Published in final edited form as:

Neurosci Lett. 2019 January 19; 691: 44–50. doi:10.1016/j.neulet.2018.07.038.

PET Imaging of Synaptic Density: A New Tool for Investigation of Neuropsychiatric Diseases

Zhengxin Cai, Songye Li, David Matuskey, Nabeel Nabulsi, and Yiyun Huang

PET Center, Department of Radiology and Biomedical Imaging, Yale University, New Haven, CT 06520, USA

Abstract

The synaptic vesicle glycoprotein 2A (SV2A) is one of three isoforms of the synaptic vesicle glycoprotein 2. SV2A is expressed ubiquitously in neurons of the central nervous system, and is the binding target of the anti-epileptic drug levetiracetam. Because of the availability of positron emission tomography (PET) ligands targeting SV2A, recently there is increasing enthusiasm using SV2A PET in the study of a variety of neuropsychiatric diseases. This review discusses the recent development of radioligands for PET imaging of SV2A and its potential use in a variety of neuropsychiatric diseases.

Keywords

SV2A; PET; synaptic density; Alzheimer's disease; Parkinson's disease; epilepsy; stroke; multiple sclerosis; Huntington's disease; autism spectrum disorder; depression; schizophrenia

1. Introduction

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

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

tomography (PET) imaging of synaptic vesicle glycoprotein 2A (SV2A) was developed as the first-in-class noninvasive method to measure synaptic density *in vivo* [29].

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

Because SV2A is ubiquitously expressed in essentially all presynaptic vesicles [5], it can be used as a suitable biomarker for synaptic density among other proteins expressed in the presynaptic proteome and synaptic vesicles [7]. We have recently demonstrated that SV2A can be imaged and quantified by PET imaging with the novel SV2A-specific radioligand [¹¹C]UCB-J [30, 66]. Further, we have demonstrated that SV2A PET signals correlated with SV2A expression levels measured *in vitro* in different regions of the nonhuman primate brain, and that brain regional SV2A levels closely correlated with those of synaptophysin, another commonly used marker for synaptic density [29]. Hence, *in vivo* imaging of synaptic density has now become possible with the use of SV2A PET. In this brief review, we illustrate recent developments in SV2A PET imaging agents, and discuss the potential applications of SV2A PET in the investigations of neuropsychiatric diseases [72].

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

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

signals [29], while [^{11}C]UCB-A presenting slow binding kinetics in the human brain and challenges in quantitative analysis [56], and [^{18}F]UCB-H displaying rather low specific binding signals [4]. Therefore, [^{11}C]UCB-A and [^{18}F]UCB-H have significant limitations as PET radioligands for imaging and quantifying SV2A in human brains.

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

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

3.1. PET imaging of SV2A in AD

AD affects more than 35 million people worldwide, and the number is estimated to quadruple in 40 years if there remains no cure [37]. AD is characterized by the accumulation of β -amyloid ($\text{A}\beta$) plaques and hyperphosphorylated tau protein aggregates, with significant loss of neurons and atrophy at late stage, and can only be definitively diagnosed with postmortem histology staining of brain tissues [22, 83, 95]. Early symptoms of AD are marked by the impairment of declarative memories, and accumulating evidence suggests that this occurs as the hippocampal synapses are compromised by soluble β -amyloid protein oligomers during the earliest phases of AD [46–48]. Evidence also suggests that neuropathophysiological changes occur many years, if not decades, before clinical presentations start, with synapse loss preceding the accumulation of $\text{A}\beta$ plaques [80]. As one of the earliest and most consistent hallmarks of AD, regional synapse loss correlates with the severity of AD from a postmortem study of AD patients [77]. Regional synapse loss in the hippocampus and prefrontal cortex is also directly related to memory and cognitive dysfunction in prodromal AD [78]. This might happen before the extensive onset of $\text{A}\beta$ plaques and hyperphosphorylated tau tangles [81], with soluble oligomeric $\text{A}\beta$ as the main culprit for synaptic toxicity [38]. Based on this concept, interventions targeting to interrupt the toxic interactions between $\text{A}\beta$ oligomers and synapses/neurons, *e.g.*, mGluR5 antagonist, Sig2R antagonist, nAChR α_7 agonist, etc. are under active pursuit [10, 34, 40, 41, 55, 82].

SV2A PET, as a synapse marker, will be a suitable method for monitoring the therapeutic effects of these new interventions [88]. Longitudinal SV2A, $\alpha\beta$, and tau PET imaging covering the whole spectrum from preclinical AD to dementia could provide temporal information and hints on the relationship of these AD hallmarks.

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

3.2. PET imaging of SV2A in PD

As the second most common neurodegenerative disease after AD, Parkinson's disease (PD) affects more than 10 million people worldwide, and causes enormous socioeconomic burden. There is evidence showing synaptic density changes in PD animal models and post-mortem brain tissues of PD patients [70]. Though the loss of dopaminergic neurons in the striatum leads to the symptomatic disconnection of thought and action [3], synaptic loss has also been found outside of the nigrostriatal system and involves non-dopaminergic neurons in the cortex in PD [39]. Hence, synaptic dysfunction is centrally involved in PD and regional synaptic density changes are characteristic in its pathogenesis. SV2A PET imaging of synaptic density in the brains of PD patients may not only reveal disease progression, but also serve as a diagnosis or prognosis tool to facilitate the development of more effective disease-modifying interventions. A pilot SV2A PET imaging study in two PD subjects found the most significant synapse loss in the substantia nigra (25% lower uptake relative to healthy controls) (Fig. 4). Although larger cohort studies are currently underway to understand the usefulness and meaning of SV2A PET imaging in PD, these preliminary results have been very encouraging.

3.3. PET imaging of SV2A in epilepsy

Epilepsy is the fourth most common neurological disorder that affects people of all ages, with a prevalence rate of 0.5-1% [9, 71]. Patients with glioma often develop epilepsy [45].

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

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

3.4. PET imaging of SV2A in other neuropsychiatric disorders

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

Multiple sclerosis (MS) is a neurological disorder that can lead to disability from cognitive dysfunction [17]. Cognitive deficits have been reported in 40-65% of MS patients at all stages and in all subtypes [50]. These cognitive deficits are related to demyelination associated with loss of synaptic density and brain atrophy [24]. Postmortem brain pathology showed hippocampal demyelination in MS as well as significant synaptic density loss (~50%) [24, 64, 94]. Significant reduction of cortical axonal density was observed only in demyelinated areas of cortical gray matter, but loss of synapses was present also in normal appearing gray matter [44]. Hence, as a synaptic density biomarker, SV2A PET imaging may be used to monitor the progression of MS in relation to cognitive dysfunction, and treatment effects of disease-modifying therapies. MS patients also often suffer from

disabling tremors which are difficult to treat [84] and muscle spasticity[36]. Both of these conditions have been shown to improve by levetiracetam [36, 84], leading to the possibility of SV2A PET imaging in these symptoms as well.

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

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

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

4. Perspectives and future directions

SV2A has shown great promise as a biomarker for synaptic density, because of its ubiquitous expression in synapses. Although the clinical utility of SV2A imaging is largely speculative at this point, SV2A PET has the potential to be an important and valuable biomarker in the study, diagnosis, and staging of a variety of neurodegenerative and neuropsychiatric disorders, as well as in the evaluation of therapeutic effects. Clinical validation studies of this method are needed to pave the way for its uses in clinics.

Nonetheless, with the emergence of more readily available ^{18}F -labeled SV2A imaging probes, SV2A PET is expected to lead to new insights into the etiology of, and treatment strategies for neuropsychiatric disorders, as abnormal synaptic changes have been indicated in the vast majority of these diseases. SV2A PET is also expected to contribute to the drug discovery process by facilitating patient stratification, monitoring therapeutic responses, and checking the efficacy of drugs in clinical trials.

Acknowledgements

This work was supported by NIH K01EB023312, R01AG058773 and Yale internal funds. The authors thank Dr. Richard E. Carson for providing the PET images.

References

- [1]. Details on the development and evaluations of new SV2A PET imaging agents will be reported elsewhere.
- [2]. Details on the evaluation of UCB-A in nonhuman primates will be reported elsewhere.
- [3]. Albin RL, Young AB, Penney JB, The functional anatomy of basal ganglia disorders, *Trends Neurosci* 12 (1989) 366–375. [PubMed: 2479133]
- [4]. Bahri MA, Plenevaux A, Aerts J, Bastin C, Becker G, Mercier J, Valade A, Buchanan T, Mestdagh N, Ledoux D, Seret A, Luxen A, Salmon E, Measuring brain synaptic vesicle protein 2A with positron emission tomography and [(18)F]UCB-H, *Alzheimers Dement (N Y)* 3 (2017) 481–486. [PubMed: 29124105]
- [5]. Bajjalieh S, Frantz G, Weimann J, McConnell S, Scheller R, Differential expression of synaptic vesicle protein 2 (SV2) isoforms, *The Journal of Neuroscience* 14 (1994) 5223–5235. [PubMed: 8083732]
- [6]. Bao W, Jia H, Finnema S, Cai Z, Carson RE, Huang YH, PET Imaging for Early Detection of Alzheimer's Disease: From Pathologic to Physiologic Biomarkers, *PET Clin* 12 (2017) 329–350. [PubMed: 28576171]
- [7]. Bayes A, Grant SGN, Neuroproteomics: understanding the molecular organization and complexity of the brain, *Nat. Rev. Neurosci* 10 (2009) 635–646. [PubMed: 19693028]
- [8]. Becker G, Warnier C, Serrano ME, Bahri MA, Mercier J, Lemaire C, Salmon E, Luxen A, Plenevaux A, Pharmacokinetic Characterization of [(18)F]UCB-H PET Radiopharmaceutical in the Rat Brain, *Mol. Pharm* 14 (2017) 2719–2725. [PubMed: 28651055]
- [9]. Bell GS, Sander JW, The epidemiology of epilepsy: the size of the problem, *Seizure : the journal of the British Epilepsy Association* 10 (2001) 306–314; quiz 315–306.
- [10]. Beraldo FH, Ostapchenko VG, Caetano FA, Guimaraes AL, Ferretti GD, Daude N, Bertram L, Nogueira KO, Silva JL, Westaway D, Cashman NR, Martins VR, Prado VF, Prado MA, Regulation of Amyloid beta Oligomer Binding to Neurons and Neurotoxicity by the Prion Protein-mGluR5 Complex, *J. Biol. Chem* 291 (2016) 21945–21955. [PubMed: 27563063]
- [11]. Bourgeron T, From the genetic architecture to synaptic plasticity in autism spectrum disorder, *Nat Rev Neurosci* 16 (2015) 551–563. [PubMed: 26289574]
- [12]. Buckley K, Kelly RB, Identification of a transmembrane glycoprotein specific for secretory vesicles of neural and endocrine cells, *J. Cell Biol* 100 (1985) 1284–1294. [PubMed: 2579958]
- [13]. Cai H, Mangner TJ, Muzik O, Wang M-W, Chugani DC, Chugani HT, Radiosynthesis of ^{11}C -Levetiracetam: A Potential Marker for PET Imaging of SV2A Expression, *ACS Med. Chem. Lett* 5 (2014) 1152–1155. [PubMed: 25313330]
- [14]. Cai Z, Li S, Finnema S, Lin S.-f., Zhang W, Holden D, Carson R, Huang Y, Imaging synaptic density with novel ^{18}F -labeled radioligands for synaptic vesicle protein-2A (SV2A): synthesis and evaluation in nonhuman primates, *J. Nucl. Med* 58 (2017) 547. [PubMed: 28153955]
- [15]. Calhoun ME, Jucker M, Martin LJ, Thinakaran G, Price DL, Mouton PR, Comparative evaluation of synaptophysin-based methods for quantification of synapses, *J. Neurocytol* 25 (1996) 821–828. [PubMed: 9023727]

- [16]. Chen M, Mecca AP, Naganawa M, et al., Assessing synaptic density in alzheimer disease with synaptic vesicle glycoprotein 2a positron emission tomographic imaging, *JAMA Neurology* (2018) doi:10.1001/jamaneurol.2018.1836.
- [17]. Chiaravalloti ND, DeLuca J, Cognitive impairment in multiple sclerosis, *Lancet Neurol* 7 (2008) 1139. [PubMed: 19007738]
- [18]. Crevecoeur J, Kaminski RM, Rogister B, Foerch P, Vandenplas C, Neveux M, Mazzuferi M, Kroonen J, Poulet C, Martin D, Sadzot B, Rikir E, Klitgaard H, Moonen G, Deprez M, Expression pattern of synaptic vesicle protein 2 (SV2) isoforms in patients with temporal lobe epilepsy and hippocampal sclerosis, *Neuropathol Appl Neurobiol* 40 (2014) 191–204. [PubMed: 23617838]
- [19]. Crowder KM, Gunther JM, Jones TA, Hale BD, Zhang HZ, Peterson MR, Scheller RH, Chavkin C, Bajjalieh SM, Abnormal neurotransmission in mice lacking synaptic vesicle protein 2A (SV2A), *Proc Natl Acad Sci U S A* 96 (1999) 15268–15273. [PubMed: 10611374]
- [20]. Danish A, Namasivayam V, Schiedel AC, Muller CE, Interaction of Approved Drugs with Synaptic Vesicle Protein 2A, *Arch. Pharm. (Weinheim)*. 350 (2017) 1700003.
- [21]. Dong M, Yeh F, Tepp WH, Dean C, Johnson EA, Janz R, Chapman ER, SV2 Is the Protein Receptor for Botulinum Neurotoxin A, *Science* 312 (2006) 592–596. [PubMed: 16543415]
- [22]. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, Bakardjian H, Benali H, Bertram L, Blennow K, Broich K, Cavedo E, Crutch S, Dartigues J-F, Duyckaerts C, Epelbaum S, Frisoni GB, Gauthier S, Genthon R, Gouw AA, Habert M-O, Holtzman DM, Kivipelto M, Lista S, Molinuevo J-L, O'Bryant SE, Rabinovici GD, Rowe C, Salloway S, Schneider LS, Sperling R, Teichmann M, Carrillo MC, Cummings J, Jack CR, Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria, *Alzheimer's & Dementia* 12 (2016) 292–323.
- [23]. Duman RS, Aghajanian GK, Sanacora G, Krystal JH, Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants, *Nat Med* 22 (2016) 238–249. [PubMed: 26937618]
- [24]. Dutta R, Chang A, Doud MK, Kidd GJ, Ribaudo MV, Young EA, Fox RJ, Staugaitis SM, Trapp BD, Demyelination causes synaptic alterations in hippocampi from multiple sclerosis patients, *Annals of neurology* 69 (2011) 445–454. [PubMed: 21446020]
- [25]. Edvinsson J, Warfvinge K, Edvinsson L, Modulation of inflammatory mediators in the trigeminal ganglion by botulinum neurotoxin type A: an organ culture study, *The Journal of Headache and Pain* 16 (2015) 73.
- [26]. Esterlis I, Pietrzak R, DellaGioia N, Matuskey D, Huang H, Krystal J, Duman R, Carson R, Finnema S, 389. In Vivo Evidence of Lower Synaptic Density in Depression and Associated Mood and Cognitive Deficits: A [11C]UCB-J PET Imaging Study, *Biol. Psychiatry* 81 (2017) S159.
- [27]. Estrada S, Lubberink M, Thibblin A, Sprycha M, Buchanan T, Mestdagh N, Kenda B, Mercier J, Provins L, Gillard M, Tytgat D, Antoni G, [11C]UCB-A, a novel PET tracer for synaptic vesicle protein 2 A, *Nucl. Med. Biol* 43 (2016) 325–332. [PubMed: 27260773]
- [28]. Feng G, Xiao F, Lu Y, Huang Z, Yuan J, Xiao Z, Xi Z, Wang X, Down-regulation synaptic vesicle protein 2A in the anterior temporal neocortex of patients with intractable epilepsy, *J Mol Neurosci* 39 (2009) 354–359. [PubMed: 19757204]
- [29]. Finnema SJ, Nabulsi NB, Eid T, Detyniecki K, Lin SF, Chen MK, Dhaheer R, Matuskey D, Baum E, Holden D, Spencer DD, Mercier J, Hannestad J, Huang Y, Carson RE, Imaging synaptic density in the living human brain, *Sci. Transl. Med* 8 (2016) 348ra396.
- [30]. Finnema SJ, Nabulsi NB, Mercier J, Lin SF, Chen MK, Matuskey D, Gallezot JD, Henry S, Hannestad J, Huang Y, Carson RE, Kinetic evaluation and test-retest reproducibility of [(11)C]UCB-J, a novel radioligand for positron emission tomography imaging of synaptic vesicle glycoprotein 2A in humans, *J. Cereb. Blood Flow Metab* 0 (2017) 271678X17724947.
- [31]. Fourie C, Kim E, Waldvogel H, Wong JM, McGregor A, Faull RLM, Montgomery JM, Differential Changes in Postsynaptic Density Proteins in Postmortem Huntington's Disease and Parkinson's Disease Human Brains, *Journal of Neurodegenerative Diseases* 2014 (2014) 14.

- [32]. Gillard M, Chatelain P, Fuks B, Binding characteristics of levetiracetam to synaptic vesicle protein 2A (SV2A) in human brain and in CHO cells expressing the human recombinant protein, *European journal of pharmacology* 536 (2006) 102–108. [PubMed: 16556440]
- [33]. Gillard M, Fuks B, Leclercq K, Matagne A, Binding characteristics of brivaracetam, a selective, high affinity SV2A ligand in rat, mouse and human brain: relationship to anti-convulsant properties, *European journal of pharmacology* 664 (2011) 36–44. [PubMed: 21575627]
- [34]. Haas LT, Strittmatter SM, Oligomers of Amyloid β Prevent Physiological Activation of the Cellular Prion Protein-Metabotropic Glutamate Receptor 5 Complex by Glutamate in Alzheimer Disease, *J. Biol. Chem* 291 (2016) 17112–17121. [PubMed: 27325698]
- [35]. Hanaya R, Hosoyama H, Sugata S, Tokudome M, Hirano H, Tokimura H, Kurisu K, Serikawa T, Sasa M, Arita K, Low distribution of synaptic vesicle protein 2A and synaptotagmin-1 in the cerebral cortex and hippocampus of spontaneously epileptic rats exhibiting both tonic convulsion and absence seizure, *Neuroscience* 221 (2012) 12–20. [PubMed: 22766234]
- [36]. Hawker K, Frohman E, Racke M, Levetiracetam for phasic spasticity in multiple sclerosis, *Arch. Neurol* 60 (2003) 1772–1774. [PubMed: 14676055]
- [37]. Holtzman DM, John CM, Goate A, Alzheimer's Disease: The Challenge of the Second Century, *Sci. Transl. Med* 3 (2011) 77sr71–77sr71.
- [38]. Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, Merry KM, Shi Q, Rosenthal A, Barres BA, Lemere CA, Selkoe DJ, Stevens B, Complement and microglia mediate early synapse loss in Alzheimer mouse models, *Science* 352 (2016) 712–716. [PubMed: 27033548]
- [39]. Hou Z, Lei H, Hong S, Sun B, Fang K, Lin X, Liu M, Yew DTW, Liu S, Functional changes in the frontal cortex in Parkinson's disease using a rat model, *J. Clin. Neurosci* 17 (2010) 628–633. [PubMed: 20116257]
- [40]. Izzo NJ, Staniszewski A, To L, Fa M, Teich AF, Saeed F, Wostein H, Walko T, III, Vaswani A, Wardius M, Syed Z, Ravenscroft J, Mozzoni K, Silky C, Rehak C, Yurko R, Finn P, Look G, Rishton G, Safferstein H, Miller M, Johanson C, Stopa E, Windisch M, Hutter-Paier B, Shamloo M, Arancio O, LeVine H, III, Catalano SM, 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 (2014) e111898. [PubMed: 25390368]
- [41]. Izzo NJ, Xu J, Zeng C, Kirk MJ, Mozzoni K, Silky C, Rehak C, Yurko R, Look G, Rishton G, Safferstein H, Cruchaga C, Goate A, Cahill MA, Arancio O, Mach RH, Craven R, Head E, LeVine H, III, Spires-Jones TL, Catalano SM, Alzheimer's Therapeutics Targeting Amyloid Beta 1–42 Oligomers II: Sigma-2/PGRMC1 Receptors Mediate Abeta 42 Oligomer Binding and Synaptotoxicity, *PLoS One* 9 (2014) e111899. [PubMed: 25390692]
- [42]. Janz R, Goda Y, Geppert M, Missler M, Sudhof TC, SV2A and SV2B function as redundant Ca^{2+} regulators in neurotransmitter release, *Neuron* 24 (1999) 1003–1016. [PubMed: 10624962]
- [43]. Jette N, Sander JW, Keezer MR, Surgical treatment for epilepsy: the potential gap between evidence and practice, *Lancet Neurol* 15 (2016) 982–994. [PubMed: 27478955]
- [44]. Jurgens T, Jafari M, Kreutzfeldt M, Bahn E, Bruck W, Kerschensteiner M, Merkler D, Reconstruction of single cortical projection neurons reveals primary spine loss in multiple sclerosis, *Brain : a journal of neurology* 139 (2016) 39–46. [PubMed: 26667278]
- [45]. Kerkhof M, Vecht CJ, Seizure characteristics and prognostic factors of gliomas, *Epilepsia* 54 (2013) 12–17. [PubMed: 24328866]
- [46]. Koffie RM, Meyer-Luehmann M, Hashimoto T, Adams KW, Mielke ML, Garcia-Alloza M, Micheva KD, Smith SJ, Kim ML, Lee VM, Hyman BT, Spires-Jones TL, Oligomeric amyloid β associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques, *Proceedings of the National Academy of Sciences* 106 (2009) 4012–4017.
- [47]. Lacor PN, Buniel MC, Chang L, Fernandez SJ, Gong Y, Viola KL, Lambert MP, Velasco PT, Bigio EH, Finch CE, Krafft GA, Klein WL, Synaptic Targeting by Alzheimer's-Related Amyloid β Oligomers, *The Journal of Neuroscience* 24 (2004) 10191–10200. [PubMed: 15537891]
- [48]. Lacor PN, Buniel MC, Furlow PW, Sanz Clemente A, Velasco PT, Wood M, Viola KL, Klein WL, A β Oligomer-Induced Aberrations in Synapse Composition, Shape, and Density Provide a

Molecular Basis for Loss of Connectivity in Alzheimer's Disease, *The Journal of Neuroscience* 27 (2007) 796–807. [PubMed: 17251419]

- [49]. Lamberty Y, Detrait E, Leclercq K, Michel A, De Ryck M, Behavioural phenotyping reveals anxiety-like features of SV2A deficient mice, *Behav Brain Res* 198 (2009) 329–333. [PubMed: 19041904]
- [50]. Langdon DW, Cognition in multiple sclerosis, *Curr.Opin.Neurol* 24 (2011) 244. [PubMed: 21519256]
- [51]. Lepeta K, Lourenco MV, Schweitzer BC, Martino Adami PV, Banerjee P, Catuara - Solarz S, de La Fuente Revenga M, Guillem AM, Haidar M, Ijomone OM, Nadorp B, Qi L, Perera ND, Refsgaard LK, Reid KM, Sabbar M, Sahoo A, Schaefer N, Sheean RK, Suska A, Verma R, Vicidomini C, Wright D, Zhang XD, Seidenbecher C, Synaptopathies: synaptic dysfunction in neurological disorders – A review from students to students, *J. Neurochem* 138 (2016) 785–805. [PubMed: 27333343]
- [52]. Li J-Y, Plomann M, Brundin P, Huntington's disease: a synaptopathy?, *Trends Mol. Med* 9 414–420. [PubMed: 14557053]
- [53]. Li S, Cai Z, Holden D, Nabulsi N, Labaree D, Shirali A, Teng J.-k., Carson R, Huang Y, 18F-SDM-8: A novel radiotracer for PET imaging of synaptic density, *J. Nucl. Med* 59 (2018) 68.
- [54]. Li S, Cai Z, Zhang W, Nabulsi N, Finnema S, Holden D, Ropchan J, Gao H, Teng J-K, Carson R, Huang Y, Synthesis and in vivo evaluation of 18F-UCB-J: Radiotracer for PET imaging of synaptic density, *J. Nucl. Med* 58 (2017) 851.
- [55]. Lombardo S, Maskos U, Role of the nicotinic acetylcholine receptor in Alzheimer's disease pathology and treatment, *Neuropharmacology* 96, Part B (2015) 255–262. [PubMed: 25514383]
- [56]. Lubberink M, Appel L, Daging J, Lindskog K, Danfors T, Larsson E-M, Kumlien E, Antoni G, Tracer kinetic analysis of the SV2A ligand 11C-UCBA as a PET marker for synaptic density in humans, *J. Nucl. Med* 58 (2017) 631.
- [57]. Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, Fuks B, The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam, *Proc Natl Acad Sci U S A* 101 (2004) 9861–9866. [PubMed: 15210974]
- [58]. MacDonald ME, Ambrose CM, Duyao MP, Myers RH, Lin C, Srinidhi L, Barnes G, Taylor SA, James M, Groot N, MacFarlane H, Jenkins B, Anderson MA, Wexler NS, Gusella JF, Bates GP, Baxendale S, Hummerich H, Kirby S, North M, Youngman S, Mott R, Zehetner G, Sedlacek Z, Poustka A, Frischauf A-M, Lehrach H, Buckler AJ, Church D, Doucette-Stamm L, O'Donovan MC, Riba-Ramirez L, Shah M, Stanton VP, Strobel SA, Draths KM, Wales JL, Dervan P, Housman DE, Altherr M, Shiang R, Thompson L, Fielder T, Wasmuth JJ, Tagle D, Valdes J, Elmer L, Allard M, Castilla L, Swaroop M, Blanchard K, Collins FS, Snell R, Holloway T, Gillespie K, Datson N, Shaw D, Harper PS, A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes, *Cell* 72 (1993) 971–983. [PubMed: 8458085]
- [59]. Martinkovic L, Hecimovic H, Sulc V, Marecek R, Marusic P, Modern techniques of epileptic focus localization, *Int Rev Neurobiol* 114 (2014) 245–278. [PubMed: 25078505]
- [60]. Masliah E, Mallory M, Hansen L, Richard D, Alford M, Terry R, Synaptic and neuritic alterations during the progression of Alzheimer's disease, *Neurosci. Lett* 174 (1994) 67–72. [PubMed: 7970158]
- [61]. Mattheisen M, Muhleisen TW, Strohmaier J, Treutlein J, Nenadic I, Alblas M, Meier S, Degenhardt F, Herms S, Hoffmann P, Witt SH, Giegling I, Sauer H, Schulze TG, Rujescu D, Nothen MM, Rietschel M, Cichon S, Genetic variation at the synaptic vesicle gene SV2A is associated with schizophrenia, *Schizophr Res* 141 (2012) 262–265. [PubMed: 23017826]
- [62]. Mecca AP, Chen M-K, Naganawa M, Finnema SJ, Toyonaga T, Lin S.-f., McDonald JW, Michalak HR, Nabulsi NB, Huang Y, Arnsten AF, Carson RE, van Dyck CH, Poster Number: NR 14 - Initial Experience with PET Imaging of Synaptic Density (SV2A) in Alzheimer's Disease: A New Biomarker for Clinical Trials?, *The American Journal of Geriatric Psychiatry* 26 (2018) S145–S146.
- [63]. Mercier J, Archen L, Bollu V, Carre S, Evrard Y, Jnoff E, Kenda B, Lallemand B, Michel P, Montel F, Moureau F, Price N, Quesnel Y, Sauvage X, Valade A, Provins L, 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 (2014) 693–698. [PubMed: 24446373]

- [64]. Michailidou I, Willems JG, Kooi EJ, van Eden C, Gold SM, Geurts JJ, Baas F, Huitinga I, Ramaglia V, Complement Clq-C3-associated synaptic changes in multiple sclerosis hippocampus, *Annals of neurology* 77 (2015) 1007–1026. [PubMed: 25727254]
- [65]. Nabulsi N, Hannestad J, Holden D, Mercier J, Najafzadeh S, Lin S.-f., Labaree D, Laruelle M, Carson R, Huang Y, [11C]UCB-J: A novel PET tracer for imaging the synaptic vesicle glycoprotein 2A (SV2A), *J NUCL MED MEETING ABSTRACTS* 55 (2014) 355.
- [66]. Nabulsi NB, Mercier J, Holden D, Carre S, Najafzadeh S, Vandergeten MC, Lin SF, Deo A, Price N, Wood M, Lara-Jaime T, Montel F, Laruelle M, Carson RE, Hannestad J, Huang Y, 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 (2016) 777–784. [PubMed: 26848175]
- [67]. Novak MJ, Tabrizi SJ, Huntington's disease, *BMJ* 340 (2010) c3109. [PubMed: 20591965]
- [68]. Pakkenberg B, Pelvig D, Marner L, Bundgaard MJ, Gundersen HJG, Nyengaard JR, Regeur L, Aging and the human neocortex, *Exp. Gerontol* 38 (2003) 95–99. [PubMed: 12543266]
- [69]. Peng L, Tepp WH, Johnson EA, Dong M, Botulinum Neurotoxin D Uses Synaptic Vesicle Protein SV2 and Gangliosides as Receptors, *PLoS Path* 7 (2011) e1002008.
- [70]. Picconi B, Piccoli G, Calabresi P, Synaptic Dysfunction in Parkinson's Disease In: Kreutz MR, Sala C (Eds.), *Synaptic Plasticity: Dynamics, Development and Disease*, Springer Vienna, Vienna, 2012, pp. 553–572.
- [71]. Picot MC, Baldy-Moulinier M, Daures JP, Dujols P, Crespel A, The prevalence of epilepsy and pharmaco-resistant epilepsy in adults: a population-based study in a Western European country, *Epilepsia* 49 (2008) 1230–1238. [PubMed: 18363709]
- [72]. Rabiner EA, Imaging Synaptic Density: A Different Look at Neurologic Diseases, *J. Nucl. Med* 59 (2018) 380–381. [PubMed: 29123011]
- [73]. Radhakrishnan R, Skosnik P, Finnema S, Rotolo R, Forselius-Bielen K, Creatura G, Nabulsi N, Carson R, D' Souza D, 962. In-vivo Evidence of Decreased Synaptic Density in Schizophrenia: A [11C]UCB-J PET Imaging Study, *Biol. Psychiatry* 81 (2017) S389.
- [74]. Roberts RC, Barksdale KA, Roche JK, Lahti AC, Decreased synaptic and mitochondrial density in the postmortem anterior cingulate cortex in schizophrenia, *Schizophr Res* 168 (2015) 543–553. [PubMed: 26210550]
- [75]. Robinson JL, Molina-Porcel L, Corrada MM, Raible K, Lee EB, Lee VM-Y, Kawas CH, Trojanowski JQ, Perforant path synaptic loss correlates with cognitive impairment and Alzheimer's disease in the oldest-old, *Brain* 137 (2014) 2578–2587. [PubMed: 25012223]
- [76]. Ross CA, Aylward EH, Wild EJ, Langbehn DR, Long JD, Warner JH, Scahill R.L., Leavitt BR, Stout JC, Paulsen JS, Reilmann R, Unschuld PG, Wexler A, Margolis RL, Tabrizi SJ, Huntington disease: natural history, biomarkers and prospects for therapeutics, *Nature Reviews Neurology* 10 (2014) 204. [PubMed: 24614516]
- [77]. Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ, Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment, *Neurology* 68 (2007) 1501–1508. [PubMed: 17470753]
- [78]. Scheff SW, Price DA, Schmitt FA, Mufson EJ, Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment, *Neurobiol. Aging* 27 (2006) 1372–1384. [PubMed: 16289476]
- [79]. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, Tooley K, Presumey J, Baum M, Van Doren V, Genovese G, Rose SA, Handsaker RE, Schizophrenia C. Working Group of the Psychiatric Genomics, Daly MJ, Carroll MC, Stevens B, McCarroll SA, Schizophrenia risk from complex variation of complement component 4, *Nature* 530 (2016) 177–183. [PubMed: 26814963]
- [80]. Selkoe DJ, Alzheimer's Disease Is a Synaptic Failure, *Science* 298 (2002) 789–791. [PubMed: 12399581]
- [81]. Shankar G, Walsh D, Alzheimer's disease: synaptic dysfunction and Abeta, *Mol. Neurodegener* 4 (2009) 48. [PubMed: 19930651]

- [82]. Smith LM, Strittmatter SM, Binding Sites for Amyloid-beta Oligomers and Synaptic Toxicity, Cold Spring Harb. Perspect. Med 7 (2017) a024075. [PubMed: 27940601]
- [83]. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies A, Morrison-Bogorad M, Wagster MV, Phelps CH, Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimer's & Dementia 7(2011)280–292.
- [84]. Striano P, Coppola A, Vacca G, Zara F, Brescia Morra V, Orefice G, Striano S, Levetiracetam for cerebellar tremor in multiple sclerosis, J. Neurol 253 (2006) 762–766. [PubMed: 16683063]
- [85]. Stroemer RP, Kent TA, Flulsebosch CE, Increase in synaptophysin immunoreactivity following cortical infarction, Neurosci. Lett 147 (1992) 21–24. [PubMed: 1480319]
- [86]. Tang Y, Nyengaard JR, De Groot DMG, Gundersen HJG, Total regional and global number of synapses in the human brain neocortex, Synapse 41 (2001) 258–273. [PubMed: 11418939]
- [87]. Theodore WH, Presurgical Focus Localization in Epilepsy: PET and SPECT, Seminars in nuclear medicine 47 (2017) 44–53. [PubMed: 27987556]
- [88]. Toyonaga T, Smith L, Finnema S, Gallezot J-D, Naganawa M, Bini J, Cai Z, Huang Y, Strittmatter S, Carson R, Synaptic density imaging with ¹¹C-UCB-J detects treatment effects of a Fyn tyrosine kinase inhibitor on Alzheimer's disease mice, J. Nucl. Med 59 (2018) 197. [PubMed: 28798032]
- [89]. van Spronsen M, Hoogenraad CC, Synapse Pathology in Psychiatric and Neurologic Disease, Curr. Neurol. Neurosci. Rep 10 (2010) 207–214. [PubMed: 20425036]
- [90]. van Vliet EA, Aronica E, Redeker S, Boer K, Gorter JA, Decreased expression of synaptic vesicle protein 2A, the binding site for levetiracetam, during epileptogenesis and chronic epilepsy, Epilepsia 50(2009)422–433. [PubMed: 18717715]
- [91]. Wang L, Shi J, Wu G, Zhou F, Hong Z, Hippocampal low-frequency stimulation increased SV2A expression and inhibited the seizure degree in pharmacoresistant amygdala-kindling epileptic rats, Epilepsy research 108 (2014) 1483–1491. [PubMed: 25205164]
- [92]. Warnier C, Lemaire C, Becker G, Zaragoza G, Giacomelli F, Aerts J, Otabashi M, Bahri MA, Mercier J, Plenevaux A, Luxen A, Enabling Efficient Positron Emission Tomography (PET) Imaging of Synaptic Vesicle Glycoprotein 2A (SV2A) with a Robust and One-Step Radiosynthesis of a Highly Potent ¹⁸F-Labeled Ligand ([¹⁸F]UCB-H), J. Med. Chem 59 (2016) 8955–8966. [PubMed: 27598384]
- [93]. Warnock G.L., Aerts J, Bahri MA, Bretin F, Lemaire C, Giacomelli F, Mievie F, Mestdagh N, Buchanan T, Valade A, Mercier J, Wood M, Gillard M, Seret A, Luxen A, Salmon E, Plenevaux A, Evaluation of ¹⁸F-UCB-H as a novel PET tracer for synaptic vesicle protein 2A in the brain, J. Nucl. Med 55 (2014) 1336–1341. [PubMed: 24935992]
- [94]. Wegner C, Esiri MM, Chance SA, Palace J, Matthews PM, Neocortical neuronal, synaptic, and glial loss in multiple sclerosis, Neurology 67 (2006) 960–967. [PubMed: 17000961]
- [95]. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Cedarbaum J, Green RC, Harvey D, Jack CR, Jagust W, Luthman J, Morris JC, Petersen RC, Saykin AJ, Shaw L, Shen L, Schwarz A, Toga AW, Trojanowski JQ, 2014 Update of the Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception, Alzheimer's & Dementia 11 (2015) e1–e120.

Highlights

- Dysfunction of synapses has been implicated in a variety of neuropsychiatric disorders.
- Positron emission tomography (PET) imaging of synaptic vesicle glycoprotein 2A (SV2A) has recently been pursued for measuring synaptic density in living animal and human brains.
- This review highlights PET ligands targeting SV2A, and their uses in ongoing neurodegenerative and psychiatric diseases.
- We also discuss other potential applications of SV2A PET imaging in relevant, but yet unexplored disease areas.

Figure 1.

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

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

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

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

Table 1.

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

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

* Values are the averages of n measurements.

Table 2.

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

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