Wiley
Neural Plasticity
Volume 2025, Article ID 9423232, 14 pages
https://doi.org/10.1155/np/9423232

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Review Article

Evidence for Neuroplasticity in the Human Brain in Health and Disease: A Systematic Review Focusing on Molecular Imaging Using PET

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Received 10 November 2024; Revised 5 June 2025; Accepted 16 June 2025

Academic Editor: Massimo Grilli

Neuroplasticity is the ability of the brain to show persistent structural and/or functional modifications in response to external changes. Understanding this process is crucial for developing neurotherapeutic strategies for brain injury recovery. Neuroplasticity may be adaptive or maladaptive and is tightly linked with brain development and skill learning. Positron emission tomography (PET) is a molecular imaging technique that enables the analysis of neurochemical processes, including neurotransmitter function. Synaptic plasticity is fundamental for brain rewiring, and PET may be pivotal in assessing this process at the molecular level, though its relevance remains underestimated. Most brain plasticity studies rely on indirect measures like gray matter (GM) thickness. Studies employing PET have the potential to provide direct correlates of neuroplasticity at a molecular level, thus, contributing to a deeper understanding of brain reorganization. This systematic review provides a comprehensive overview of evidence for neuroplasticity in healthy and diseased human brains, focusing on PET studies. This approach offers an innovative perspective on the underlying neurobiological mechanisms in various clinical contexts. This review includes 15 studies: nine provide direct quantitative molecular evidence for plasticity, while others suggest potential adaptive responses. The findings highlight the need for clearer conceptual clarity regarding the definite existence of plasticity. Some studies do not definitively commit to the presence or absence of plasticity, allowing alternative interpretations. Nevertheless, the studies suggest that molecular quantification of synaptic status is a promising approach to studying neuroplasticity. It emphasizes the need for more objective and direct criteria in plasticity studies. Understanding this dynamic phenomenon is essential to enhance rehabilitation processes and postinjury clinical outcomes.

Keywords: molecular imaging technique; neuroplasticity; neurotransmitters; PET

1. Introduction

Most of the classical evidence that the human brain is able to modify itself to face new demands has so far been restricted to the early stages of development and childhood [1]. Currently, it is believed that even in adulthood the human brain may possess the ability to adapt structurally and/or functionally in response to (or absence of) extrinsic and/or intrinsic stimuli, such as

sensory deprivation, normal learning, or injury [2–5]. This adaptive capacity is inherent in the concept of neuroplasticity: an intrinsic and continuous process which may putatively persist throughout the human lifespan [6]. However, evidence in humans remains controversial because most imaging techniques, such as magnetic resonance imaging (MRI) do not have access to molecular measures of plasticity and can only report indirect measures such as gray matter (GM) levels.

Plastic changes can be adaptive and contribute to resilience to environmental demands [4, 5]. For instance, individuals who intensively learn a new language exhibit an increase in GM in the hippocampus and the superior temporal gyrus, which is correlated with linguistic proficiency [4]. However, these changes can also be maladaptive, leading to dysfunctional reorganization that results in neuropathology [4, 5]. As an example, the amputation of a limb can cause alterations in motor mapping, causing adjacent anatomical areas in the cortex to expand their representation into the deafferented region, sometimes resulting in phantom limb pain (pain felt in a limb that is no longer present) [4, 7].

Neuroplastic changes following injury can occur independently of therapeutic interventions. Consequently, a profound understanding of this dynamic phenomenon is essential, as strategically applied interventions have the potential to enhance intrinsic neuroplasticity mechanisms. Therefore, the incorporation of neuroplasticity principles during rehabilitation becomes pivotal in optimizing adaptive behavior and, consequently, enhancing postinjury clinical outcomes [7].

In recent decades, advances in the development of functional and molecular imaging techniques, such as positron emission tomography (PET), have provided relevant insights into the study of the remodeling capacity of the healthy and diseased human brain [8, 9]. Through the radiolabeling of organic molecules, PET can be utilized to gather information related to various pre- and postsynaptic neurochemical and neurophysiological processes, for example, by measuring biochemical markers such as neurotransmitter receptors and transporters in the living human brain [8, 10].

Neurons and glial cells, despite being apparently stable, contribute to highly dynamic neuronal networks that acquire new properties in response to environmental and intrinsic demands [1]. Synaptic plasticity allows for the modulation of connections between neurons through the regulation of crucial neurotransmitters and their receptors and transporters, including γ-aminobutyric acid (GABA), dopamine (DA), serotonin (5-HT), glutamate (Glu), and acetylcholine (ACh) [11, 12]. When a neuron is stimulated, neurotransmitters stored in presynaptic vesicles can be released into the synaptic cleft, acting on receptors in the postsynaptic membrane to transmit signals to the postsynaptic neuron. The type and quantity of neurotransmitters released and their ligand density can influence the efficiency of the neuronal network and, thus, alter synaptic plasticity [13].

While the concept of neuroplasticity has been used in neuroscience for over a century, it was only in the mid-20th century that the understanding that the brain could adapt and restore functions of damaged areas increased, becoming a relevant topic to comprehend brain functions [3, 14]. However, challenges persist regarding its mechanisms in health and disease and the most effective therapeutic approaches to induce adaptive neuroplastic changes. This is in part due to the limited understanding of intrinsic neuroplasticity processes [9], as current techniques predominantly provide indirect measures of plasticity. Additionally, there is significant variability among individuals and in different neurobiological contexts [15].

Thus, brain plasticity has been a subject of study in neuroscience as its understanding holds the potential for significant advancements in the treatment of neurological diseases [3]. Therefore, the objective of this systematic review is to provide a comprehensive overview of the literature on evidence of molecular plasticity in the human brain, focusing on studies conducted through PET on the neurotransmission of the main neurotransmitters: GABA, DA, 5-HT, Glu, and ACh.

We anticipate that PET as a molecular imaging technique will provide evidence of the potential of molecular-level brain studies, offering robust and direct molecular evidence of neuroplasticity. This is because it is widely believed that the locus of plasticity is believed to occur at the synaptic level, which is accessible to a molecular imaging technique such as PET. Consequently, the systematic review of these findings may provide a significant contribution to the comprehension of neuroplastic phenomena, thereby facilitating the implementation of novel molecular based strategies that promote functional improvement based on neuroplasticity.

2. Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Eligibility Criteria and Selection Process. Our research strategy was based on the PICO (population–intervention/indicator–comparison–outcome) method: "Can we obtain evidence of molecular neuroplasticity (outcome) in the healthy or diseased human brain (population) through the use of PET imaging (indicator), focusing on the main neurotransmitters receptors/transporters such as GABA, Glu, 5-HT, DA, and ACh?"

We searched two major online databases—PubMed and Web of Science—performed by two members of the review team (Mariana Ferreira and Francisca Matias). To optimize our search, we combined search terms using appropriate Boolean logical operators such as "AND" and "OR." The search string used for this review was as follows: (Human* OR Subject* OR Individual* OR People OR Person* OR Population) AND (PET OR "Positron?Emission Tomography Imag*" OR "Positron?Emission Tomography" OR "PET Scan*" OR "PET Imag*" OR "Molecular Imag*") AND ("Synaptic Plasticit*" OR "Neuronal Plasticit*" OR Neuroplasticit* OR "Neural Plasticit*" OR "Brain Plasticit*" OR "Synaptic Pruning*" OR "Neuronal Pruning*" OR "Dendrit* Pruning*" OR "Neuronal remodeling*" OR "Dendritic Remodeling*" OR "Neuronal Network Remodeling*") AND (Dopamine OR DA OR Serotonin OR Acetylcholine OR ACh OR "Gamma?Aminobutyric Acid" OR GABA OR Glutamate OR Glu). This approach allowed us to retrieve a comprehensive set of relevant articles investigating molecular neuroplasticity in the human brain

Table 1: Exclusion and inclusion criteria for reviewed studies.

Criteria domain	Exclusion criteria	Inclusion criteria
Article characteristics	• Meta-analyses and systematic review • Conference abstracts and proceedings, unpublished data, and case reports • Articles not written in English • Animal studies	• Original research articles • Peer-reviewed journals • Observational studies • Analytical studies • All publication years accepted • The sample was well-described • Studies in humans • Studies in clinical or healthy populations
Study design	• Studies with only one subject • Studies not utilizing PET imaging technique as a methodology • Studies that do not address the neurotransmitters GABA, DA, 5-HT, Glu, and ACh • Studies not related to neuroplasticity	• All age groups eligible • Studies investigating neuroplasticity through outcomes derived from the PET imaging technique • Neuroplasticity around the main neurotransmitters, their receptors, and transporters: GABA, DA, 5-HT, Glu, and ACh

Note: 5-HT, serotonin.
Abbreviations: ACh, acetylcholine; DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; PET, positron emission tomograph.

using PET imaging and exploring specified neurotransmitters, resulting in the identification of 184 publications.

Article selection was carried out following a standardized protocol, as presented in Table 1. The inclusion criteria encompassed the following requirements: (1) original research articles published in peer-reviewed scientific journals; (2) articles written in English; (3) studies involving healthy or diseased human subjects of any age; (4) neuroplasticity approach related to neurotransmitters; and (5) utilization of PET imaging methodology in the studies. The following were excluded from the analysis (1) meta-analyses; (2) systematic reviews; and (3) case studies. There was no restriction on the year of publication. The data frame for this search concluded on November 3, 2023.

Therefore, two members of the review team (Mariana Ferreira and Francisca Matias) independently used the Rayyan screening tool [16] to exclude duplicate articles and to assess eligibility based on title and abstract. The same reviewers then read the full text of studies potentially relevant for final inclusion and excluded articles that did not meet the eligibility criteria. Any discrepancies between reviewers were resolved through collaboration with a third author (Castelo-Branco Miguel). In total, 15 articles met the eligibility criteria, as illustrated in Figure 1 (results section).

2.2. Data Collection. Data extraction was independently performed by Mariana Ferreira and Francisca Matias. Pertinent information was systematically extracted from each eligible article, including the first author, year of publication, participant characteristics (composition and size of study group(s), age, and gender distribution), neurotransmitter under investigation, radiopharmaceutical utilized and PET target, imaging techniques employed in addition to PET, and main conclusions related to evidence of neuroplasticity. All these details are summarized in Table 2 (results section).

2.3. Quality Assessment. Two reviewers (Mariana Ferreira and Francisca Matias), with consultation with other co-authors (Castelo-Branco Miguel) assessed the risk of bias for each study using the evaluation tool from the Joanna Briggs Institute (JBI) [32]. The checklist for case–control studies included 10 questions related to the representativeness of groups, appropriate matching of groups, assessment of exposure and condition, strategies to address confounding factors, evaluation of results, and statistical analysis. For analytical cross-sectional studies, there were eight questions about sample inclusion criteria, sample and environmental characterization, assessment of exposure and condition, strategies to address confounding factors, evaluation of results, and statistical analysis. In the case of cohort studies, the form comprised 11 questions covering the similarity of study groups, measurement of exposures, strategies to address confounding factors, characteristics at the study's outset, evaluation of results, follow-up reporting, strategy to address incomplete follow-up, and statistical analysis.

Each question was assigned one of four possible answers: "Yes," "Unclear," "Not Applicable," or "No." Following the Joanna Briggs Reviewer's Manual [33], we adopted the following scoring system: "high" risk of bias when up to 49% of the questions received a "Yes" response, "moderate" risk of bias when 50%–69% of the questions received a "Yes" response, and "low" risk of bias when more than 70% of the questions received a "Yes" response. The bias risk assessment is presented in Table 2 in the results section, along with the identification of the study type closely associated with the questionnaire used for bias evaluation.

3. Results

3.1. Experimental Flow. The systematic search in online databases resulted in 184 articles, of which 75 were removed through automated tools, and 19 were identified as duplicates. Of the remaining 90 studies, 65 were excluded after screening titles and abstracts. After a thorough reading of the remaining 25 studies, 15 met all inclusion criteria for the final analysis in this systematic review. Figure 1 illustrates the study selection phases we underwent to arrive at our cohort of eligible studies.

3.2. Overview of Eligible Studies. Table 2 provides a comprehensive overview of all the studies included in this systematic review using the data compiled.

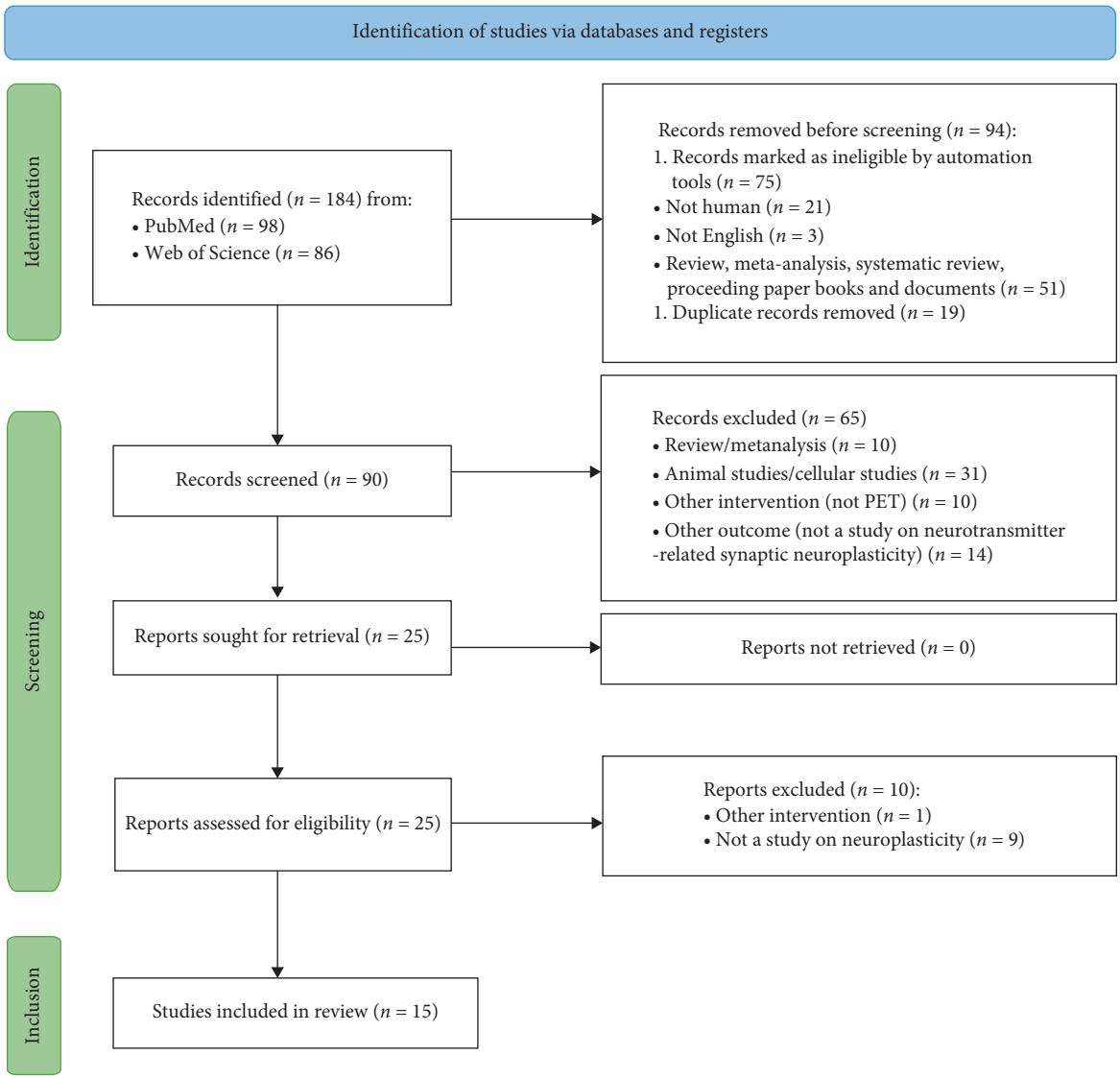

FIGURE 1: PRISMA flowchart for the various phases of eligible study selection (identification, screening, and inclusion) in the systematic review.

All the studies analyzed were published between 2001 and 2022. Among the examined studies, 11 focused on the human brain under pathological conditions, addressing topics such as epilepsy, stroke, fibromyalgia with chronic pain, Parkinson's disease (PD), major depressive disorder (MDD), Alzheimer's disease (AD), alcohol use disorder (AUD), and early-onset torsion dystonia (DYT1). Conversely, four studies specifically concentrated on the healthy human brain.

Our search identified four studies related to the GABAergic system, another four to the dopaminergic system, three to the serotonergic system, three to the glutamatergic system, and one to the acetylcholinergic system. Within the set of analyzed studies, nine of them provided direct molecular evidence of neuroplasticity, while the remaining six explored functional changes, suggesting the possibility of neuroplasticity, but without specifying that it is directly neuroplasticity, just describing the alterations observed.

Figure 2 provides a schematic overview of the 15 studies included in this systematic review, detailing their distribution across different neurotransmitter systems and the proportion of studies reporting direct molecular evidence of neuroplasticity. The figure also indicates the type of plasticity described (adaptive, maladaptive, or unclear) and the study populations investigated (healthy vs. pathological), offering an integrated summary of the key findings.

Table 3 complements this schematic representation by offering a more refined understanding of the molecular and functional indicators of neuroplasticity across conditions.

3.2.1. GABAergic System. All the studies mentioned here addressed the $GABA_A$ receptor binding and utilized the drug flumazenil (FMZ) in the PET imaging technique [17, 22, 24, 25].

Kim et al. [24] conducted a longitudinal study with [^{18}F] FMZ PET in 10 stroke patients and 15 healthy individuals. The

Table 2: Summary of the 15 included studies grouped by neurotransmitter system, with population characteristics, PET radiotracers, key findings, and neuroplasticity type.

Article	Study population	Number of sample Sex, M/F	Age	Neurotransmitter	PET tracer PET target	Other imaging techniques used	Evidence directly attributable to synaptic plasticity?	Bias
[17]	Epilepsy	CE: 20 AE: 10 HC: 5	CE: 9.4 ± 4.1 (2–17) years AE: 29 ± 7 years HC: 40 ± 9 years	GABA	[^{11}C]FMZ; $GABA_A$ receptors	MRI	Yes The high volume of distribution of FMZ in early childhood may be linked to a specific function of benzodiazepine-sensitive $GABA_A$ receptors in crucial synaptic plasticity periods during human brain development.	⚠ (1)
[18]	Idiopathic Parkinson's disease	Experiment I PD: 16; HC: 11 Experiment II PD: 41 (G1 [$n = 3$]; G2 [$n = 18$]; G3 [$n = 10$]) HC: 16	PD: G1 = 63 ± 7 years; G2 = 62 ± 8 years; G3 = 57 ± 3 years HC: 49 ± 6 years	DA	[^{18}F]DOPA; synthesis of DA	T1 MRI	Yes Loss of dopaminergic neurons results in compensatory upregulation in the nigropallidal projection to the GPi.	✓ (1)
[19]	Epilepsy with a failed cortical resection	E: 19; 12/7 EC: 10; 5/5 HC: 7	E: 8.7 (2.1–17.5) years EC: 5.8 (1.5–15.2) years HC: 9.7 years	5-HT	AMT; synthesis of 5-HT	T1, T2 MRI, FLAIR, and SPGR	Yes Increase in striatal serotonin as a compensatory response to cortical resection.	✓ (1)
[20]	Healthy humans	H: 15; 7/8	H: 56 ± 8 (41–65) years	DA	[^{11}C]Raclopride; DA-D2R [^{11}C]FLB 457; DA-D2R	T1 and T2 MRI	No Implicit and explicit learning correlate with dopaminergic function in the associative and sensorimotor striatum. Implicit learning exhibited a selective preference for dopaminergic mechanisms in the limbic striatum.	✓ (2)
[21]	Healthy humans	H: 35; 18/17	H: 26.6 ± 6.8 (21–52) years	5-HT	[^{11}C]WAY-100635; $5\text{-}HT_{1A}$ receptors	T1 MRI	No Take into account the role of neuroplasticity mediated by 5-HT1A receptors as an explanatory model for changes in gray matter in the human brain.	✓ (2)
[22]	Newborns	Nb: 6; 3/3	Nb: (9–114 days)	GABA	[^{11}C]FMZ; $GABA_A$ receptors	—	Yes FMZ binding to the $GABA_A$ receptor differs in newborns compared to older children/adults (neurodevelopment).	⚠ (2)
[23]	Parkinson's disease	PD: 4 (2 with and 2 without intensive treadmill training); 3/1 HC: 2 (with intensive treadmill training); 1/1	PD: 50–63 years HC: 53–58 years	DA	[^{18}F]Fallypride; DA-D2R	T1 MRI	Yes Treadmill exercise promotes neuroplasticity in dopaminergic signaling in the basal ganglia in PD.	✓ (1)
[24]	Unilateral ischemic stroke	S: 10; 3/7 HC: 15; 5/10	S: 62.7 ± 10.5 years (46–77) years HC: 57.5 ± 5.7 years	GABA	[^{18}F]FMZ; $GABA_A$ receptors	MRI	Yes Changes in GABA receptor availability over time are significantly related to motor recovery after stroke.	✓ (3)
[25]	Fibromyalgia patients with chronic pain	FCP: 26 HC: 25	FCP: 61.0 ± 5.4 years HC: 61.0 ± 7.6 years	GABA	[^{18}F]FMZ; $GABA_A$ receptors	T1 MRI	No Data interpretation suggests that gray matter reduction may be due to an underlying process of neurodegeneration, which is compensated for by GABAA receptor upregulation in some areas, while in other regions, increased gray matter could be associated with heightened neuronal matter.	✓ (1)

Table 2: Continued.

Article	Study population	Number of sample Sex, M/F	Age	Neurotransmitter	PET tracer PET target	Other imaging techniques used	Evidence directly attributable to synaptic plasticity?	Bias
[26]	Major depressive disorder	MDD: 47; 17/30 HC: 40; 21/19	MDD: 39.1 ± 12.1 (20–70) years HC: 38.0 ± 15.4 (18–69) years	5-HT	[^{11}C]WAY-100635; 5-HT$_{1A}$ receptors	T1 MRI	No Differences in serotonin receptor-GMV relationships exist between healthy individuals and those with MDD, but these differences are only indirect evidence for neuroplasticity.	✓ (1)
[27]	Alzheimer's disease	AD: 9; 3/6 HC: 10; 3/7	AD: 77.3 ± 5.7 years HC: 68.5 ± 9.6 years	Glu	ABP; mGluR5	T1 MRI	No Interpretation of negative regulation of mGluR5 in the hippocampus and amygdala as a potential adaptive mechanism in AD.	! (1)
[28]	Parkinson's disease	PD: 14; 8/6 On-PD: 7; 4/3 Off-PD: 7; 4/3 HC: 9; 5/4	PD: 64.79 ± 5.15 (59–73) years On-PD: 65.86 ± 5.36 years Off-PD: 63.71 ± 5.09 years HC: 62.22 ± 4.49 (58–68) years	DA	[^{11}C]Raclopride; DA-D2R	T1 MRI and fMRI	Yes The relationship between brain functional activity and molecular-level synaptic changes (unimodal and multimodal covariance) reflects circuit reorganization in PD, suggesting evidence of neuroplasticity.	✓ (1)
[29]	Early-onset torsion dystonia	DYT1: 20; 13/7 HC: 20; 13/7	DYT1: 43.7 ± 14.2 (22–75) years	ACh	[^{18}F]FEOBV; VAChT	T1 MRI and resting-state fMRI	Yes A decrease in VAChT binding in the striatum of DYT1 patients, suggests it is a compensatory mechanism of the disease. Greater resting-state functional connectivity was observed in the motor network of the patients compared to the healthy controls.	✓ (1)
[30]	Alzheimer's disease	AD: 8, 3/5	AD: 79.1 ± 4.6 years	Glu	[^{11}C]ITMM; mGluR1	T1 MRI	No Stability in the availability of the mGluR1 receptor over several years in the early to mid-stages of AD as a putative compensatory mechanism.	✓ (3)
[31]	Alcohol use disorder	AUD_t$_1$: 14; 11/3 AUD_t$_2$: 11; 9/2 HC: 23; 16/7	AUD_t$_1$: 41.0 ± 7.25 years AUD_t$_2$: 39.9 ± 7.24 years HC: 40.5 ± 13.1 years	Glu	[^{18}F]FPEB; mGluR5	T1 MRI and resting-state fMRI	No Changes in brain connectivity and the availability of mGlu5 receptors suggest brain adaptations during alcohol abstinence.	✓ (3)

Note: E: epilepsy with a failed cortical resection; EC: epilepsy controls without cortical resections; 5-HT: serotonin; SPGR: volumetric spoiled gradient echo; H: healthy human; ABP: [^{11}C]-ABP688; on-PD: patients with medication for PD; off-PD: patients without medication for PD; DYT1: early-onset torsion dystonia; AUD_t$_1$: 1–3 days apart during early abstinence; AUD_t$_2$: 26–27 days after last drink. JBI critical appraisal checklist for (1) case–control studies; (2) analytical cross-sectional studies; and (3) cohort studies. Risk of bias classification: ✓: low; !: moderate; and ✗: high. DA-D2R, D2 dopaminergic receptors.
Abbreviations: ACh, acetylcholine; AD, Alzheimer's disease; AE, adults with epilepsy; AMT, alpha[^{11}C]methyl-L-tryptophan; AUD, alcohol use disorder; CE, children with epilepsy; DA, dopamine; FCP, fibromyalgia with chronic pain; FLAIR: fluid-attenuated inversion recovery; FMZ, flumazenil; G1/G2/G3, Group 1/Group 2/Group 3; GABA, gamma-aminobutyric acid; Glu, glutamate; HC, healthy controls; MDD, major depressive disorder; mGluR1, metabotropic glutamate receptor 1; mGluR5, metabotropic glutamate receptor 5; MRI, magnetic resonance imaging; Nb, newborns; PD, Parkinson's disease; S, stroke; VAChT, vesicular acetylcholine transporters.

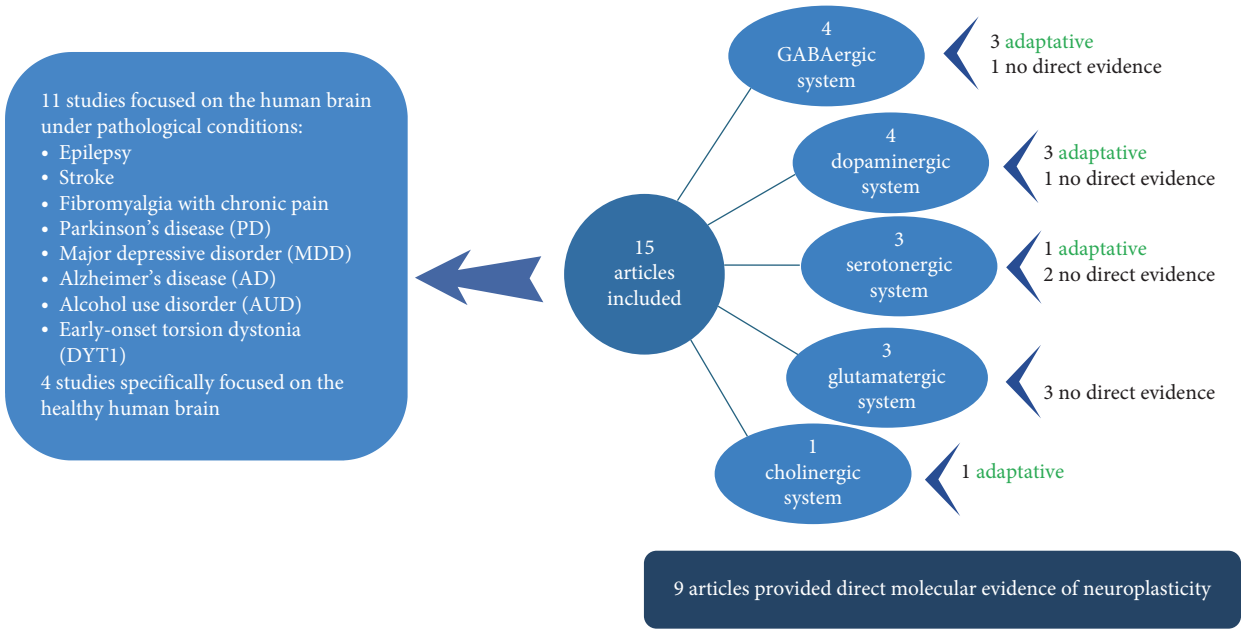

FIGURE 2: Overview of the 15 included studies by neurotransmitter system, plasticity type, and study population (pathological or healthy brain).

results revealed an increase in GABAergic binding 1 month after the stroke within the contralateral cerebellum, suggesting a window for plasticity within this period. Subsequently, throughout the temporal follow-up of the study, GABAergic activity in patients decreased, especially in the cortical and subcortical white matter in the contralateral cerebellum. Consequently, the authors hypothesized that the increased GABAergic activity 1 month after the stroke in the contralateral cerebellum might be related to increased contralateral cortical excitability, possibly promoting functional recovery. Motor recovery correlated with changes in GABAergic binding in the thalamus. These changes in the GABAergic system may reflect a reorganization necessary for motor recovery in post-stroke patients [24].

Chugani et al. [17] employed [^{11}C]FMZ to quantify benzodiazepine binding sites on $GABA_A$ receptors during the development of the nervous system. The main research question was to understand neurodevelopmental plasticity by studying the contralateral putatively healthy hemispheres to the epileptic focus in epileptic children and adults with and without epilepsy. The results revealed significant increases in specific brain regions such as the temporal lobe and thalamus in children compared to adults. FMZ binding exhibited an exponential decrease with age. These findings suggest that alterations in GABA neurotransmission may be associated with adaptive synaptic plasticity during cerebral development in health and disease. This study has the significant limitation of using data from individuals with brain disorders to investigate neurodevelopment [17].

Twelve years later, Chugani et al. [22], employing the same radiopharmaceutical, [^{11}C]FMZ, demonstrated a distinct pattern in the expression of $GABA_A$ receptors within the newborn group presented in the study and the older children/adults group presented in a previous study [17]: notably they reported high binding levels, especially in the amygdala and hippocampus in newborns. This result is suggestive of the role played by neuroplasticity in human development, reinforcing the idea that different brain areas exhibit different levels or patterns of synaptic plasticity throughout neurodevelopment. Once again, data from individuals with brain disorders were used to investigate neurodevelopment [22].

Finally, Pomares et al. [25] carried out a study that explored the possible relationship between GM changes in fibromyalgia and the concentration of $GABA_A$ receptors using [^{18}F]FMZ. The results suggest that the $GABA_A$ receptor concentration appears to play a significant relationship with changes in GM. On the other hand, the decrease in GM cannot be linearly related to the concentration of GABAergic receptors. Although direct evidence of neuroplasticity was not identified, the most likely hypothesis is that neural loss is present but masked by the concomitant compensatory increase in $GABA_A$ receptors [25]. Indirectly, we can assume that there is a possibility of an adaptive response from the nervous system that may be adjusting its function and structure in response to fibromyalgia, even in the presence of signs of possible regional neural loss.

3.2.2. Dopaminergic System. Three of the four articles related to the dopaminergic system focus on PD [18, 23, 28], with the remaining one being a learning study in the healthy human brain [20, 23].

Whone et al. [18] investigated the uptake of [^{18}F]DOPA in the striatal complex in PD compared to healthy controls. The results demonstrated that decreases in the radiopharmaceutical uptake at the onset of PD in the putamen are associated with increases in uptake in the internal segment of the globus pallidus (GPi). Additionally, PD patients were grouped into three groups based on visual inspection of the pattern of decreased [^{18}F]DOPA uptake in the putamen, allowing comparison

Table 3: Summary of the 15 studies included in this systematic review, categorized by neurotransmitter system.

Neurotransmitter system	Article	Study population	PET tracer	PET finding	Plasticity type
GABAergic system	[17]	Epilepsy	[^{11}C]FMZ	✔ Neurodevelopmental plasticity (decrease in $GABA_A$-R with age)	↗ Adaptive
	[22]	Newborns	[^{11}C]FMZ	✔ Neurodevelopmental plasticity	↗ Adaptive
	[24]	Ischemic stroke	[^{18}F]FMZ	✔ GABAergicreorganization supports motor recovery	↗ Adaptive
	[25]	Fibromyalgia	[^{18}F]FMZ	✖ Neurodegeneration or increased neuronal matter	✖ No direct evidence
Dopaminergic system	[18]	Parkinson	[^{18}F]DOPA	✔ Nigropallidal upregulation compensates dopaminergic loss	↗ Adaptive
	[20]	Healthy	[^{11}C]Raclopride	✖ Learning processes link dopaminergic function to striatal regions	✖ No direct evidence
	[23]	Parkinson	[^{18}F]Fallypride	✔ Attenuation of overactivation in the striatopallidal pathway	↗ Adaptive
	[28]	Parkinson	[^{11}C]Raclopride	✔ Increased DA-D2R binding between putamen and parietal eye field activity compensates for frontal eye field dysfunction	↗ Adaptive
Serotonergic system	[19]	Epilepsy	AMT	✔ Increase in striatal serotonin as a response to cortical resection	↗ Adaptive
	[21]	Healthy	[^{11}C]WAY-100635	✖ Positive correlation between 5-HT1A receptors and gray matter, but causality cannot be determined	✖ No direct evidence
	[26]	Depression	[^{11}C]WAY-100635	✖ Increased 5-HT1A receptors contribute to greater gray matter only in healthy individuals	✖ No direct evidence
Glutamatergic system	[27]	Alzheimer	ABP	✖ Reduction of mGluR5 in the hippocampus and amygdala	✖ No direct evidence (adaptive plasticity or synaptic loss = unclear)
	[30]	Alzheimer	[^{11}C]ITMM	✖ Consistent availability of mGluR1 over the follow-up period	✖ No direct evidence (indirectly adaptive plasticity)
	[31]	AUD	[^{18}F]FPEB	✖ Greater mGluR5 availability promotes increased global connectivity and reduced network-specific connectivity	? Unclear adaptive (increased global conectivity) and maladaptive (reduced connectivity in the default mode network)
Cholinergic system	[29]	Dystonia	[^{18}F]FEOBV	✔ Reduced VAChT binding in the putamen and caudate nucleus (striatum) and cerebellum (posterior cerebelar vermis)	? Unclear both adaptive and maladaptive

Note: ABP, [^{11}C]-ABP688; DA-D2R, D2 dopaminergic receptors; 5-HT, serotonin. The table details the study population, PET tracers used, main PET findings, and the type of neuroplasticity identified (adaptive, maladaptive, or unclear).

Abbreviations: AMT, alpha[^{11}C]methyl-L-tryptophan; FMZ, flumazenil; GABA, gamma-aminobutyric acid; $GABA_A$-R, $GABA_A$ receptors; mGluR5, metabotropic glutamate receptor 5; mGluR1, metabotropic glutamate receptor 1; VAChT, vesicular acetylcholine transporters.

between PET data and clinical status. The decrease in uptake in the putamen from Group 2 was significantly greater and more extensive than in Group 1, although the clinical assessment scores were practically identical. This suggested the possibility of a compensatory process that counteracts symptom progression in Group 2. Thus, the loss of dopaminergic innervation of the nigrostriatal pathway seems to lead to a compensatory upregulation of the nigropallidal projection to the GPi [18].

In a similar context, Fisher et al. [23] present in an exploratory study, using [^{18}F]fallypride, of the mechanisms underlying changes in dopaminergic neurotransmission (binding of D2 receptors, DA-D2R, in the striatum) induced by physical exercise. There was a significant increase in DA-D2R binding and an improvement in motor performance in PD patients who exercised compared to those who did not. Thus, the authors proposed that the increase in DA-D2R results from the attenuation of the overactivation of the striatopallidal pathway, restoring balance with the striatonigral pathway. Given that the radiopharmaceutical 18F-Fallypride is independent of endogenous DA levels, it can be concluded that an increase in binding potential is not directly associated with a reduction in endogenous DA [23].

Rebelo et al. [28] investigated whether functional brain plasticity is associated with striatal postsynaptic reorganization of DA-D2R in the oculomotor network in PD patients. Molecular imaging ([^{11}C]-raclopride PET) and functional neuroimaging (functional MRI [fMRI]) were employed in this study. During fMRI participants performed two tasks—eye movements towards the target (prosaccades [PSs]) and in the opposite direction (antisaccades [ASs]). The PSs condition revealed that, in PD, high-level processing (frontal eye field (FEF) activity) leads to compensatory increased activity in low-level processing (parietal eye field (PEF) activity). Conversely, the ASs condition evoked additional recruitment of the caudate as an adaptive process. In controls, the binding sites availability correlated positively between the FEF and basal ganglia, in controls. In PD patients this positive correlation was observed between the PEF and basal ganglia and was absent for the FEF. In contrast to controls, patients exhibited higher molecular–molecular (binding of DA-D2R) between the putamen and PEF, indicating a compensatory mechanism for DA loss in the striatum. The positive correlation between DA-D2R binding and FEF BOLD activity observed in controls was reversed to negative in patients, suggesting a failure of striatal-FEF connectivity. The association between DA-D2R binding and reorganization of the saccadic cortical network reflects a redirection from the frontostriatal network to parietostriatal network, in response to the progressive decline of DA. In other words, the PEF shows compensatory activity and increased molecular and functional connectivity with the putamen, as an adaptation to the functional loss of the FEF. Thus, the authors found a strong association between functional activation and synaptic changes at the molecular level, reflecting likely neuroplasticity in PD [28].

Contrary to the three PD-related studies that provided direct evidence of neuroplasticity, the study conducted by Karabanov et al. [20] did not directly interpret results of plasticity in the learning process of healthy individuals. They assessed DA-D2R density using [^{11}C]Raclopride PET in striatal regions and [^{11}C]FLB 457 PET in extra-striatal regions. Sequential learning was measured using the procedure dissociation of processes (PDPs), in which the performance in two tasks was compared: (1) when explicit (conscious) and implicit (intentional) knowledge both contribute to performance, and (2) only explicit knowledge facilitates performance. The results indicate that implicit and explicit learning are distinctly related to the binding potential in DA-D2R within functional subregions of the striatum. Only implicit learning performance shows a significant negative correlation with binding potential in the limbic striatum. Both types of learning correlate negatively with binding potential in the associate and sensorimotor striatum. Thus, implicit learning exhibited a selective preference for dopaminergic mechanisms in the limbic striatum, while the associative and sensorimotor striatum are involved in both types of learning. In this way, although the authors did not explicitly address the notion of neuroplasticity, given the links between learning and plasticity, this study establishes a connection between the inherently plastic process of learning and the dopaminergic system [20].

3.2.3. Serotonergic System. Regarding the serotonergic system, there are three eligible studies [19, 21, 26]. Each employed distinct approaches in different study populations. The first study utilized alpha[^{11}C]methyl-l-tryptophan (AMT) to analyze 5-HT activity/synthesis in epilepsy patients with failed cortical resection [19]. The two subsequent studies employed [^{11}C]WAY-100635 for visualization and quantification of 5-HT_{1A} receptors. One was conducted in patients diagnosed with MDD [26], while the other involved healthy individuals [21].

Chugani et al. [19] investigated brain plasticity in response to postresection effects on the reorganization of serotonergic projections using the radiopharmaceutical AMT. They observed a differential effect on the synthesis of 5-HT in the thalamus (decrease) and the striatum (increase in the ipsilateral lentiform nucleus). Therefore, the authors suggest that the increased striatal 5-HT functions as a compensatory response to surgical intervention. A highlighted limitation in this study is the lack of information about the specific region of resection in the participants' epileptic brains. Since different brain areas serve distinct functions, removing a specific region may have varied impacts on the neuroplasticity of the serotoninergic system. Identifying the exact site of resection could be crucial for a more in-depth understanding of how this surgical intervention can influence brain plasticity [19].

The study by Kraus et al. [21], with the [^{11}C]WAY-100635 radiotracer, showed a positive correlation between the 5-HT_{1A} receptor concentration and GM in regions such as the hippocampus and temporal cortex in both healthy hemispheres. However, this correlation was not observed in the insula. The concentration of 5-HT_{1A} autoreceptors in the raphe nucleus also showed a positive association with GM in the anterior cingulate cortex. This publication provides evidence of plasticity in the serotonergic system in adult humans, as the authors propose that the neuroplastic effects of 5-HT_{1A} receptors influence GM in specific brain regions. However, as the authors

point out, the causality of these associations does not necessarily imply neuroplasticity. To address this, it would be interesting in future studies to conduct longitudinal or interventional approaches, such as implementing training sessions [21].

Zanderigo et al. [26] expanded the Kraus et al. [21] study in the healthy brain in patients diagnosed with MDD untreated with antidepressants, using the radiopharmaceutical [^{11}C] WAY-100635. They replicated previous findings, but failed to extend them to the MDD brain. Accordingly, a higher concentration of 5-HT_{1A} receptors contributes to increased GM volume only in healthy individuals, but this association is lost in MDD patients. Thus, the authors suggested that their findings provide evidence of neuroplastic mechanisms in healthy individuals. Additionally, they observed a tendency of an inverse relationship between 5-HT_{1A} autoreceptors in the raphe nucleus and GM for both groups. The association between serotoninergic binding and brain structure may indicate that the serotonergic system plays a role in controlling brain plasticity [26].

3.2.4. Glutamatergic System. Two of the three articles related to the glutamatergic system focus on AD [27, 30], while the third concentrates on AUD [31]. None of the articles provided direct evidence of neuroplasticity, as they only explicitly mention reorganization, but not necessarily the formal presence of plastic processes. They describe changes resulting from pathological conditions, but the authors do not commit themselves to conclusive statements about the impact of neural reorganization.

Treyer et al. [27] used [^{11}C]ABP688 (ABP) to investigate metabotropic Glu receptor 5 (mGluR5) in AD patients. This exploratory study involved a small sample ($n = 9$). They observed a reduction in these receptors in the hippocampus and amygdala compared to healthy controls. mGluR5 is associated with β-amyloid monomer-dependent long-term synaptic potentiation, and therefore, the findings suggest synaptotoxicity in AD. Consequently, the authors suggest that this reduction in mGluR5 could be a brain regulatory mechanism in response to AD. However, positive correlations between cognitive performance and mGluR5 density indicate synaptic loss rather than a compensatory mechanism [27].

In the study by Ishibashi et al. [30], [^{11}C]ITMM was employed to analyze metabotropic Glu receptor 1 (mGluR1) in AD. The findings indicated a consistent availability of mGluR1 over the follow-up period (~2.8 years), corresponding to the early/mid stages of the pathology. The authors do not make direct inferences on neuroplasticity and only indirectly establish a direct relationship with compensatory processes. It is possible to infer from these results that the unchanged availability of mGluR1 may suggest, to some extent, potential adaptations of the nervous system in AD [30].

Smart et al. [31] conducted a multimodal study using [^{18}F] FPEB PET and fMRI to investigate mGluR5 availability and functional connectivity in AUD patients (results of primary PET analyses were previously published [34]). After 4 weeks of abstinence, global connectivity of the orbitofrontal cortex was significantly higher in the AUD group compared to healthy controls, but functional connectivity within the default mode network was lower. The authors suggest that the greater availability of the mGluR5 may enhance global connectivity at the expense of network-specific activity, rendering it less efficient. So, the authors address both types of plasticity: the increased global connectivity in the orbitofrontal cortex can be interpreted as compensatory neuroplasticity, while the reduced functional connectivity within the default mode network may suggest maladaptive changes [31].

3.2.5. Cholinergic System. Mazere et al. [29] employed fMRI and [^{18}F]-fluoroethoxybenzovesamicol (FEOBV) PET to examine cholinergic neural populations, specifically vesicular ACh transporters (VAChTs), in patients with early-onset torsion dystonia (DYT1). The findings revealed a reduction in VAChT binding in the posterior putamen and caudate nucleus of young DYT1 patients compared to age-matched controls, suggesting the existence of a compensatory mechanism (via downregulation) that neutralizes the excessive ACh production in young patients. It is plausible that in older patients, the effectiveness of this regulatory mechanism may be diminished due to age-associated limitations in brain plasticity. Additionally, the study identified reduced VAChT expression in the posterior cerebellar vermis. Here, the decrease in ACh contributes to reduced GABAergic activity, which plays a critical role in the pathophysiology of dystonia (maladaptive plasticity), in contrast to the compensatory process proposed for the striatum. The study also highlighted increased resting-state functional connectivity in the motor network of patients, which may lead to maladaptive changes, such as repetitive movements, or instead compensatory adjustments, such as more efficient motor control [29]. The authors address both types of plasticity, however, they do not specify which predominates in the pathophysiology of DYT1 dystonia, whether adaptive or maladaptive.

3.3. Multimodal Studies. Except for three studies, all others chose to integrate anatomical and molecular imaging information, taking advantage of both modalities. This was achieved by acquiring T1-weighted structural MRI for subsequent coregistration with PET images, enabling analyses of radiopharmaceutical uptake in anatomically well-defined regions. Chugani et al. [17] conducted MRI scans to exclude the presence of cortical or subcortical lesions in participants with epilepsy. They opted for an alternative approach to manually define regions of interest (ROIs), utilizing FMZ uptake images corresponding to activity summed between 10 and 20 min after injection [17]. Similarly, the study by Chugani et al. [22] did not perform MRI and used a summed PET image acquired between 10 and 30 min after FMZ injection for ROI delineation. In the study by Kim et al. [24], MRI was employed to validate the presence of unilateral subcortical infarcts in patients, determine the location and size of these infarcts, and rule out potential structural lesions in healthy individuals.

Only one study adopted a comprehensive approach by incorporating T2 MRI, fluid attenuation inversion recovery (FLAIR), and volumetric spoiled gradient echo (SPGR) to examine both structural pathology and provide a better characterization of cerebral morphology [19].

The work of Rebelo et al. [28] demonstrated the ambition of implementing a multimodal functional approach, with the innovative use of multimodal covariance statistics combining molecular and task-based imaging of the oculomotor system to reveal its reorganization. In addition to using PET to assess synaptic plasticity, they incorporated fMRI with a paradigm to gather crucial information about the reorganization of brain activity patterns [28]. Two other studies also adopted fMRI to assess functional connectivity in the resting state [29, 31].

4. Discussion

Neuroplasticity refers to the ability of neural systems to adjust and reorganize from the molecule to the circuit level in response to intrinsic and extrinsic factors [2–5]. This remarkable capacity for neurobiological change may enable recovery in the face of challenges or injuries, facilitating the sustained optimization of synaptic connections, and promoting positive adaptations [15, 35]. However, maladaptive plasticity may also occur, resulting in functional syndromes, such as the pain felt in a phantom limb that has been amputated [4, 7].

Neuroplasticity is a circuit-level phenomenon that is closely connected with synaptic modifications which makes it relevant to study changes at the neurotransmitter level (including receptoral and transporters domains) using molecular imaging techniques, such as PET [36, 37]. Surprisingly, this technique is the only one that can directly track synaptic plasticity in humans and is still scarcely used.

This review, through a systematic synthesis of the literature, investigates both direct and indirect evidence of neuroplasticity in the human brain, with a specific focus on studies utilizing PET as a molecular imaging modality. This approach allows for the assessment of the impact of main neurotransmitters (GABA, DA, 5-HT, Glu, and ACh) and their receptors and transporters on brain plasticity. Thus, this work highlights the potential occurrence of neuroplasticity and analyzes the resulting neural changes but also provides valuable insights into the dynamic interaction between neurotransmitters and adaptive/maladaptive processes in the human brain.

4.1. GABAergic System. Three studies presented direct evidence of neuroplasticity [17, 22, 24], observing that increased GABAergic binding may be associated with adaptive reorganization during human development [17, 22] and motor recovery after a stroke [24]. Conversely, a study on fibromyalgia, while not explicitly mentioning neuroplasticity, found that evidence for an increase in $GABA_A$ receptor expression also played a significant role in this condition, which can be interpreted as an adaptive response, even in the presence of potential neurodegeneration [25].

4.2. Dopaminergic System. The dopaminergic system is involved in various neurophysiological functions, such as motor control, emotiona,l and reward processing as well as reinforcement learning. Furthermore, impaired DA neurotransmission is a causal mechanism in PD [38]. In PD pathophysiology, patients show decreased levels of DA due to the loss of dopaminergic neurons in the nigrostriatal pathway, which results in the overactivation of the striatopallidal pathway that contributes to the characteristic motor symptoms [23].

Here, we found consistent evidence of synaptic plasticity in response to degeneration of the nigrostriatal pathway. All studies revealed specific changes putatively contributing to partially restore balance in dopaminergic networks, targeting motor function improvement, that is, adaptive neuroplastic responses to PD. These adaptations include increased dopaminergic innervation in the basal ganglia as a compensatory process for the dopaminergic loss in the nigrostriatal pathway interpreted as an adaptive response to compensate for dopaminergic neurons loss [18]; elevated DA-D2R in the striatum due to physical exercise is a compensatory adaptation that inhibits striatopallidal projections and restores balance with the nigrostriatal pathway [23], redirection to the parietostriatal network in response to declining DA in the frontostriatal network and additional recruitment of the caudate as compensatory plastic processes [28]. These alterations are considered adaptive, as they enable functional compensation within dopaminergic circuits. These neuroplastic strategies are promising as they suggest that the brain actively reorganizes to cope with reduced DA, thereby restoring balance in neural circuits to mitigate motor symptoms.

In contrast, no direct evidence of synaptic plasticity was been identified in healthy human brain during skill learning, although a relation with learning was postulated. It has been demonstrated that implicit and explicit learning have distinct and selective preferences for dopaminergic mechanisms in different brain regions. The dopaminergic mechanisms in the limbic striatum are preferentially employed for facilitating implicit learning rather than explicit learning [20].

4.3. Serotonergic System. Two studies suggest that the serotonergic system plays a significant role in events underlying neuroplasticity. In one study, increased 5-HT synthesis in the striatum is identified as a compensatory response (adaptative plasticity) to cortical resection in epilepsy patients [19], potentially supporting functional recovery through serotonergic modulation of subcortical circuits. In another, the neuroplastic effects of $5\text{-}HT_{1A}$ receptors are highlighted for their influence on GM volume in various regions of the healthy human brain [21], which may reflect adaptive neuroplasticity linked to normal physiological processes such as learning. In contrast, a third study linked serotonergic changes and GM in patients with MDD. Although it did not provide direct evidence, the findings suggested that 5-HT may play a significant role in adaptative neuroplastic processes only in healthy individuals, as the expected structure–function associations were observed in this group [26].

4.4. Glutamatergic System. The studies on the glutamatergic system provide only indirect inference of synaptic plasticity [27, 30, 31]. In the context of AD, a decrease in mGluR5 has been demonstrated as a factor that could reduce synaptotoxicity, representing a neuroprotective strategy, which could reflect an adaptive neuroplastic response aimed at minimizing excitotoxic damage. However, an alternative explanation is that it may be solely due to the synaptic loss associated with the pathology [27]. Therefore, it is essential to recognize that the

decrease in mGluR5 may not necessarily represent an active neuroplastic process. Moreover, synaptic loss and adaptive neuroplasticity may coexist and/or present similarly in molecular imaging, making it difficult to clearly distinguish between the two with current methodologies. Furthermore, the stability of mGluR1 expression in the early stages of the disease suggests an adaptive response of the organism to maintain homeostasis in glutamatergic signaling [30]. In AUD, the greater availability of mGluR5 causes greater network-level connectivity [31].

4.5. Cholinergic System. The only study on the cholinergic system presents robust evidence of neuroplasticity in young individuals with early-onset torsion dystonia (DYT1). The pathophysiology of DYT1 is attributed to the negative regulation of DA-D2R, leading to an increase in ACh synthesis. The decrease in VAChT reduces the release of ACh. Thus, this pattern has been interpreted as a putative compensatory mechanism aimed at attenuating the excessive muscular activity characteristic of dystonia [29]. These findings reflect a clear example of adaptive synaptic plasticity, in which cholinergic transmission is reorganized to maintain functional balance in response to dopaminergic dysregulation (excessive activity of striatal projection neurons). However, other results from the same study, such as reduced cholinergic activity in the cerebellar vermis and increased resting-state functional connectivity within the motor network, point to maladaptive plasticity, potentially contributing to sustained muscle contractions and abnormal movements [29]. Therefore, the study highlights both adaptive and maladaptive forms of plasticity in the cholinergic system in DYT1 dystonia.

4.6. General Discussion. Taking all together, our analysis of these articles revealed convincing evidence of neuroplasticity through the use of PET imaging techniques, despite the heterogeneity among study groups. However, most of these studies only suggested that the observed outcomes could be compensatory adaptive or maladaptive mechanisms of the brain without conclusively establishing causality. The lack of direct evidence of neuroplasticity in some research might be due to difficulties and methodological issues that have a substantial influence on the validity and reliability of the results. Moreover, even studies that prove the existence of plasticity encounter problems that must be addressed to gain a deeper understanding of the findings. These challenges include limitations in experimental design, making causal inference difficult and often generating uncertainty on whether the presence of an external stimulus or pathology is the real trigger for the observed neuroplastic mechanisms. Additionally, another relevant issue is the intrinsic difficulty in measuring plasticity with currently available techniques in humans. PET stands out as a valuable tool for quantifying neuroplasticity from a molecular perspective, particularly at the level of neurotransmitter receptors/transporters, allowing detailed insights into the underlying mechanisms of neuroplasticity.

Importantly, several studies raise concerns about sample size and participant selection [22, 23, 27, 28, 30, 31], as small samples do not yield results with high statistical power and limit the generalizability of findings to the overall population. Furthermore, except for three studies [24, 30, 31], all the others adopted a cross-sectional design, which further restricts the ability to establish causal inferences. Individual participant factors and heterogeneity in the extent, location, and progression of the disease must be considered because they can introduce variability into the results [30]. For example, PD is a heterogeneous disease where patients exhibit different clinical symptoms and progression patterns, although some studies tried to select patients at similar early stages. As described, some of the healthy controls may present preclinical AD, which is often not excluded, minimizing differences between patients and controls [27]. The same applies to stroke, where heterogeneity in the location and extent of the lesion can result in considerably distinct GABAergic responses between patients [24]. The study that includes participants with cerebral resection has as a limiting factor the lack of identification of the removed brain regions. It is highly likely that the heterogeneity among these regions, considering the influence of the resection location, also represents a restrictive factor in understanding neuroplasticity [19].

There is also a risk of bias when not considering factors that may influence radiopharmaceutical uptake, such as inflammation, immune response, or metabolic changes, in addition to compensatory effects unrelated to the neurotransmitter under study. Endogenous changes should also be considered, as certain measured alterations may result from changes in the endogenous concentration of the neurotransmitter or the presence of other endogenous ligands for the receptor. The use of simplified models in the analysis represents a limitation as well. For example, one article considered the rest of the brain beyond the lesion as relatively preserved in epilepsy, and this assumption may not be valid, as changes in other brain areas may occur in response to localized abnormalities [17].

Likewise, the interference of medication needs to be considered. Even if participants are not using drugs that directly compete with the radiopharmaceutical, anticonvulsant medications can cause allosteric changes in the receptor, thus, altering the affinity with the radiopharmaceutical [17]. Some participants with AD were using antidepressants, cholinesterase inhibitors, and memantine, which can affect neurotransmitters interacting with mGluR5 or mGluR1. Therefore, the potential influence of these medications on the results cannot be entirely ruled out [27, 30]. The administration of lorazepam to alleviate withdrawal symptoms in some participants further introduces individual variability. This problem was directly addressed in the study of Rebelo et al. [28] by confirming the results with nonmedicated patients.

Considering these limitations, future studies must pay particular attention to including the analysis of relevant covariates, such as medication use, even when, a priori, there is no direct competition with the radiotracer, as well as individual factors and variability in pathological states (such as disease progression or lesion location and extent), since all of these aspects can substantially influence the neuroplasticity findings obtained through PET. In addition, future studies should include larger populations and longitudinal analyses to better understand changes over time and establish causal relationships. Furthermore, it is recommended that future research consider

potential sex/gender-related differences in neurotransmitter-associated neuroplasticity mechanisms, whenever such differences are reported. These variables may substantially influence the generalizability of findings, as biological and hormonal factors can modulate neuronal receptor expression.

We also emphasize that the bias assessment through JBI questionnaires presents limitations, as each flaw is given the same weight, regardless of its potential significance.

In conclusion, the PET imaging technique has great potential to highlight mechanisms of neuroplasticity in the diseased and healthy human brain, because it allows to provide molecular insights into the reorganization of synaptic circuits. Through the intravenous injection of small amounts of radiopharmaceuticals, without interference with the physiology in PET studies enables (1) to analyze the binding and transport of neurotransmitters, providing insights into neuronal communication and (2) to analyze the density of specific neuronal receptors, which is crucial for understanding synaptic plasticity mechanisms.

In sum, the use of PET with radiopharmaceuticals focused on synaptic molecules known to be involved in plasticity enables the scientific enquiry neurobiological processes underlying functional brain reorganization in both normal and pathological conditions. One must keep investigating synaptic plasticity mechanisms to develop more effective and personalized therapeutic approaches for treating numerous pathologies as well as to understand maladaptive plasticity. By taking advantage of all the information at the molecular level that PET provides, we can deepen all the knowledge surrounding neuroplasticity and contribute to significant advancements in enhancing individuals' quality of life.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Ferreira M., Matias F., Martins R., and Castelo-Branco M. contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Ferreira M. and Matias F. The first draft of the manuscript was written by Ferreira M. and all authors commented on previous versions of the manuscript. Ferreira M., Matias F., Martins R., Abrunhosa A., and Castelo-Branco M. commented on previous versions of the manuscript. Castelo-Branco M. provided critical feedback on the manuscript.

Funding

This work was supported by the Projects funded by Fundação para a Ciência e Tecnologia: Grants UIDB/4950/2020 (https://doi.org/10.54499/UIDB/04950/2020) and 2025, UIDP/4950/2020 and 2025 (https://doi.org/10.54499/UIDP/04950/2020), FCT/UIDB/2020/4950, FCT/UIDP/2020/4959, 2022.02963.PTDC (https://doi.org/10.54499/2022.02963.PTDC), CEECINST/00041/2018/CP1568/CT0005 (https://doi.org/10.54499/CEECINST/00041/2018/CP1568/CT0005), and 2023.00376.BDANA.

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