{18}F]FDG and SV2A as competing techniques, but to define when they are redundant and when they are complementary. In that framework, [^{18}F]FDG may remain superior for mapping global metabolic network failure, while SV2A may better capture synaptic terminal loss, regional vulnerability, and disease-specific propagation patterns. This distinction is particularly important in AD and DLB, where metabolic impairment can exceed synaptic loss, suggesting that hypometabolism reflects a broader biological construct rather than presynaptic degeneration alone. A comparative overview of SV2A PET in relation to established neuroimaging biomarkers, including its biological specificity, clinical applicability, and main limitations, is provided in Table 4.

The same logic applies to movement disorders, where SV2A PET may add information that disease-specific tracers cannot provide. In PD, one of the most interesting clinical questions is whether SV2A PET can help distinguish body-first from brain-first phenotypes [45]. This is a genuinely relevant challenge, because the two trajectories may differ in their earliest anatomical involvement, time of spread, and relative contribution of autonomic versus central pathology. A presynaptic synaptic tracer such as [^{11}C]

UCB-J or [^{18}F]SynVesT-1 could help define the central component of the disease process, especially in the substantia nigra, brainstem, caudate, and cortical projection areas. However, by itself it may not fully separate peripheral autonomic degeneration from central synaptopathy. That is where the comparison with iodine-123 metaiodobenzylguanidine ([^{123}I]mIBG) becomes especially valuable [46, 47]. Cardiac [^{123}I]mIBG reflects postganglionic sympathetic denervation, and therefore provides a peripheral marker of DLB biology that is conceptually different from a central SV2A readout [48]. In practice, a combined strategy could be powerful: [^{123}I]mIBG might indicate the autonomic footprint of a body-first process, whereas SV2A PET could reveal the burden and topography of central presynaptic loss. Such a multimodal approach may be more informative than any single tracer for phenotype classification, prognostication, and patient stratification in therapeutic trials. The same principle extends to dopaminergic imaging: DAT tracers remain essential for nigrostriatal terminal integrity, but they are pathway-specific rather than synapse-wide, whereas SV2A PET might represent a broader measure of presynaptic alterations. Consequently, the field should move toward comparative studies that directly test whether SV2A PET adds incremental diagnostic and prognostic information beyond DAT imaging, [^{123}I]mIBG, and, where appropriate, [^{18}F]FDG.

Another major future direction is the maturation of [^{18}F]-labeled SV2A radiotracers. The shift from [^{11}C]-labeled compounds to [^{18}F]-labeled analogs is not merely a logistical convenience; it is a prerequisite for broader dissemination, multicenter implementation, and routine clinical use. However, the field still needs rigorous validation of [^{18}F]-based ligands, both biologically and methodologically. In particular, the current validation phase of [^{18}F]SynVesT-2 should include head-to-head comparisons with established tracers, reproducibility testing, kinetic characterization, and direct assessment of sensitivity to disease stage, age, and comorbid pathology [49]. Simplified reference tissue models could play a decisive role here. If these models are shown to reproduce dynamic full-kinetic results with acceptable bias and precision, they would lower the operational burden of SV2A PET and make broader adoption much more realistic [50]. At the same time, simplified modeling should not be treated as a shortcut: it needs careful cross-validation against arterial-input or robust dynamic reference approaches, because the choice of model can materially affect group differences, effect sizes, and longitudinal sensitivity. In this sense, the next phase of the field should focus on methodological convergence: the same tracer should be tested across centers, scanners, and quantification strategies, with explicit attention to how acquisition duration, motion correction, reference region selection, and partial volume correction influence the final biological interpretation.

Technological innovation may also help solve some of the current bottlenecks in SV2A imaging. Dedicated devices such as NeuroExplorer are particularly interesting because they may improve visualization of deep brain structures, where small nuclei and high background-to-signal challenges can limit interpretability [51, 52]. This is especially relevant for disorders involving the brainstem, substantia nigra, basal ganglia, thalamus, and limbic structures, where subtle synaptic changes may be clinically important but difficult to detect with conventional systems. If dedicated hardware can improve spatial resolution, sensitivity, or quantitative stability, it could strengthen the case for SV2A PET in early disease detection and in disorders with small target structures [53]. Parallel progress in artificial intelligence (AI) and deep learning is equally important [54]. Reconstruction approaches that operate at the sinogram level may improve noise handling, partial count recovery, and lesion detectability, potentially allowing shorter acquisitions or lower injected activity without sacrificing quantitative reliability [55]. More advanced neural reconstruction pipelines may also support motion correction, harmonization across scanners, and robust automatic segmentation, all of which are critical for multicenter deployment. Still, AI-based reconstruction must be validated against truth standards, phantom data, and external cohorts; otherwise, it risks creating visually appealing but quantitatively unstable images. The best future scenario is therefore a convergent one: [^{18}F]-labeled tracers, simplified kinetic modeling, dedicated acquisition hardware, and AI-enhanced reconstruction should evolve together, not separately, to produce a clinically

Table 4 Comparative overview of SV2A PET versus other biomarkers

Domain	SV2A PET	[^{18}F]FDG PET	Amyloid PET	Tau PET	DAT imaging
Biological target	SV2A presynaptic expression	Glucose metabolism	Aβ deposition	Tau aggregates	Dopamine terminals
Specificity	High (presynaptic)	Low-moderate	High	High	High (pathway-specific)
Temporal stage	Early	Mid-late	Early	Mid	Disease-specific
Clinical use	Emerging	Established	Established	Emerging	Established
Main limitation	Standardization	Indirect measure	Weak clinical correlation	Cost/availability	Limited scope

SV2A, synaptic vesicle glycoprotein 2A; PET, positron emission tomography

Table 5 Conceptual framework for the current clinical applications of SV2A PET imaging

Key question	Current evidence	Remaining challenges
What biological process does SV2A PET measure?	Presynaptic SV2A availability as a surrogate of synaptic integrity	Not a direct measure of total synapse number; regional and disease-related variability of SV2A expression
What is the added value compared to MRI and [^{18}F]FDG PET?	Earlier detection of presynaptic alterations; stronger biological specificity	Incremental clinical value still requires prospective validation
What are the major methodological issues?	PVC, kinetic modeling, reference region selection, tracer choice	Need for harmonization across centers
What supports clinical translation?	Consistent reductions across AD, PD, FTD, PSP, and HD	Mostly cross-sectional evidence
What gaps remain?	Longitudinal studies emerging	Test–retest reproducibility, multicenter validation, treatment monitoring

AD, Alzheimer's disease; FTD, frontotemporal dementia; HD, Huntington's disease; MRI, magnetic resonance imaging; PD, Parkinson's disease; PET, positron emission tomography; PSP, progressive supranuclear palsy; PVC, partial volume correction; SV2A, synaptic vesicle glycoprotein 2A

scalable and scientifically robust SV2A PET platform. Table 5 synthesizes the current evidence according to the major questions concerning the potential implementation of SV2A PET in clinical practice.

Notably, despite encouraging cross-sectional findings, longitudinal evidence remains limited. Only a small number of studies have evaluated disease progression, generally including modest sample sizes, relatively short follow-up intervals, and heterogeneous acquisition and quantification protocols. Furthermore, although test–retest reproducibility has been reported as generally favorable for both [^{11}C]UCB-J and emerging [^{18}F]-labeled tracers in healthy individuals, additional multicenter studies are required to establish the sensitivity of SV2A PET for detecting clinically meaningful longitudinal changes and therapeutic effects [39]. Consequently, current evidence supports SV2A PET primarily as a research biomarker rather than a fully established clinical tool for monitoring disease progression or treatment response.

In conclusion, PET imaging is emerging as a powerful and biologically grounded tool to investigate presynaptic SV2A alterations in vivo, with the potential to reshape our understanding of neurodegenerative diseases, although its definitive clinical role will depend on further methodological standardization and large-scale longitudinal validation.

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Code availability Not applicable.

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