Neuroscience and Biobehavioral Reviews 185 (2026) 106623

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Molecular connectivity studies of cerebral glucose metabolism and blood flow: A scoping review

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https://doi.org/10.1016/j.neubiorev.2026.106623
Received 11 November 2025; Received in revised form 9 February 2026; Accepted 28 February 2026
Available online 5 March 2026

ARTICLE INFO

Keywords:
PET
SPECT
Perfusion
Neuroimaging
Neurodegeneration
Networks
Multivariate

ABSTRACT

The brain's functional organization relies on neural, metabolic, and vascular interactions. Molecular neuroimaging offers powerful tools for assessing macroscale brain connectivity by capturing relationships between regional perfusion and glucose metabolism. This review summarizes molecular connectivity studies of cerebral blood flow (CBF) and metabolism, focusing on methodological approaches and key findings. A systematic search across MEDLINE, EMBASE, and Scopus identified studies employing radiotracers to examine brain perfusion or glucose metabolic connectivity. Data extraction focused on tracer type, connectivity methodology, population, and clinical relevance. Overall, 384 studies were included, covering healthy condition, dementia, movement disorders, psychiatric diseases, epilepsy, and disorders of consciousness. Both resting-state and task-based paradigms were identified, with perfusion studies being popular for detecting fast task-induced molecular connectivity changes. Metabolic connectivity, assessed via [^{18}F]FDG-PET at rest, emerged as robust marker of functional integrity and disease progression, especially in neurodegenerative conditions. Multimodal PET/MRI studies revealed partial overlap between metabolic and hemodynamic connectivity. Noteworthy findings include the identification of default mode network through the study of CBF and disease-related covariance patterns in neurodegenerative disorders through the study of glucose metabolism. Integrating macroscale molecular brain organization studies with neurophysiological techniques will deepen the understanding of brain connectivity in health and disease. Additionally, total-body PET/MRI data may in the future elucidate brain–body interactions fostering a more comprehensive connectome framework.

1. Introduction

The brain is an energy-intensive organ, driven by both oxidative and glucose metabolism in the production of adenosine triphosphate (ATP). Additionally, along with brain metabolism, its function relies on a complex balance between chemical and electrical signaling underlying excitatory and inhibitory neural activity (Jamadar et al., 2025). Neural signals emerge when populations of excitatory and inhibitory neurons interact, generating complex chemical and electrical signals with firing patterns that differ across brain regions. To this process, glial cells differently contribute to the so-called tripartite synapsis, enriching with new metabolic and signaling features the functional segregation across brain areas (Bonvento and Bolaños, 2021).

Modern neuroimaging methods capitalize on these metabolic and hemodynamic responses—such as cerebral blood flow (CBF), oxygen consumption, and glucose metabolism—to infer neural activity (Voigt et al., 2023).

Positron emission tomography (PET) with water ([^{15}O]H_2O) is commonly used tracer to measure cerebral perfusion or regional CBF (rCBF). [^{15}O]H_2O is a freely diffusible and metabolically inert molecule with a near-complete extraction fraction, allowing for a direct and linear relationship between tissue uptake and perfusion (Ter-Pogossian and Herscovitch, 1985). The short half-life of Oxygen-15 (122 s) facilitates quick scanning protocols and minimizes radiation exposure but requires on-site cyclotron production (Ter-Pogossian and Herscovitch, 1985). Perfusion PET imaging reflects the immediate vascular response to neural activity, giving a snapshot of fluctuations in brain function (Fig. 1). Single photon emission computed tomography (SPECT) with Technetium-99m ethyl cysteinate dimer ([^{99m}Tc]ECD) or hexamethylpropyleneamine oxime ([^{99m}Tc]HMPAO) tracers can measure rCBF, albeit with lower spatial resolution.

Further, while perfusion reflects the immediate vascular response to

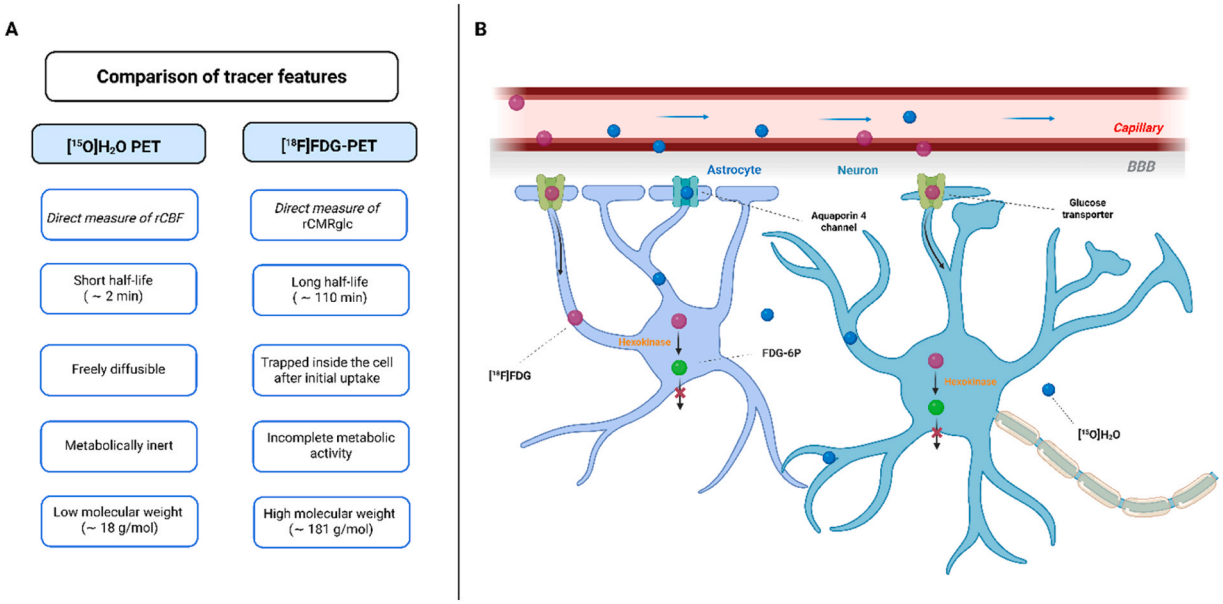

Fig. 1. Comparison between perfusion and [^{18}F]FDG glucose metabolism PET. (A) Comparison of molecular features of [^{15}O]H_2O and [^{18}F]FDG. [^{15}O]H_2O and [^{18}F]FDG tracers, for perfusion and glucose metabolism, respectively. (B) From the blood vessels, [^{18}F]FDG enters the astrocytes and neurons through glucose transporters. Inside the cell, [^{18}F]FDG is metabolized by the hexokinase into FDG-6P, which cannot exit the cell, thus allowing the measurement of brain metabolism. [^{15}O]H_2O, instead, can either enter the cell through the aquaporin 4 channel and allow the direct measurement of cerebral blood flow. Abbreviations: [^{18}F]Fluorodeoxyglucose ([^{18}F]FDG), approximately (~), blood brain barrier (BBB), cerebral metabolic rates of glucose consumption (rCMRglc), Fluorodeoxyglucose 6-phospate (FDG-6P), minutes (min), Oxygen-15 labelled water ([^{15}O]H_2O), positron emission tomography (PET), regional cerebral blood flow (rCBF).

neural activity, brain glucose metabolism captures the brain energy requirements over a longer period (few seconds to minutes) (Herscovitch et al., 1987), providing insight into the sustained demands of network function (Jamadar et al., 2019) (Fig. 1). The brain's immense energy demands are largely fueled by oxidative metabolism as well as glycolysis, the latter of which is a process tightly coupled with neural activity and rCBF. A recent study in drosophila has reinforced the strong link between neural activity and metabolism, showing that intracellular calcium fluctuations closely align with metabolic shifts, particularly in pyruvate levels (Mann et al., 2020). PET with the fluorodeoxyglucose ([^{18}F]FDG) tracer is widely used to study glucose metabolism or regional cerebral metabolic rates of glucose consumption (rCMRglc). Upon entering the brain, [^{18}F]FDG is phosphorylated by hexokinase, becoming trapped in neurons and glial cells, and provides a quantitative measure of regional glucose uptake (Sokoloff, 1979).

Pioneering studies by Horwitz et al. first observed that anatomically and functionally connected brain regions exhibit correlated rCMRglc, paving the groundwork for what is now termed **molecular connectivity** (Horwitz et al., 1984). Molecular connectivity refers to the study of relationships between biological signals across different brain regions, typically obtained using molecular neuroimaging, such as PET or SPECT.

The development of sophisticated statistical approaches has expanded our ability to investigate molecular connectivity (Sala et al., 2023). Building on Mesulam's (1990) (Mesulam, 1990) conceptualization of neural networks, Friston and colleagues introduced the correlation analysis of perfusion time-series, on the assumption that CBF patterns reflect functional interactions across the brain (Friston et al., 1993a). In the early 1990s, researchers began applying computational network modeling to [^{15}O]H_2O-PET data, using perfusion imaging to investigate connectivity substrates of cognitive function (for a review, see (Friston et al., 1996)).

To address the complexity of the brain, bi- and multivariate methods have emerged as powerful tools to extract molecular connectivity. These approaches can be applied to static data (single snapshots of tracer distribution, as in conventional PET or SPECT) as well as dynamic data (time-resolved acquisitions that capture how tracer uptake evolves, providing information on physiological processes over time). These methods consider interdependencies among multiple brain regions, allowing for a more complete understanding of neural activity. Unlike univariate approaches that analyze individual regions in isolation, bi- and multi-variate techniques identify complex relationships that underlie cognitive function and neurological disorders (Habeck, 2010). Notably, these methods can reveal functional networks, distinguish between disease states, and reduce data dimensionality to extract key features.

Among the most widely used bi- and multivariate approaches to general molecular connectivity networks different approaches can be employed (Yakushev et al., 2017; Hahn et al., 2019), including data-driven (e.g., principal component analysis – PCA, and independent component analysis - ICA), seed-based correlation (e.g., interregional correlation analysis – IRCA), and ROI-based methods (e.g., correlation-based approaches, such as sparse inverse covariance estimation – SICE or graph-based ones) (Table 1**).**

While these methods are not dissimilar to those applied in the widely available fMRI-based works on functional connectivity, compelling evidence suggests that fMRI alone may be insufficient to accurately characterize neural activity. Task-related fluctuations in BOLD signals appear to be only partially coupled with variations in cerebral or oxygen metabolism, highlighting that fMRI alone may be insufficient to fully capture neural activity (Stiernman et al., 2021; Devor et al., 2008; Epp et al., 2025). This emerging body of work suggests that the field is currently at an inflection point, where reliance on hemodynamic measures alone may be insufficient.

This work reviews how molecular connectivity approaches in perfusion and metabolic imaging contribute to the characterization of brain function; addressing an urgent need for integrative and multimodal frameworks that support clinical translation in healthy and pathological conditions, including dementia, movement disorders, psychiatric disorders, epilepsy, and disorders of consciousness.

Table 1
Classification of statistical approaches used in molecular brain connectivity studies by methodological category.

Approach Category	Included Methods
Seed-based Correlation Approaches	IRCA (interregional correlation analysis), IRCA – PPI (Psychophysiological interaction), PLS (Partial Least Squares), KLSE (Kullback–Leibler Divergence Similarity Estimation), IRCA + PCA (Principal Component Analysis)/SEM (structural equation modeling) combinations, MCM (Metabolic Connectivity Mapping)
Data-driven techniques	ICA (Independent Component Analysis), PLS (Partial Least Squares), CVA / OrT (Ordinal Trends)-CVA (Canonical Variates Analysis), SSM (Scaled Subprofile Modeling)/ SSM-PCA, Similarity Network Fusion, Nonmetric Multidimensional Scaling, Metabolic covariance pattern, PCA, Spatial Covariance Analysis (SCA), Partial least squares (PLS), Spectral covariance decomposition
ROI-based methos	Regional Correlations, Regional Partial Correlations, Pearson correlation, Correlation matrices, JSSE (Jensen-Shannon Divergence Similarity Estimation), Euclidean distance
Graph-based Methods	Graph Theory, gLASSO (graphical Least Absolute Shrinkage and Selection Operator)/SICE (Sparse Inverse Covariance Estimation), Network analysis, Topological Data Analysis (TDA)

Statistical analysis methods were grouped into seven major categories based on shared computational principles and analytical goals: Each group includes specific techniques frequently employed in neuroimaging studies, particularly in analyses of metabolic and perfusion imaging data.

2. Methods

This scoping review was carried out in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses, guidelines extension for scoping reviews, or PRISMA-ScR) (Stiernman et al., 2021). The analysis was conducted using the PRISMA-ScR checklist. A study protocol was prepared in open science framework (OSF) prior to the initiation of data collection to ensure methodological rigor and transparency.

2.1. Methodology for searching

On July 14, 2023, three bibliographic databases — MEDLINE (via Ovid), EMBASE (via Elsevier), and Scopus (via Elsevier)—were searched for original papers On December 31, 2024, a second search was conducted. The two main topics for the search strategy were (1) connectivity and (2) PET and SPECT. **Annex I** contains a list of the entire search technique (Devor et al., 2008).

2.2. Criteria for eligibility

According to predetermined inclusion and exclusion criteria, molecular imaging studies that looked at functional interconnections between different parts of the brain were included. The following explains the definition of the eligibility requirements (inclusion and exclusion criteria). These requirements included original research that: a) used brain PET or SPECT, and b) evaluated CBF or metabolism. Preclinical research, studies that examined areas other than the brain, post-mortem examinations, and studies that used monoclonal antibody imaging methods were excluded. Lastly, conference abstracts, review papers, letters, and commentaries—including non-English articles—were also excluded (Supplementary Table 1).

2.3. Data extraction and study selection

Initially, two investigators (D.E.P. and M. S.) independently evaluated abstracts and titles to remove records that did not meet inclusion criteria. In case of disagreement, the third investigator (M. V.) assumed the position of third peer. Afterwards, two further investigators (C.C. and S. P. C.) independently screened the complete text of each unremoved article. We considered papers where the terminology differs from molecular connectivity, networks, or connectomics, and were published before 1993 (formal description of brain functional connectivity (Epp et al., 2025). Given their common goal of examining functional relationships between brain regions, these articles were judged pertinent to assure an inclusive search strategy. For each of these included papers, the authors created a pre-defined data sheet in which they arranged and extracted comprehensive information. This information covered a number of topics, such as authors' names, year the study was published, Study population characteristics (both patient and healthy control groups), type of tracer used, putative marker type and specification, protocol and analysis type, methods used for connectivity analysis, software used, main findings, validation type (if applicable), multimodality type (if applicable), and any reported metrics of multimodality performance and similarity. This methodical procedure made sure that all pertinent information from every included study was fully documented, which made it easier to conduct a thorough analysis and synthesize the results.

3. Results

3.1. Search results

After removing duplicates, a total of 3649 references were retrieved from database searches (3213 in July 2023, 355 in April 2024, and 81 in June 2025). Following title and abstract screening, 757 references were selected for full-text review. Ultimately, 422 of these met the eligibility criteria and underwent data extraction. Full texts were excluded primarily due to irrelevant radiotracers, analysis (i.e., lacking molecular connectivity), or population. From the eligible studies, a subset of 384 articles specifically addressing neural function (perfusion and metabolism) were included in this review. The identification of these articles was based on the biological target of interest. Fig. 2 shows the PRISMA flow chart describing the articles selection process.

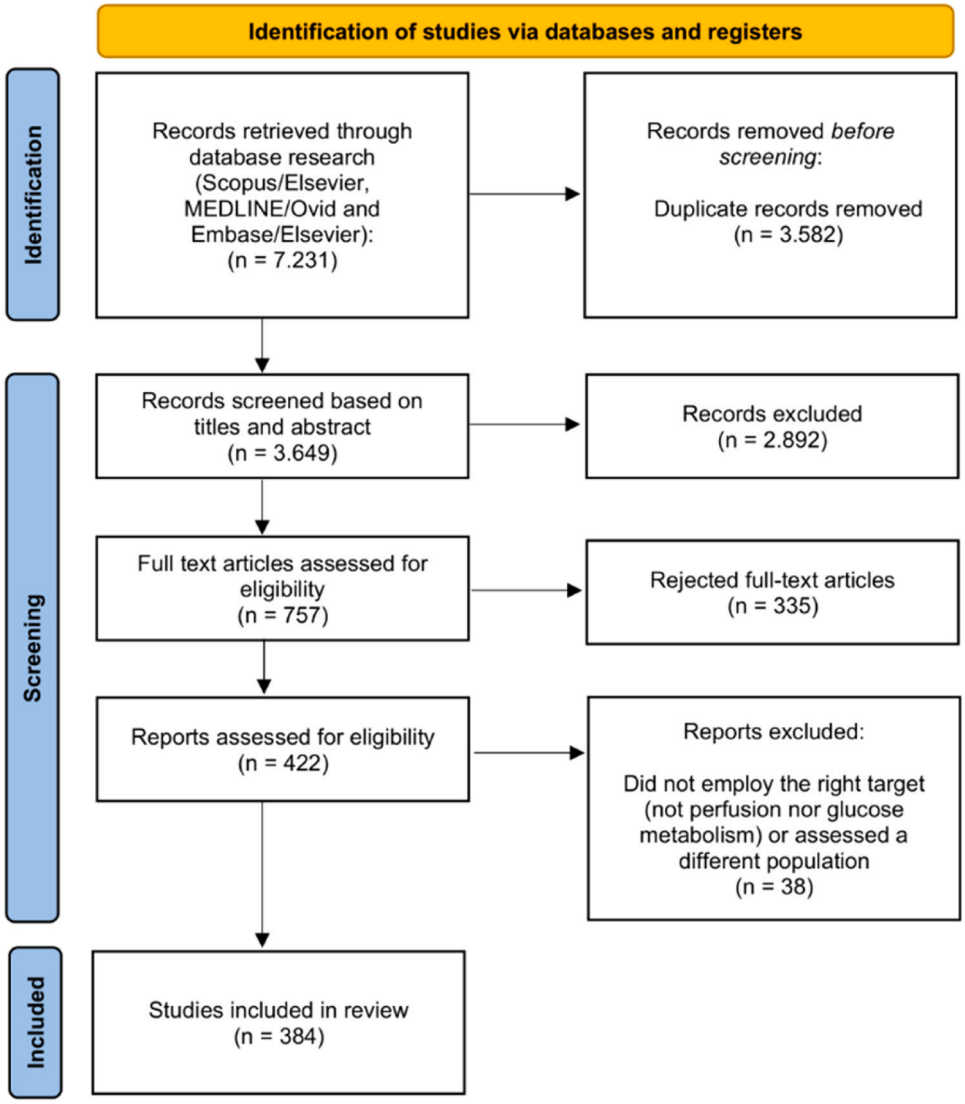

Fig. 2. PRISMA flow diagram of study selection. A total of 7231 records were identified, 3582 duplicates removed, 3649 records screened, 757 full texts assessed, and 384 studies included in the final review.

3.2. Studies characteristics

Studies were first categorized based on the sample population, identifying six different populations of interest, namely healthy subjects, dementia, movement disorders, psychiatric conditions, epilepsy, and disorders of consciousness (Fig. 3). When a study investigated multiple disorders, it was assigned to a single category based on the larger sample size in that study. Only conditions with more than 5 studies were included in the report. The resulting literature comprised 84 studies on healthy control (HC) subjects, 136 on the dementia (DEM) spectrum, including Alzheimer's diseases (AD), Dementia with Lewy bodies (DLB), Fronto-Temporal Lobar Degeneration (FTLD), 113 on movement disorders (MDS), including Parkinson's disease (PD), Huntington's disease (HD), Tourette syndrome, parkinsonisms, and dystonia, 20 psychiatric (PSY) studies, including schizophrenia, major depression, bipolar disorder, post-traumatic stress disorder - PTSD, 21 on epilepsy (EPI), and 8 on disorders of consciousness (DoC).

We observed a clear shift in the past two decades, from perfusion to glucose metabolism studies (Fig. 4), and from task-related to resting-state analyses.

3.3. Molecular brain connectivity in healthy controls

3.3.1. Brain connectivity in healthy volunteers in sensory, motor and cognitive tasks

Initially, most studies adopted perfusion PET - through task-related paradigms - to investigate different sensorimotor and cognitive domains. Several studies, adopting different methodologies for connectivity extraction, explored perfusion changes while participants performed linguistically demanding tasks to shed light on the networks recruited during distinct aspects of **speech and language** (Friston, 1991; Friston et al., 1993b; Horwitz and Braun, 2004; Schulz et al., 2005; Sidtis, 2012). Of note, by applying PCA to these data, Friston and colleagues were among the first to demonstrate the existence of functional networks whose neural activity change progressively with time, irrespective of the tasks the subject was engaged in (Friston et al., 1993b). Brain functional connectivity during linguistic tasks was also explored by means of [^{18}F]FDG-PET (Karbe et al., 1998; Schreckenberger et al., 1998) combined with regional correlation-based methods. Across perfusion and metabolic imaging studies, language processing consistently engaged a left-lateralized perisylvian network—centered on frontal and temporal regions—whose functional connectivity reorganized dynamically according to linguistic task demands (Horwitz and Braun, 2004; Sidtis, 2012; Karbe et al., 1998; Schreckenberger et al., 1998). In addition, Barret observed a modulation of connectivity among the anterior cingulum, insula, thalamus and parahippocampal gyrus by applying repetitive transcranial magnetic stimulation (TMS) on the left dorsolateral prefrontal cortex (Barrett et al., 2004).

Another cognitive domain that has received considerable attention from the scientific community is **memory**. Perfusion PET studies investigated network connectivity underlying memory abilities using a seed-based approach (Grady et al., 2001; McIntosh et al., 1997; Nyberg and Tulvingl, 1996; Rajah and McIntosh, 2005). These perfusion PET connectivity studies demonstrated the engagement of a network involving prefrontal and temporal regions during episodic memory retrieval (Grady et al., 2001; McIntosh et al., 1997; Nyberg and Tulvingl, 1996) and the ability of the brain to flexibly reconfigure its connectivity to meet the cognitive demands of different memory tasks (i.e. episodic vs semantic memory) (McIntosh et al., 1997; Rajah and McIntosh, 2005). Moreover, two studies using [^{11}C]butanol-PET to investigate episodic memory-related connectivity in healthy subjects, reported the involvement of the frontal network during encoding (Krause et al., 2000, 1999). On the other hand, molecular connectivity analyses revealed that the parahippocampus, posterior cingulate and precuneus were linked to memory retrieval (Krause et al., 1999). Some studies examined brain connectivity during working memory tasks, showing shifts in brain connectivity depending on the nature and cognitive demands of the task at hand (McIntosh et al., 1996; Cornette et al., 2001). Finally, Krause et al. observed an overlap of brain regions involved in working memory and episodic memory related networks, such as the prefrontal, cingulate, and parietal cortices (Krause et al., 2000).

Rajah and colleagues , in a perfusion PET study, reported molecular connectivity between bilateral occipito-temporal and medial temporal regions during **face encoding**, and a positive feed-forward loop, in the right hemisphere, between right occipito-temporal and frontal cortex during **recognition** tasks (Rajah et al., 1999).

Some studies also investigated, brain connectivity during **attention**

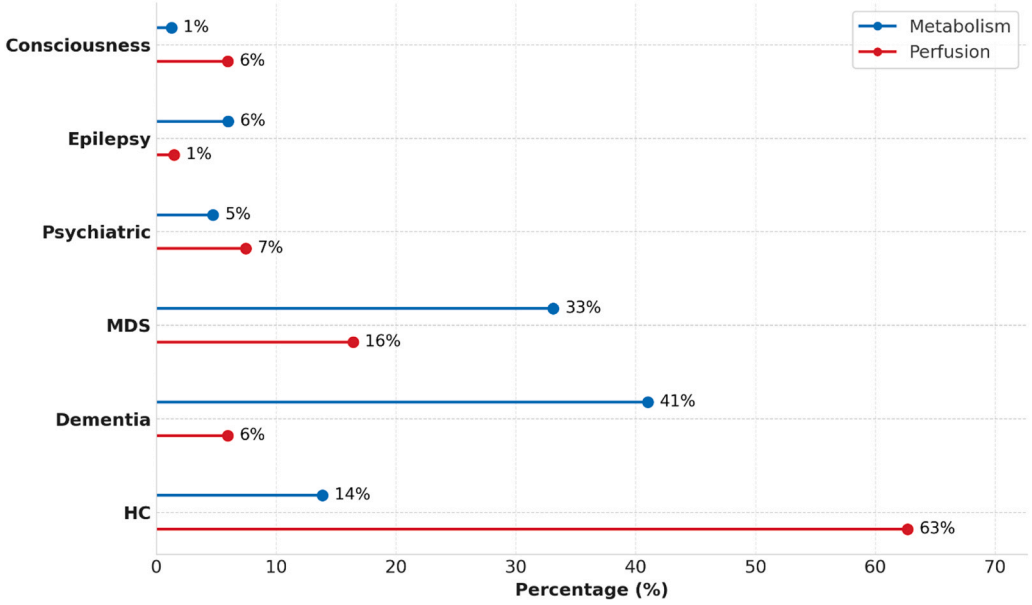

Fig. 3. Percentage of studies performed with PET metabolism and/or perfusion across different clinical populations. Groups include healthy controls (HC), dementia, movement disorders (MDS), psychiatric disorders, epilepsy, and disorders of consciousness. Percentages were calculated relative to the total number of studies for each PET modality.

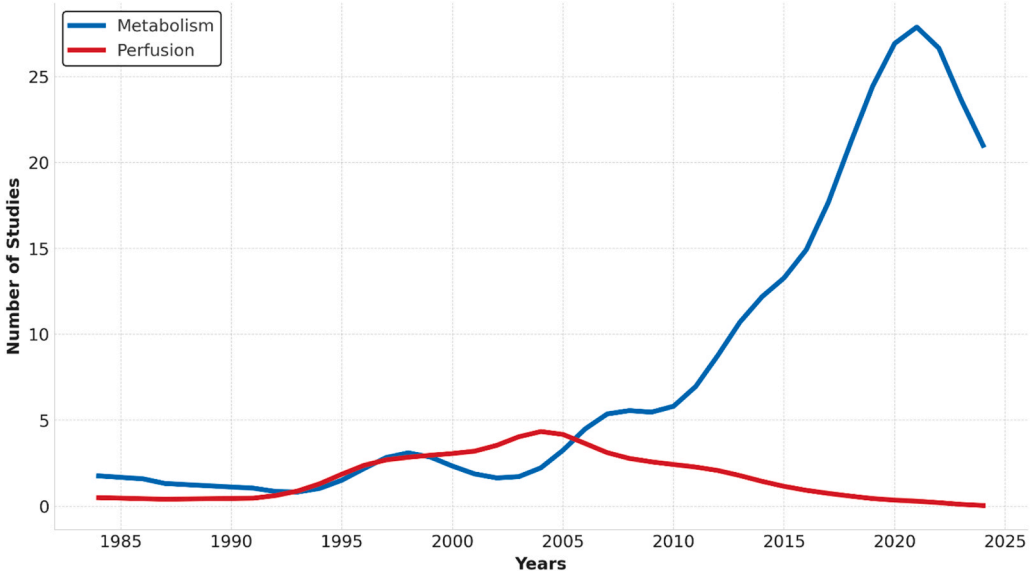

Fig. 4. Temporal trend in the number of published studies using PET imaging. Studies were stratified into Metabolism and Perfusion PET. Data are aggregated per year and smoothed to highlight general tendencies.

and alertness tasks in a cohort of healthy participants, suggesting a role of molecular connectivity between prefrontal regions, the anterior cingulate cortex and the thalamus in coordinating, maintaining and shifting attentional focus (Mottaghy et al., 2006; Harrison et al., 2005). In addition, Harrison and colleagues demonstrated the role of the ventral visual circuit in suppressing irrelevant information during cognitive tasks (Harrison et al., 2005). Coull and colleagues demonstrated the effects of clonidine administration both at rest (enhanced network integration) and during attention tasks (connectivity suppression) (Coull, 1999).

The above studies are crucial in reinforcing the main theories of classical neuropsychology, adding an extremely important insight into the modularity and plasticity of the cognitive neural systems.

Motor and sensory learning studies highlighted connectivity features depending on the tasks' requirements. Specifically, Paus et al. identified positive and negative rCBF correlations between motor and sensory regions, during two different sensory-motor learning tasks (Paus et al., 1996). McIntosh et al. observed different patterns of rCBF connectivity of the medial temporal lobe depending on the subject's awareness during sensory learning (McIntosh et al., 2003). Penhune and Doyon discovered predominant motor and cerebellar perfusion connectivity during motor learning (Penhune and Doyon, 2005). Mitelman et al. instead, by comparing connectivity extracted from grey matter volume (GMV) and glucose metabolism during verbal learning, supported the different value of these two approaches (Mitelman et al., 2006). Indeed, metabolic connectivity showed widespread thalamocortical interactions while GMV connectivity was more limited and involved thalamocortical interaction only in the right hemisphere (Mitelman et al., 2006).

Both perfusion and [^{18}F]FDG-PET studies investigating how the healthy brain processes **sensory** information, revealed an interplay of task-specific brain regions involved in different sensory systems (Zald et al., 1998; McIntosh et al., 1998). For example, the interaction between amygdala and orbito-frontal cortices during aversive odors. Further perfusion studies investigated how sensory systems encode different stimuli: McIntosh et al. observed greater right interhemispheric interactions during different visual tasks (McIntosh et al., 1994) whereas Habib and colleagues observed distinct pathways responsible for encoding novel vs. familiar stimuli (Habib et al., 2003). This malleability of neural networks was interpreted as reflecting the brain's integrated ability to respond to cognitive demands, sensory stimuli and learned experiences.

Another area of interest for perfusion studies is **pain**. Pain perception has been associated with a network involving the thalamus, insula, and anterior cingulate cortex (Lorenz et al., 2003; Petrovic et al., 2002). Lorenz et al. using PCA demonstrated the role of the dorsolateral prefrontal cortex in modulating the perception of painful experiences, by increasing or reducing effective connectivity among subcortical regions (Lorenz et al., 2003). Faymonville et al., by exploring the analgesic effect of hypnosis, observed increased metabolic connectivity between the cingulate cortex and several cortical and subcortical regions, resulting in diminished pain perception (Faymonville et al., 2003). Another [^{18}F] FDG-PET study demonstrated an inverse relationship between cortical and brainstem activity during sympathetic thermoregulatory activation, possibly explaining other conditions for induced sympathetic hyperactivity (Fechir et al., 2010).

Several studies have also explored the effect of healthy **aging** on brain connectivity during the performance of different cognitive and sensorimotor tasks. Perfusion PET studies highlighted reconfiguration of connectivity within regions involved in cognitive and motor control in elderly participants to possibly optimize performances execution (Stern, 2005; Cabeza et al., 1997; Rowe et al., 2006; Sharp et al., 2005). In detail, the cingulo-frontal connectivity increases with age, reflecting greater cognitive activation to compensate for performances decline (Stern, 2005; Sharp et al., 2005). Similarly, aging leads to a compensatory enhanced influence of the premotor cortex on sensory, motor cortices and SMA, as well as a reduced influence on the anterior cingulate cortex, to balance motor system efficiency (Rowe et al., 2006). Of note, evidence suggests that, during aging, a non-pathological decline in memory performances can be predicted by higher default mode network (DMN) coherence and node-to-node relationships during task performance, as well as progressive decline in precuneus covariance (Beason-Held et al., 2017). Della-Maggiore and colleagues observed the engagement of different neural networks in young and elderly people during a short-term memory task, with a greater involvement of dorsolateral prefrontal cortex, middle cingulate gyrus, and caudate nucleus in the elderly, despite comparable behavioral performances with younger adults (Della-Maggiore et al., 2000). Similarly, Krause et al. , in a multimodal [^{11}C]butanol PET and magnetic resonance imaging (MRI) study, observed widespread activations of the inferior parietal regions and prefrontal regions in elderly participants performing both episodic or working memory tasks (Krause et al., 2000).

3.3.2. Brain connectivity in healthy subjects at rest

Following pioneering correlation studies with resting PET, researchers focused on the investigation of brain connectivity within specific networks while the subjects were lying at rest, to investigate the baseline functional architecture of the brain (Horwitz et al., 1986). Several resting-state, perfusion and [^{18}F]FDG-PET studies were conducted to shed light on different neurocognitive systems.

One of the first [^{18}F]FDG-PET studies suggested that in the resting-state paradigm emerged the crucial role of the primary **somatosensory** and **premotor** areas as central hubs of integration (i.e. regions showing largest correlation coefficients) (Horwitz et al., 1984). Functional connectivity of primary somatosensory areas was further investigated though [^{11}C]butanol PET by Young et al. who showed a partial overlap of human brain connectivity with the known anatomical connections in macaques, suggesting comparable features within human somatosensory network (Young et al., 2003).

Szabo and colleagues using [^{18}F]FDG-PET identified at rest two different components, one related to the limbic system and the other to the sensory-motor network (Szabo et al., 1992). Notably, the limbic system explained 70% of total variance, suggesting that under conditions of motor rest and sensory deprivation, limbic structures are the determinant of brain metabolism (Szabo et al., 1992).

Further information regarding the functional organization of the brain at rest was provided by Metter and colleagues, who identified two distinct [^{18}F]FDG-PET metabolic networks: a superior system involving decision-making and visual processing regions, and an inferior system linked to language processing (Metter et al., 1984).

Vogt and colleaguesused [^{18}F]FDG-PET not only to map metabolic activity but also to infer patterns of functional connectivity, demonstrating that metabolic connectivity can effectively capture the distinct network affiliations of dorsal and ventral posterior cingulate cortex (PCC). Ventral PCC is preferentially connected with the subgenual cingulate cortex, supporting self-referential and emotional processing, whereas the dorsal PCC interacts mainly with cingulate motor and premotor areas, integrating visuospatial information for body orientation (Vogt et al., 2006).

[^{18}F]FDG-PET studies highlighted the role of fronto-parietal connectivity in affecting our **working memory** abilities, with increased connectivity in case of better working memory performance (Yakushev et al., 2013; Zou et al., 2015).

Lee et al. validated IRCA as a reliable approach for mapping metabolic connectivity from PET images, demonstrating that IRCA-extracted connectivity patterns depend on the anatomical location of the considered region and are robust to methodological choice, such as atlas selection (Lee et al., 2008).

3.3.3. Factors influencing brain connectivity at rest

Several studies have explored the effects of healthy **aging** on brain functional connectivity adopting the resting-state paradigm. Similarly to task-based paradigms, some resting-state studies highlighted a connectivity reduction, particularly in regions supporting complex cognitive processes, such as fronto-parietal regions and regions involved in the DMN, attention and executive control networks (Horwitz et al., 1986; Mertens et al., 2022). Further studies, investigating brain connectivity by means of **graph theory** analysis, observed disrupted small-world parameters in older subjects, suggesting reduced brain connectivity efficiency (Liu et al., 2014). Whereas Di and colleagues proposed a model of metabolic aging in which metabolic decline in specific brain regions affects other regions that are relatively spared or compensate for this decline (Di et al., 2019). Research studies focusing on brain development during **childhood** highlighted the significant modifications in metabolic connectivity involving fronto-thalamic, fronto-hippocampal, and fronto-cerebellar networks. depicting the increase in global network efficiency and reorganization of brain modules that occurs from childhood to adolescence (Huang et al., 2020a; Trotta et al., 2016).

Another interesting research area which emerged recently concerns brain connectivity differences between male and female populations. These studies showed the existence of several **sex-specific differences** in both metabolic activity and brain connectivity. Specifically, women showed stronger connectivity compared to men between sensory and motor regions (Hu et al., 2013). Furthermore, in women, brain hubs are mainly located in bilateral frontal areas, while in men, these are more lateralized and located in the right occipital and left frontal regions (Hu et al., 2015). Ottowitz , investigating the effect of estrogen on brain connectivity, revealed the role of female hormones in enhancing connectivity between amygdala and fronto-temporal regions, as well as between prefrontal and hippocampal areas (Ottowitz et al., 2008; Ottowitz, 2014). Interestingly, Savic & Lindström examined the structural and functional differences in brain asymmetry and connectivity among heterosexual and homosexual men and women, revealing sex-atypical amygdala patterns in homosexual individuals, with connectivity predominantly involving the anterior cingulate cortex in men and prefrontal regions in women (Savic and Lindström, 2008).

In a resting state [^{18}F]FDG-PET study, Kim et al. explored the effect of **education levels** on brain functional connectivity. Graph theory analysis revealed that higher education level was associated with an optimized global network topology, characterized by greater small-worldness, global efficiency, and resilience. This finding was accompanied by differences in hub architecture: the highly educated group relied on hubs centered on limbic and memory-related regions, namely the bilateral olfactory cortex, hippocampus, parahippocampus, amygdala, and midbrain, whereas the low education group relied mainly on hubs centered in the pallidum and pons. Finally, in the high education group, they identified greater betweenness centrality in the hippocampus, underling its central role in the information transfer (Kim et al., 2015). In another study, Kim et al. used 7 T MRI to investigate subnuclei within the basal ganglia and identified metabolic correlations—via [^{18}F]FDG-PET—and namely new functional correlations between dorsal striatum and insula (Kim et al., 2018a).

Some studies on the effect of **genetic polymorphisms** on the brain activity and connectivity showed that the serotonin polymorphism affects the regulation of stress and emotional responses by increasing negative correlation between the pregenual cingulate cortex on the amygdala (Kilpatrick et al., 2015), whereas Brain-Derived Neurotrophic Factor polymorphism affects functional connectivity within the prefrontal-hippocampal networks, with significant differences between men and women (Wei et al., 2012). Finally, the genetic vulnerability - apolipoprotein E (APOE) ε4 - to AD may alter whole-brain functional networks even before symptoms onset (Seo et al., 2013a; Didic et al., 2015; Yao et al., 2015).

3.3.4. Multimodal investigations in healthy subjects

Recently, research interest has shifted toward multimodal investigations of brain connectivity within the same cohort of subjects. This approach allows for a deeper understanding of brain function, as different imaging modalities provide complementary information (Di et al., 2012; Jamadar, 2021; Savio, 2017a; Tomasi, 2017; Verger, 2020a; Yakushev, 2022).

A study comparing different PET tracers for measuring perfusion and oxygen consumption in identifying the DMN found that [^{15}O]H_2O-PET was more sensitive to spontaneous brain activity than [^{15}O]O_2-PET (Aoe et al., 2018). Furthermore, multimodal studies, combining [^{18}F]FDG-PET and MRI, demonstrated coupling of cortical thickness measures and metabolic activity, with strong functional connectivity in the presence of significant cortical thinning in older subjects, as well as the importance of balance between segregation and integration networks to support the coupling between functional and structural connectivity (Huang, 2024; Romero-Garcia et al., 2014). Lizarraga et al. (2024) explored to which extent structural connectivity derived from diffusion weighted imaging relates to different proxy measures of brain connectivity, namely [^{18}F]FDG-PET and GMV covariance as well as fMRI derived functional connectivity (Lizarraga et al., 2024). They revealed

that around half of PET and fMRI functional connection correlate with structural connectivity and that [^{18}F]FDG-PET derived connections significantly correlate with fMRI derived functional connectivity (Lizarraga et al., 2024a). This supports [^{18}F]FDG-PET covariance as index of brain functional connectivity, comparable to fMRI.

Di et al. first employed ICA to identify brain networks from [^{18}F]FDG-PET data, revealing **similarities** with networks derived from resting-state fMRI (Di et al., 2017). However, notable discrepancies were observed in the DMN, where PET revealed weaker connectivity compared to fMRI. This suggests that metabolic covariance may not reflect functional connectivity patterns in the same way as the temporal synchrony measured with fMRI. Another study, instead,

reported an overlap between functional connectivity and metabolic activity within key regions of the DMN, thus reinforcing the evidence of a strong coupling between local metabolism and the functional connectivity (Passow et al., 2015).

Di and Colleagues' work relied on inter-individual correlations of *static* PET images where connectivity is estimated from across-subject covariance (Di et al., 2017). The technical advances leading to functional PET (fPET) protocols enabled the assessment of metabolic connectivity at an intra-individual level (Jamadar et al., 2019; Villien et al., 2014). This approach utilizes constant tracer infusion, thus allowing the tracking of **dynamic glucose cellular processes** with a higher temporal resolution compared to conventional static PET (sPET) protocols (Jamadar et al., 2019). fPET metabolic connectivity showed greater similarity to blood oxygenation level dependent (BOLD)-functional MRI (fMRI) connectivity than to sPET covariance, primarily in the fronto-parietal regions (Jamadar et al., 2021). Hahn et al. Hahn, 2017 observed how the performance of simple tasks, such as finger tapping, can elicit widespread brain changes – that extend beyond the primary resting-state networks - in functional (fMRI) connectivity and brain metabolism (fPET) as well as in white matter microstructure, highlighting the complementary role of these imaging approaches (Hahn, 2017).

Of note, Voigt and colleagues showed the complementary nature of [^{18}F]FDG-PET and fMRI techniques in understanding brain-behavior relationships by observing that both modalities showed strong relationship between fronto-parietal connectivity and cognitive measures (Voigt et al., 2023). However, functional connectivity measured by fMRI was associated with broader number of cognitive domains compared to [^{18}F]FDG-PET only associated with executive functioning (Voigt et al., 2023). This may be due in part to the modality, or to the degrees of freedom of the modality, with fMRI having many more measured timepoints than PET.

Using dynamic PET data, Volpi et al., explored the impact of time series normalization in individual-level metabolic connectivity, and observed that Euclidean distance-based approaches provide more biologically relevant and reproducible findings than Gaussian ones; later, they proposed a metabolic connectivity mapping framework based on Euclidean distance and kinetic modeling which demonstrated stronger correlations between PET-derived connectivity and fMRI-based functional networks (Volpi et al., 2021, 2023). Li and colleagues showed that multivariate methods provide more consistent activations across task studies compared to univariate methods like general linear model (Li et al., 2020).

Finally, Hansen et al. extended this multimodal perspective by integrating molecular, metabolic, and structural connectivity data. Their findings revealed that molecular connectivity modes, such as gene expression and receptor density, play a crucial role in shaping cortical organization, further differentiating the contributions of PET-derived metabolic connectivity from structural measures (Hansen et al., 2023).

For a summary of connectivity studies on HC see Supplementary Table 2**.**

3.4. Brain connectivity in dementia spectrum

PET is a crucial tool for diagnosing, monitoring, and researching neurodegenerative disorders, representing a unique, highly sensitive tool for differential diagnosis.

3.4.1. Focus on AD

As for **perfusion studies**, the four articles here identified applied [^{15}O]H_2O-PET in AD. Some studies used resting state PET scans to identify differences in cerebral perfusion between AD patients, individuals with **mild cognitive impairment** (MCI), and HC. Alterations in the resting state networks may indicate underlying early disease processes (Scarmeas et al., 2004; Devanand et al., 2006). At the same time, other studies employed cognitive activation paradigms, such as verbal recognition tasks or delayed match-to-sample tasks, to assess how brain networks respond to specific cognitive demands in AD patients compared to controls (Hansen et al., 2023; Štokelj et al., 2023). These studies provide some evidence on how AD affects the brain's capacity to recruit and coordinate different regions during cognitive processing (Hansen et al., 2023). Common findings across these studies include the identification of significant differences in brain activation patterns between healthy individuals and those affected by AD. Specifically, healthy elderly people typically showed a more efficient and coordinated network response during cognitive tasks, whereas AD patients often showed either compensatory recruitment of additional brain regions or reliance on alternative networks that differ from those used by HC (Volpi et al., 2023; Štokelj et al., 2023).

From a methodological point of view, multivariate approaches such as Scaled Subprofile Modeling (SSM) or Partial Least Squares (PLS) were often found to be more sensitive than traditional univariate methods (Statistical Parametric Mapping, ROI analysis) in detecting group differences and predicting cognitive decline (Scarmeas et al., 2004; Devanand et al., 2006; Grady, 2001). Accordingly, multivariate methods capture the covariance between brain regions, reflecting network-level changes that may be missed by examining individual regions in isolation.

3.4.2. Metabolic connectivity as a marker of integrity and progression

As for **glucose metabolism**, most studies utilized different cohorts that include HC, individuals with MCI, and patients diagnosed with dementia due to AD or other neurodegenerative diseases, employing both resting state and task-related approaches (Yakushev et al., 2022; Carbonell et al., 2014a). The characteristics of the studied cohorts vary widely, potentially affecting classification performances (Štokelj et al., 2023). For example, studies often include participants of various ages, levels of education and cognitive impairment. Research by Perani et al. focused on bilingual individuals, suggesting that higher **cognitive reserve**, as indexed by education and bilingualism, may modulate metabolic connectivity and resilience in the face of neurodegenerative pathology (Perani et al., 2017). Participants in these studies typically range from younger adults to the elderly, with varying degrees of cognitive impairment assessed using tools like the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) scale (Morbelli et al., 2012; Ng et al., 2022).

3.4.3. From preclinical stages to conversion

The more clinically-relevant studies focused on preclinical AD and the evolution of cognitive decline, identifying different metabolic patterns between normative aging and subjects with positive AD biomarkers (amyloid-β and tau) and their relationship (Arnemann et al., 2018; Chang et al., 2019; Ossenkoppele et al., 2019; Sun et al., 2020; Maleki Balajoo et al., 2023; Blazhenets et al., 2021a, 2021b; Jiang et al., 2022; Li et al., 2022; Meles et al., 2017; Perovnik et al., 2022a), or on individuals with subjective cognitive decline (SCD), a potential precursor to AD (Son et al., 2015, 2017; Dong et al., 2020; Zhang et al., 2023; Lemercier et al., 2021), or again on prodromal AD and MCI

(Morbelli et al., 2012; Li et al., 2018a). While several authors (Blazhenets et al., 2019; Li et al., 2018b; Zheng et al., 2019; Wang et al., 2020a, 2019a, 2020b; Blazhenets et al., 2020; Perovnik et al., 2023) developed a tool based on metabolic connectivity profiles for predicting AD conversion in patients with MCI, Chung et al (Chung et al., 2016). focused on the differentiation of **early-onset** vs. late-onset AD using [^{18}F]FDG-PET imaging and graph theory analysis. Perovnik et al., instead, built two machine learning classifiers based on [^{18}F]FDG-PET-derived features, for differential diagnosis of common dementia syndromes (Perovnik et al., 2022a). Others analyzed multimodal neuroimaging data, including MRI and [^{18}F]FDG-PET, also in combination with other PET tracers as such as with dynamic [^{11}C]-labelled Pittsburgh Compound B ([^{11}C]-PIB) (Peretti et al., 2021, 2022) showing the different contribution of each modality and the progressive network disruptions as AD progresses (Li et al., 2018b; Seo et al., 2013b; Ortiz et al., 2015; Romero-Garcia et al., 2016; Pagani et al., 2017; Yao et al., 2018; Ripp et al., 2020; Dyrba et al., 2020; Ling et al., 2022). Of note, Horwitz et al. observed that functional metabolic connectivity is able to highlight early network disruption in AD, even in the presence of a global level of glucose metabolism comparable to controls, supporting the hypothesis of AD as a disconnection syndrome (Horwitz et al., 1987). Finally, few studies analyzed the effect of treatments (e.g., deep brain stimulation techniques – DBS or aerobic training) on brain metabolism in patients with dementia, demonstrating a modulatory effect of these approaches in the direction of the normally expected resting-state metabolic patterns of specific disease-affected networks (Smith et al., 2012; Porto et al., 2018).

As for **AD** characterization, several studies (Yao et al., 2016; Carbonell et al., 2016, 2014b) employed a relatively large sample size of patients with dementia to differentiate between metabolic connectivity patterns, revealing the effects of amyloid-β on cerebral metabolism. Similarly, Sala et al . focused on bilingual and monolingual groups, assessing their respective metabolic connectivity in the context of cognitive decline associated with AD (Sala et al., 2022a). Resting state networks, such as DMN, are reported as often disrupted in AD (Fu, 2018; Kuang, 2019; Lin, 2023; Mattis, 2016; Metter et al., 1984; Morbelli, 2013; Mosconi et al., 2004; Munilla et al., 2017; Sanabria-Diaz et al., 2013; Spetsieris, 2015; Zammit, 2020; Iccarino, 2020). In particular the posterior cingulate cortex and precuneus are critical areas where metabolic activity is significantly reduced in AD compared to HC, even when different connectivity modeling are applied (Huang et al., 2010, 2011, 2020b). In contrast, Gupta et al . using graph theory analysis described cerebellar connectivity alterations in AD and suggested that hypermetabolism in regions like the cerebellum and lingual gyrus precedes symptoms progression in AD (Gupta et al., 2023). Moreover, Ballarini et al.found that certain neuropsychiatric symptoms correlate with altered metabolic activity in specific networks (increases in the salience and decreases in the DMN), suggesting a more nuanced view of brain function in dementia sub-syndromes (i.e. apathetic, hyperactivity, affective, and psychotic one) (Ballarini et al., 2016).

Similarly, task-related PET studies often reveal a compensatory mechanism in which some areas of the brain may increase their activity to maintain cognitive functions despite underlying pathology. For instance, Iaccarino et al (Iccarino, 2020). reported that altered connectivity patterns in dopaminergic pathways were associated with neuropsychiatric symptoms in AD patients. This is consistent with the observations that cognitive task may activate a broader network of brain regions, suggesting a recruitment of additional resources to cope with cognitive demands (Habeck et al., 2008; Toussaint et al., 2012). Moreover, the interaction between cognitive load and metabolic connectivity has been shown to be influenced by factors such as age and sex, leading to variations in how different groups respond to cognitive challenges (Ng et al., 2022; Malpetti et al., 2017; Caminiti et al., 2023). While several studies report similar patterns of reduced connectivity in AD during both resting and task conditions, there are differences in how these alterations manifest based on the specific cognitive tasks employed. For example, studies investigating brain-behavior correlations with cognitive tasks requiring executive function (Stroop test or memory recall tasks), often show more pronounced disruptions in prefrontal regions connectivity in AD patients (Massa et al., 2020). In contrast, regions associated with basic sensory integration, such as the occipital lobes, may remain relatively intact even in the presence of cognitive decline (Wang et al., 2023a).

3.4.4. Focus on FTLD

While many studies report similar patterns of hypometabolism in regions related to AD, differences can surface when analyzing various subtypes of dementia (Lehmann et al., 2013; Laforce et al., 2014; Herholz et al., 2018; Perani et al., 2014). Metabolic connectivity was able to discriminate between AD and behavioral variant of **fronto-temporal dementia** (bvFTD), with the latter characterized by greater anterior DMN and salience network involvement (Singleton et al., 2020). Advanced methods integrating data from diffusion tensor imaging (DTI) in the estimation of [^{18}F]FDG uptake networks inter-subject covariance improved classification accuracy and stability in distinguishing between AD and FTD (Wang et al., 2022). Additionally, Katako et al . demonstrate superior performances of support vector machines (SVM) in the differentiation of neurodegenerative dementias (Katako et al., 2018).

FTD, as many other neurodegenerative conditions, does not have a unique phenotypic manifestation, indeed, Corriveau-Lecavalier et al. were able to identify five latent patterns of metabolism, correlating with specific genetic mutations and clinical phenotypes (Corriveau-Lecavalier et al., 2024). The same author, applied an unsupervised machine learning algorithm to [^{18}F]FDG-PET data and identified four distinct dysexecutive subtypes in clinically heterogeneous AD patients, displaying distinct spatial patterns of tau distribution and neurodegeneration (Corriveau-Lecavalier et al., 2023). Of note, Malpetti and colleagues observed distinct disruption of brain metabolic connectivity in the frontal behavioural (DMN and executive control networks) and temporo-limbic (limbic and salience networks) variants of bvFTD (Malpetti et al., 2019). The semantic variant of Primary Progressive Aphasia (sv-PPA) was characterized by whole-brain network reconfiguration, thus framing sv-PPA as a network-level disorder, where a focal epicenter drives an extensive and complex brain rewiring from the earliest disease stages (Boccalini et al., 2022a). Specific brain connectivity patterns were also altered in asymptomatic individuals carrying MAPT mutations, a known risk factor for FTD (Liu et al., 2022; Chu et al., 2023).

Additionally, it has been possible to identify distinct metabolic covariance clusters in frontal FTD variant, correlating with executive function and memory (Salmon et al., 2006). Another study analyzed the neural substrates of visual, semantic, and phonological naming errors in neurodegenerative dementias using [^{18}F]FDG-PET, providing new neurobiological insights the pathological correlates of clinical symptoms in neurodegenerative conditions like AD and FTD (Catricalà et al., 2020). Furthermore, researchers identified specific metabolic patterns for bvFTD in limbic circuits which correlated with cognitive decline and other symptoms, revealing the potential of metabolic connectivity as a diagnostic and prognostic biomarker for bvFTD (Nazem et al., 2018; Liu et al., 2023; Rus et al., 2023).

3.4.5. Focus on DLB

In **DLB**, metabolic connectivity patterns may differ significantly from those seen in AD (Imai et al., 2020), particularly concerning regions belonging to dopaminergic pathways (Huang et al., 2018; Huber et al., 2020; Hsu et al., 2021; Stockbauer et al., 2024), thus suggesting that distinct neurotransmitter vulnerabilities may contribute to the clinical manifestations of DLB (Caminiti et al., 2024; Kang et al., 2021), and potentially predict survival in DLB (Brumberg et al., 2024). A consistent finding across articles is represented by the identification of specific metabolic connectivity alterations in DLB patients, particularly involving posterior brain regions, namely the occipital and parietal

areas. Major changes involved the primary visual areas, which correlated with cognitive deficits such as visual hallucinations and attention impairments (Sala et al., 2019; Iaccarino et al., 2018), as well as the motor control circuits (Ko et al., 2017; Choi et al., 2022). Furthermore, DLB emerged as a complex multi-network disorder, with distinct patterns of connectivity alterations across various large-scale brain networks (Sala et al., 2019; Caminiti et al., 2017; Chen et al., 2018). Baucknehet al. (2021). work pointed out the role of age and education as independent factors negatively covaried with metabolism in DLB hallmark areas. Of note, SPM and SSM/PCA analysis yielded high and comparable accuracy in discriminate DLB patients from other synucleinopathies; however, both methods did not differentiate between PD patients at high risk of dementia and DLB patients, suggesting significant overlap in their metabolic patterns (Carli et al., 2023). The identification of vulnerable networks in DLB points to a composite network signature that is associated with core clinical symptoms, such as visual hallucinations (VH) and rapid eye movement (REM) sleep behavior disorder (RBD) (Morbelli, 2019; Sala, 2019; Yoon, 2022). This aligns with findings by Ingram et al. that using spatial covariance analysis (SCA) of [^{18}F]FDG-PET data revealed significant differences in metabolic patterns between DLB and AD, with SCA proving superior to visual analysis in diagnostic accuracy (Ingram et al., 2022).

The work of Iaccarino et al. (2018). identifies metabolic connectivity changes linked to VH in DLB, with altered functional connectivity in the occipital and temporal regions, correlated with the severity of hallucinations. Similarly, Zorzi et al. (2021). applied a graph analysis approach to confirm that DLB patients with visual hallucinations show significant alterations in the functional architecture of their brains, particularly in connectivity between visual and control networks. Nicastro et al. (2020)., instead, explored neural correlates of hallucinations in DLB patients, linking it to reduced left frontoparietal metabolism. This is complemented by other findings , reporting the mechanisms underlying hallucinations in DLB through metabolic connectivity patterns (Nicastro et al., 2021)(Nicastro et al., 2021).

Finally, metabolic connectivity in DLB emphasizes the challenges in differentiating DLB from other dementias, particularly AD (Zhou et al., 2018). While some imaging characteristics, such as the "cingulate island sign," can support the diagnosis of DLB, the overlap in pathological features between DLB and AD complicates this differentiation (Perovnik et al., 2022b). To this regard, Chen et al. by means of brain network analyses, reveal distinct hub regions among DLB, AD, and HC, such as specific hubs may serve as biomarkers in the differential diagnosis among these conditions (Chen et al., 2019). Similarly, Iizuka and Kameyama (2020) demonstrated that SSM/PCA method was able to discriminate DLB from AD, thus emphasizing different imaging features between these two conditions. Conversely, Lu et al. (2022). study highlighted comparable abnormalities in [^{18}F]FDG-PET metabolic patterns in DLB and PD dementia (PDD) underlining the potential continuum across the clinical spectrum from PD to DLB.

Accordingly, methodologies such as multivariate analysis and principal component analysis have shown higher sensitivity in detecting metabolic changes compared to traditional univariate approaches, suggesting that the choice of analytical method can significantly impact findings (Blazhenets et al., 2019; Salmon et al., 2009; Zippo et al., 2015; Pan et al., 2019; Qiu and Zhou, 2020). Moreover, previous studies have employed graph theory and network analysis to explore how metabolic connectivity varies between populations, revealing that distinct topographical patterns exist based on disease state and cognitive load (Tondo, 2020; Veronese, 2019). These methods allow for a deeper understanding of how metabolic networks operate differently in healthy brains compared to those affected by neurodegenerative diseases and open the way for more individualized approaches (Titov et al., 2017; Gonzalez-Escamilla et al., 2021).

Brain connectivity findings in dementia conditions are summarized in Supplementary Table 3.

3.5. Brain connectivity in movement disorders

Brain molecular connectivity in movement disorders (Supplementary Table 4) addressed several key topics: i) validation of signature patterns as objective biomarkers, ii) identification of neural circuitries and their reconfiguration in different PD subgroups, and iii) therapeutic effect of pharmacological and non-pharmacological treatments.

3.5.1. Motor-related metabolic and perfusion patterns in PD

First, both perfusion and metabolic molecular imaging have been employed to estimate reliable covariance patterns as diagnostic markers able to differentiate patients with PD from HC or atypical parkinsonism. The first **PD motor-related pattern** identified using [^{18}F]FDG-PET and SSM-PCA by Eidelberg and colleagues , was characterized by increased metabolic activity within putamen, thalamus, pons, and cerebellar vermis, with relatively reduced activity in the lateral frontal and parieto-occipital association regions (Eidelberg et al., 1994). The premotor-parietal network aligns with the covariance pattern of neural activation observed using [^{15}O]H_2O-PET during explicit motor learning, that in PD requires broader and less efficient cortical recruitment than healthy controls (Nakamura et al., 2001). Teune et al. using pseudo-continuous arterial spin labeling magnetic resonance imaging (PCASL-MRI) and [^{18}F]FDG-PET (Teune et al., 2014), confirmed the overlap between PD perfusion and metabolic brain patterns. This consistent pattern extensively replicated across different molecular and perfusion studies, supports the great potential for diagnostic purposes and progression monitoring (Eidelberg et al., 1994; Spetsieris and Eidelberg, 2011; Carbon et al., 2003; Schindlbeck et al., 2020a; Moeller, 1997; Rus et al., 2020; Teune et al., 2013; Tang et al., 2010a). More recent studies validated the application of the PD-related covariance pattern (PDRP) in distinguishing PD patients from HCs and atypical parkinsonism, with high accuracy (80–95%) and high reproducibility even across different PET scanners and cohorts (Peng et al., 2014; Tomše et al., 2017; Wu et al., 2013a; Eckert et al., 2007; Ma et al., 2007; Meles et al., 2020; Eidelberg et al., 1998). The PDRP provides also an objective and reproducible biomarker in PD tremor - mediated by metabolic network changes in the **cerebello-thalamo-cortical pathway** (Mure et al., 2011; Antonini et al., 1998) – and in motor symptoms severity (Matthews et al., 2018). Two metabolic gait-related covariance networks have been proposed: i) *pace gait network* (frontal cortices), which correlated with step velocity and step length; ii) *temporal variability gait network* (sensorimotor cortex, basal ganglia, hippocampus, red nucleus and thalamus), which correlated with swing and step time variability (Sigurdsson et al., 2022). Ma and colleagues further confirmed the strong association between the PDRP obtained with [^{15}O]H_2O-PET and [^{18}F]FDG-PET images in patients with PD (Ma et al., 2007). The PDRP assessed using [^{18}F]FDG-PET was symmetrical across disease stages, despite asymmetrical dopaminergic deficits (Tang et al., 2020). Of note, a recent study combining [^{18}F]FDG-PET and T1-MRI, found a significant overlap between structural and metabolic patterns (Liu et al., 2020). Only one study using dynamic PET imaging in the context of PD, specifically quantified PD motor-related pattern from [^{18}F]Fluoropropyl-Carbomethoxy-Iodophenyl-Nortropane ([^{18}F]-FP-CIT) PET and [^{18}F]FDG-PET. Single-subject scores of the PDRP derived from dopaminergic imaging significantly correlated with disease duration, motor symptoms, and analogous metabolic values (Peng et al., 2021).

Only one perfusion study has been identified by our research. Bohlhalter et al. (2009). have explored the association between neurocognitive profile and pre-frontal perfusion dysfunctions in non-demented PD patients. Of note, patients with disrupted right dorsolateral prefrontal cortex function showed impaired verbal memory functions and somatosensory discrimination.

Instead, a larger group of studies described consistent metabolic **cognition-related pattern** in PD patients (PDCP), encompassing hypometabolism in frontal and parietal associative cortices and

increased metabolism in the cerebellum (Huang et al., 2007; Rus et al., 2022). This pattern, independent from the PDRP, showed significant correlations with reduced dopamine binding within the caudate (Niethammer et al., 2013) and reduced metabolism in caudate, thalamus, and posterior cingulate cortex (Meles et al., 2015). Holtbernd and colleagues, using both [^{18}F]FDG-PET and [^{18}F]DOPA-PET found a significant association between the PDCP of metabolic covariance and dopaminergic uptake in the anterior striatum (Holtbernd et al., 2015). Interestingly, a recent study found a partial overlap between PDCP and the DMN, except for the dorsolateral prefrontal cortex, highlighting its potential to predict cognitive decline in PD (Schindlbeck et al., 2021a). The role of DMN in cognition has been further confirmed by a multimodal study by Ruppert et al. (2021)., in which DMN nodes showed reduced glucose metabolism in PD with and without MCI. Notably, cognitive performance in PD is associated with the PDCP (Huang, 2007; Schröter, 2023) but not with white matter lesions, meaning that cognitive decline is primarily due to neural metabolic alterations rather than vascular damage (Schröter et al., 2023). Altered connectivity between temporal regions and meso-cortico-limbic system has been described as the metabolic connectivity substrate of impulse control disorder in patients with PD (Verger et al., 2018a). Executive dysfunctions and psychiatric symptoms in PD have been associated with metabolism in the cerebello-thalamo-striato-cortical pathway (Riou, 2021). Consistently, the pattern of metabolic covariance associated with executive dysfunction involved ventromedial frontal regions, hippocampus, striatum, and thalamus (Lozza et al., 2004). Of note, the expression of motor but not cognitive pattern was significantly different between sporadic PD, and genetic variants, namely Leucine-Rich Repeat Kinase 2 (*LRRK2*) and Glucocerebrosidase (*GBA1*) variants (Rus et al., 2022; Schindlbeck et al., 2020b).

3.5.2. *Therapeutic modulation of brain networks*

Another group of studies using both [^{15}O]H_2O-PET and [^{18}F]FDG-PET have shown the potential role of the PDRP as biomarker to track pharmacological and non-pharmacological **treatment** effects. Hirano and colleagues compared the effects of Levodopa treatment on PDRP using both [^{15}O]H_2O-PET and [^{18}F]FDG-PET, showing a dissociation between metabolism and rCBF characterized by increased brain perfusion alongside a decreased metabolism only affecting motor circuit (Hirano et al., 2008). Levodopa treatment was also associated with more robust and efficient networks over time, despite the progression of motor symptoms (Vo et al., 2023). Additionally, Levodopa-mediated changes in cognitive dysfunction, especially in verbal learning, correlated with concurrent changes in the PDCP (Mattis et al., 2011). Recently, found a reduction in PDRP expression associated with nicotinamide riboside supplementation in PD, which is in turn associated with clinical improvement (Brakedal et al., 2022). Niethammer et al. (2018) found that after gene therapy, PD patients developed a treatment-specific brain metabolic network involving motor cortical regions. Many studies have tried to explore network modulation in response to the DBS on the subthalamic nucleus (STN) or the internal globus pallidus (GPi). STN stimulation has been found to have significant effects on the expression of PD motor-related networks, similar but non overlapping to Levodopa-mediated effects (Asanuma, 2006; Jahanshahi et al., 2010). A robust perfusion and metabolic response in PDRP has been described in subjects with STN-DBS, especially involving the supplementary motor area (Trošt et al., 2006; Park et al., 2015). Consistently, Cao et al. (2017) described motor-related regions showing a significant neuromodulatory effect of STN-DBS, namely in the supplementary motor area and putamen. The network modulation of both STN and GPi-DBS treatment assessed with [^{18}F]FDG-PET has shown a significant correlation with motor symptoms improvements, also longitudinally (Trošt et al., 2006; Fukuda, 2001; Wang et al., 2010; Ge et al., 2020). Using simultaneous [^{18}F]FDG-PET and functional MRI, Zang and colleagues have described a high spatial overlap between the sensory motor area hypermetabolism and increased fMRI functional connectivity between the sensory motor area and subthalamic nucleus in PD, both representing pathological features in PD (Zang et al., 2022). Interestingly, the implantation of DBS electrodes on the GPi-DBS had a significant effect on metabolism in the putamen and thalamus, even in absence of stimulation (Pourfar et al., 2009). The GPi firing rate correlated significantly with metabolic activity within thalamus and brainstem (Eidelberg, 1997). Ko and colleagues explored the metabolic network modulation following sham surgery in PD, showing a significant effect on cerebello-limbic circuit (Ko et al., 2014). A few studies have investigated the impact of subthalamotomy on brain metabolic networks in PD, finding a significant neuromodulatory effect on disease-specific network such as the motor associative one (Su et al., 2001; Rodriguez-Rojas et al., 2020; Eidelberg et al., 1996; Feigin et al., 2007a). Of note, Ko and colleagues considering the metabolic correlates of placebo and sham effects, found associations with the expression of a different cerebello-limbic circuit, that may be used to identify "sham--susceptible" patients consistently (Ko et al., 2014). Overall, these findings suggest the significant modulatory effect of pharmacological and non-pharmacological treatment on brain connectivity, also in association with motor symptoms improvements.

3.5.3. *Network-based and computational approaches to study PD*

In both [^{18}F]FDG-PET and [^{15}O]H_2O-PET data, disease-related patterns have been identified using PCA of multivariate spatial covariance (Spetsieris et al., 2013). Only one study from Sala and colleagues explored brain metabolic connectivity alterations across the whole brain of early-PD patients using SICE approach. Significant alterations in connectivity were observed, including decreased local connectivity in the frontal and cerebellar cortices, and decreased connectivity in the basal ganglia (Sala et al., 2017). A novel approach has been recently advanced to describe the regional metabolic connectivity within different brain networks by performing graph theoretical SICE within PD-related patterns or the whole brain (Spetsieris and Eidelberg, 2021; Spetsieris et al., 2018). Using combined PCA and SICE approaches, a core subnetwork that was common to different PD stages emerged, encompassing caudate, putamen, pons, vermis, parietal cortex, and limbic areas (Spetsieris and Eidelberg, 2023). Ko et al. (2017) used a network approach to characterize the effects of PD in patients and non-human primates, describing consistent abnormal features mostly involving putamen, globus pallidus, and thalamus. Despite the great number of studies, less is known about the individual metabolic connectome. A novel approach was the Jensen-Shannon Divergence Similarity Estimation (JSSE) method, which allowed the construction of individual metabolic networks to investigate alterations in rich-club organizations in metabolic connectome in PD patients (Peng et al., 2022). Of note, the rich club connections, encompassing occipital, mid-frontal and temporal regions, had lower strength and degree in PD compared to age-matched HC. Moreover, Li and colleagues proposed a novel brain network estimation method to derive individual metabolic connectome, able to distinguish between PD patients and HC (Li et al., 2023). Automated algorithms were also proposed to use metabolic PET imaging to distinguish patients with idiopathic PD from atypical Parkinsonian syndromes. The first automated algorithm based on PDRP pattern expression had been advanced by Tang and colleagues (Tang et al., 2010b) using logistic regression model (Tang et al., 2010b). Further works have validated this classification algorithm, proving its high specificity and sensitivity up to 90% in differentiating idiopathic PD from atypical parkinsonisms (Rus et al., 2020; Tripathi et al., 2016; Papathoma et al., 2022), also in neuropathological-confirmed patients (Tripathi et al., 2016; Mudali et al., 2015; Schindlbeck et al., 2021b). Similarly, some studies have tried to describe different clinical phenotypes of PD. Of note, Boccalini et al. found that sex may influence connectivity within dopaminergic networks as assessed by using partial correlation analysis of [^{18}F]FDG-PET imaging. Male patients were characterized by a widespread altered connectivity of nigro-striato-cortical network, while female patients showed greater

alterations within the mesolimbic network (Boccalini et al., 2021). Consistently, the same group found sex differences in clinical phenotype since the early phases, supporting different vulnerability within dopaminergic networks (Boccalini et al., 2022b).

3.5.4. Atypical Parkinsonian syndromes

A smaller number of studies using metabolic PET imaging focused on **atypical Parkinsonian syndromes**, namely Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), and Corticobasal Syndrome (CBS). Eckert and colleagues identified specific metabolic networks associated with PSP and MSA, the former involving reduced metabolism in the putamen and cerebellum, and the latter in the brainstem and frontal cortex (Eckert et al., 2008). Niethammer and colleagues identified a specific metabolic pattern associated with corticobasal degeneration, encompassing asymmetric metabolic reductions in fronto-parietal cortex, thalamus, and caudate nucleus with high specificity in distinguishing CBS from MSA (Niethammer et al., 2014). More recently, Ge et al. highlighted the consistency of the PSP-related pattern as biomarker for differential diagnosis from MSA, PD and HC with high accuracy and its clinical significance in identifying PSP-specific neural dysfunctions (Ge et al., 2018). Interestingly, an automated identification of the PSP-related pattern reduced false positives and improved sensitivity and specificity especially in non-classical PSP clinical phenotypes (Buchert et al., 2023). Poston and colleagues, described the spatial covariance pattern associated with MSA, characterized by covarying metabolic reductions in the putamen and cerebellum. This pattern was associated with motor disability and disease duration, and it is able to discriminate between MSA and PSP or PD patients with high reproducibility between different cohorts (Poston et al., 2012; Shen et al., 2020; Tomše et al., 2022).

3.5.5. REM sleep behavior disorder as a prodromal α-synucleinopathy

Only few studies analyzed the metabolic connectivity within the alpha-synuclein spectrum considering also **RBD**, a typical symptom of prodromal PD or atypical parkinsonian syndromes. RBD patients showed elevated expression of the PD-related pattern (Meles et al., 2018; Wu et al., 2014; Lövdal et al., 2024), which was associated with phenoconversion at 2–4 years follow-up (Holtbernd et al., 2014; Mattioli et al., 2023; Tang et al., 2024). Shin and colleagues derived two metabolic patterns: one in PD patients, which was associated with motor symptoms, and one in de-novo PD patients with RBD, which was associated with autonomic symptoms in RBD patients (Shin et al., 2021). The expression of PD-related pattern in RBD patients was associated with lower dopamine transporter binding (Huang et al., 2020c). Lower dopamine availability in RBD was linked to increased metabolism in the posterior putamen, consistently with compensatory neural responses. Metabolic connectivity within parieto-occipital regions was increased in RBD but declined in PD, in keeping with stage-specific compensatory mechanisms (Kim et al., 2021, 2022; Han et al., 2020). In addition, Carli et al. (2020). found a limited reconfiguration of the nigro-striato-cortical dopaminergic network in RBD as compared to PD and DLB, with an extended connectivity alteration of the noradrenergic and cholinergic networks across the whole spectrum. Interestingly, Boccalini et al (Boccalini et al., 2022c). found that RBD shared resting state network disruption with DLB, but less with PD, showing alterations within the posterior DMN, attentive and limbic networks. K-complexes, a hallmark of non-REM sleep, are reduced in patients with RBD and are correlated with metabolic connectivity within the anterior DMN (Galbiati et al., 2021).

3.5.6. Huntington's disease

Another field of study was **HD**, both using perfusion and metabolic PET imaging. The first [^{18}F]FDG-PET study by Feigin et al. identified a HD-related pattern, characterized by hypometabolism in the caudate, putamen, and medio-temporal cortex as well as hypermetabolism in the occipital cortex (Feigin, 2001). These alterations are present also in asymptomatic gene carriers, indicating that metabolic changes can precede structural atrophy and clinical symptoms. Of note, the expression of this pattern increased as the disease progressed, suggesting its role as potential biomarker for disease monitoring. A longitudinal [^{18}F]FDG-PET study revealed that worsening of the HD-related metabolic pattern was associated with progressive striatal hypometabolism and thalamic compensatory hypermetabolism in pre-clinical phases, which later declined as clinical symptoms emerged (Feigin et al., 2007b). A consistent pattern of metabolic covariance has been observed longitudinally, encompassing striatal, cerebellar and temporal regions, which was more pronounced as disease progressed (Tang et al., 2013). Only one study using [^{15}O]H_2O-PET explored, at-rest, the neurophysiological effects of globus pallidus DBS in patients with HD. The globus pallidus stimulation modulated the connectivity in the basal ganglia-thalamo-cortical circuit and sensorimotor network (Ligot et al., 2011).

3.5.7. Dystonia and related movement disorders

Metabolic and perfusion brain connectivity was also explored in **dystonia**, to describe the typical network associated with this condition. The first study focused on DYT1 dystonia, a hereditary movement disorder, using [^{18}F]FDG-PET imaging to identify two distinct metabolic patterns: i) a genetic predisposition pattern seen in both asymptomatic and symptomatic individuals, involving the basal ganglia, and supplementary motor area; ii) a movement-related pattern specific to symptomatic patients, encompassing the thalamus and cerebellum (Eidelberg et al., 1998). Consistently, a [^{15}O]H_2O-PET study described the sensorimotor activation in DYT1 dystonia in pre-symptomatic individuals, showing an increased activity in premotor cortex, supplementary motor area, and inferior parietal cortex (Carbon et al., 2010). The metabolic pathology of dopa-responsive dystonia was characterized by increased metabolism in midbrain and cerebellum, and decreased metabolism in motor and premotor cortices (Asanuma et al., 2005). More recently, Niethammer et al. studied using [^{18}F]FDG-PET imaging the X-linked dystonia-related metabolic pattern, characterized by reduced metabolism in the caudate, putamen, cingulate cortex, with compensatory increased metabolism in sensorimotor regions (Niethammer et al., 2023). The presence of a consistent pattern for each dystonia studied highlighted their distinct and specific neural pathophysiologies.

Some studies explored the metabolic basis of **Tourette's Syndrome** using [^{18}F]FDG-PET. The first study from Eidelberg et al. identified a specific metabolic covariance pattern involving basal ganglia, thalamus, and motor and prefrontal cortices (Eidelberg et al., 1997). Hypermetabolism within this pattern correlated with tic symptoms severity, while alterations in frontal cortices are associated with the comorbid obsessive-compulsive disorder (OCD). Consistently, Jeffries and colleagues identified significant alterations in the connectivity within the cortico-striato-thalamo-cortical circuit, especially between the ventral striatum and motor regions (Jeffries, 2002). The identified patterns of metabolic alterations associated with Tourette's Syndrome and comorbid OCD was further confirmed by Pourfar et al (Pourfar, 2011).

3.6. Brain connectivity in psychiatric conditions

Psychiatric disorders encompass a broad range of conditions that significantly affect emotional, cognitive, and behavioral functioning. Understanding the underlying neural mechanisms of these conditions has been a key focus of research, with recent studies exploring the role of disrupted metabolic connectivity, and their modifications due to pharmacological or non-pharmacological treatment, mainly on schizophrenia patients.

3.6.1. Perfusion-based connectivity studies in schizophrenia and other disorders

As for the [^{15}O]H_2O-PET studies, two reports focused on functional connectivity in ***schizophrenia***, particularly regarding the brain

connectivity responses during self-face and famous-face recognition tasks (Yun et al., 2014), or the effects of antipsychotic drugs on these metrics (Bolding et al., 2012). Both studies found significant alterations in perfusion within key brain networks associated with schizophrenia. Yun et al. underlined a dysfunctional connectivity pattern in the parietal lobe during self-face recognition in schizophrenia, with reduced effective connectivity observed in specific regions compared to control subjects (Yun et al., 2014). Bolding et al. noted that anti-psychotic drug treatment resulted in an increased connectivity between the medial frontal cortex and nucleus accumbens after one week, followed by a decrease in hippocampal connectivity at six weeks (Bolding et al., 2012).

Other [^{15}O]H_2O-PET studies included in this review aimed to characterize metabolic networks in civilian trauma survivors with and without **PTSD** (Gilboa, 2003), or individuals with specific **phobias** (spider or snake) (Åhs et al., 2009). The first study (Gilboa, 2003), by analysing functional networks activated by both neutral and traumatic mental imagery, emphasized the amygdala's role in emotional processing during exposure to phobic stimuli. The second study (Åhs et al., 2009), confirmed these findings, by reporting amygdala activation during phobic stimulation, and a positive correlation between amygdala activity and distress ratings.

3.6.2. Glucose metabolism and network alterations in schizophrenia

As for the glucose metabolism studies, a more heterogeneous population was investigated including schizophrenia (Biver et al., 1996; Katz et al., 1996; Buchsbaum et al., 1999; Horga et al., 2014), depression (Diaconescu et al., 2011; Wu and Baeken, 2023a, 2023b), bipolar disorders (Mah et al., 2007; Benson et al., 2008, 2014), phobias/PTSD (Verger et al., 2018b, 2020b), OCD (Horwitz et al., 1991), and one work comparing metabolic connectivity among multiple psychiatric conditions (Mallet et al., 1998). A common finding in **schizophrenia** studies is the observation of reduced metabolism in the frontal lobes as compared to controls. This finding suggests a dysfunction in the neural circuits involved in executive functions and cognitive processing, with reported altered interregional correlations in the thalamocortical and frontostriatal circuits (Katz et al., 1996; Buchsbaum et al., 1999). Moreover, the articles frequently emphasize the importance of considering connectivity patterns rather than focusing solely on localized metabolic rates, strengthening the perspective that suggest schizophrenia is characterized not only by hypometabolism in specific areas but also by disrupted connectivity between regions, potentially impacting cognitive functions (Horga et al., 2014). However, there was some variability in altered brain regions across studies perhaps due to differences in patient populations, task demands, and the specific methodologies employed in each [^{18}F]FDG-PET study. Indeed, some studies highlighted the importance of the normalization of metabolic rates to reduce differences in variability between groups, indicating that statistical approaches and analysis methods can influence connectivity metrics and thus the subsequent interpretation of results (Biver et al., 1996).

3.6.3. Connectivity and treatment response in schizophrenia

Another important theme is the use of metabolism pattern expression as an objective marker to study antipsychotic drugs-induced side effects and the neurobiological basis of antipsychotic resistance in schizophrenia. Of note, drug-induced parkinsonism (DIP) is associated with greater expression of metabolic PDRP, which can serve as a valuable tool for the development of clinically-relevant marker for DIP (Kotomin et al., 2022). According to De Simone et al. only treatment-resistant patients showed reduced connectivity in frontotemporal and striatal-cortical regions as compared to controls. These specific connectivity alterations are able to discriminate nonresponsive vs. responsive patients with moderate-to-high accuracy (De Simone et al., 2024).

3.6.4. Mood disorders: depression and bipolar spectrum

Studies on mood disorders mainly focused on investigating metabolic connectivity patterns in depression and bipolar disorder. A previous study, aiming to characterize metabolic connectivity patterns in refractory melancholic depression, showed stronger metabolic connections between the subgenual anterior cingulate cortex (sgACC) and fronto-limbic regions in depressed patients compared to HC (Wu and Baeken, 2023b). Interestingly, the left sgACC showed stronger connections with ventromedial prefrontal regions (linked to anhedonia), while the right sgACC showed stronger connections with posterior hippocampal and cerebellar regions (linked to memory and social processing) (Wu and Baeken, 2023b). Two additional studies focused on the effect of anti-psychotic drugs (Diaconescu et al., 2011), or repetitive TMS (Wu and Baeken, 2023a) on metabolic patterns and clinical outcomes, revealing distinct functional networks associated with clinical improvement, and suggesting their predictive role on clinical outcome.

Focusing instead on **bipolar and unipolar disorders**, Benson et al . employed a continuous performance task to characterize brain metabolism patterns in bipolar and unipolar patients (Benson, 2008, 2014), while Mah et al. assessed cerebral metabolic rates in patients receiving mood stabilizers revealing increased metabolism within the limbic circuit (Mah et al., 2007). Further studies reported that (i) bipolar patients had positive coherence of activity throughout the brain, while unipolar patients exhibited a reduction of normal interrelationships (Benson et al., 2008); (ii) there is a different functional connectivity pattern in the amygdala and hippocampus between the two cohorts (Benson et al., 2014).

3.6.5. Anxiety- and trauma-related disorder

Regarding findings on **phobias/PTSD**, Verger et al., adopted a task-based approach to investigate the effects of virtual reality exposure therapy on acrophobia (Verger et al., 2018b), and of Eye Movement Desensitization and Reprocessing therapy on PTSD patients (Verger et al., 2020b). While the former study analyzed the visual-motor system, the latter focused on the precuneus-cerebellum connection, but both suggested that changes in brain metabolism and connectivity are related to the effectiveness of therapy.

Metabolic connectivity in patients with **OCD** (Horwitz et al., 1991) analysed using a resting state approach, showed higher correlations for anterior limbic/paralimbic regions with frontal areas and smaller correlation with posterior brain regions compared to controls.

Mallet et al. used an exploratory correlational analysis of resting state regional cerebral metabolism demonstrating that cerebral functional connectivity is differentially changed in OCD, depressive, and schizophrenic disorders, and that metabolic connectivity can potentially track a distinctive profile to differentiate among psychiatric conditions (Mallet et al., 1998).

In summary, while [^{18}F]FDG-PET studies of brain connectivity based on glucose metabolism are more common, the specific conditions under which the brain's metabolic activity is assessed—whether at rest or during task engagement—varies across studies. The populations analyzed, from unmedicated schizophrenia patients to those with treatment-resistant depression, reflect the diversity in psychiatric conditions explored. Common themes include disrupted metabolic connectivity in specific brain areas, highlighting the complex interplay between metabolic activity and psychiatric symptoms.

Results are summarized in Supplementary Table 5.

3.7. Brain connectivity in epilepsy

Recent research on epilepsy (Supplementary Table 6) has increasingly focused on understanding how changes in metabolic brain networks impact seizure dynamics and surgical outcomes. Various studies have shown alterations in functional connectivity, mainly assessed through [^{18}F]FDG-PET imaging and graph theory approaches. Ciumas et al. (2008). were conducted the only included task-based [^{15}O]H_2O-PET study on epilepsy which revealed how seizure onset side may influence olfactory perception and is associated with brain activity.

Indeed, interictal [^{18}F]-FDG-PET is the most widely used approach to study focal epilepsy, with a predominant focus on **temporal lobe epilepsy** (TLE) (McGonigal et al., 2021). A consistent finding in patients with TLE, is the presence of metabolic connectivity alterations beyond the epileptogenic zone, including DMN nodes (Ren et al., 2021; Wang et al., 2023b) with metabolic connectivity patterns correlating with the lateralization of epileptic focus (Azari, 1999; Vanicek et al., 2016). Interestingly, medial TLE is a system neurological disorder, with disrupted networks and compensatory effects in contralateral networks (Wang et al., 2019b). Of note, more severe alterations in metabolic networks were described in patients with TLE and concomitant hippocampal sclerosis (Shim et al., 2020), with evidence of decreased effective connectivity between the non-epileptic amygdala-hippocampus complex and ventral prefrontal areas, the temporal pole and posterior cingulate cortex contralateral to hippocampal sclerosis (Trotta et al., 2013). Metabolic connectivity alterations revealed an association with clinical phenotypes, with tonic-clonic seizures in TLE patients linked with connectivity abnormalities within the supramarginal gyrus, the opercular cortex and the brain stem. Hand automatism was instead associated with increased metabolic synchronization within supplementary motor area and middle cingulate cortex (Mo et al., 2022). Furthermore, Azari (Azari, 1999) observed abnormal metabolic network patterns in TLE patients across language brain regions and the prefrontal cortex, which were associated with verbal intelligence deficits (Azari, 1999) .

Metabolic connectivity changes within the epileptogenic network are also associated with clinical outcomes after surgery, with study individual brain metabolic connectome indicators of TLE able to predict surgical outcome with high accuracy (Strýček et al., 2024). Evidence suggest that stronger brain connections in the epileptic connectome are associated with a non-free-seizure outcome (Doyen et al., 2022) whereases, unfavorable surgical outcomes in patients with hippocampal sclerosis were linked to decreased metabolic connectivity among the bilateral hippocampus, ipsilesional frontal operculum, and contralesional insula (Strýček et al., 2024). Cho et al. found increased centrality of caudate, limbic regions, temporo-occipital cortices in seizure-free rather than non-seizure free patients with TLE and hippocampal sclerosis (Cho et al., 2022)(Cho et al., 2022).

Three studies focused on **pediatric patients** corroborated the idea of epilepsy as a brain network disorder. Disruptions in metabolic activity were observed in remote brain areas in children with continuous spike-waves during sleep, reflecting systemic network disruptions contributing to psychomotor deficits (De Tiège et al., 2008). In addition, unilateral Sturge–Weber syndrome was linked with decreased global and local efficiency in the affected hemisphere that extends contralaterally and correlates with cognitive dysfunction (Kim et al., 2018b). Metabolic connectivity was also used to study the efficacy of non-pharmacological treatments, such as vagus nerve stimulation (VNS), demonstrating that reduced baseline connections among brainstem, cingulate gyrus, cerebellum, insula, and putamen were linked to non-effective VNS (Yu et al., 2018).

McGonigal and colleagues (McGonigal et al., 2021) focused on interictal [^{18}F]FDG-PET in **generalized seizure** demonstrating its ability to differentiate between patients with and without postictal generalized suppression (McGonigal et al., 2021). Finally, Zhao et al. described the aberrant metabolic connectivity pattern in focal **insular epilepsy,** which was associated with interictal disturbances in metabolic coupling between the insula and neocortical-subcortical-brainstem structures (Zhao et al., 2020).

Taken together, these findings highlight the value of molecular connectivity by [^{18}F]FDG-PET to study epilepsy within a network framework, moving beyond a purely focal perspective. By capturing large-scale metabolic interactions, these approaches provide objective markers that can improve patient stratification, guide surgical planning, and predict treatment outcomes with greater accuracy. As a result, EANM recommendation have been recently published, encouraging clinicians to consider [^{18}F]FDG-PET metabolism as a network rather than merely a combination of regional metabolic measurements (Traub-Weidinger et al., 2024).

3.8. Brain connectivity in disorders of consciousness

PET plays a crucial role in assessing DoC after coma, i.e. vegetative state (VS)/unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS), helping avoid misdiagnosis, which is challenging with bedside assessments alone (Supplementary Table 7).

Perfusion studies often assessed brain activity at rest before comparing it with activity during specific task conditions. For instance, Silva et al. measured rCBF during rest and then during proprioceptive stimulation, specifically during passive movement of the index finger (Silva et al., 2010). Similarly, Boly et al. employed auditory stimuli and noxious stimulation to gauge brain responses in patients with prolonged VS/UWS and MCS, and comparing these with control subjects during both resting state and task conditions (Boly et al., 2004, 2008). Finally, Laureys et al. examined rCBF during resting-state, and auditory and somatosensory stimulation, providing insights into the altered functional connectivity between intralaminar thalamic nuclei and prefrontal and anterior cingulate cortices in VS/UWS. Such functional connectivity reverted back to normal after recovery of consciousness (Laureys et al., 2000).

Common findings across the studies indicated significantly reduced rCBF in key cortical areas (notably the precuneus) during rest in patients with VS/UWS compared to controls, alongside increased activity in the ascending reticular activating system (ARAS) (Silva et al., 2010). During passive auditory stimulation, patients in MCS showed greater activation in higher-order cortical areas compared to those in VS/UWS, suggesting a higher level of functional connectivity and integration of sensory information (Boly et al., 2004).

Functional connectivity differences were mainly observed between primary sensory areas and associative cortices. For example, Silva et al. noted impaired functional connectivity between ARAS and the precuneus in prolonged VS/UWS, while controls demonstrated strong correlations between these regions during tactile stimulation (Silva et al., 2010). Boly et al. further highlighted that MCS patients retained some level of functional connectivity that was significantly higher than that of prolonged UWS/VS, indicating that even minimal consciousness corresponds to more integrated brain activity compared to VS/UWS (Boly et al., 2008).

Metabolism studies generally assessed brain metabolism under resting state conditions. He et al. specifically linked several resting-state metabolic patterns with clinical assessment scores (CRS-R) (He et al., 2022). In a resting-state study by Aubinet et al., some analyses found that MCS− and MCS+ patients, i.e. MCS patient not showing and showing behaviors that involve language comprehension, respectively, differed in the metabolic connectivity of the angular gyrus (Aubinet et al., 2020).

A common finding across these studies is the observation of decreased metabolism in specific brain regions associated with consciousness, particularly in frontal and temporal areas, and the role of thalamic involvement in cortical functions. Laureys et al. examined the effective connectivity in UWS/VS patients compared to HC, showing a reduced connection between various prefrontal and premotor areas and the posterior cingulate cortex, compared to control subjects (Laureys et al., 1999). He et al. confirmed significant metabolic reductions in multiple cortical areas among hypoxic-ischemic encephalopathy patients compared to HC, which correlated with their CRS-R scores (He et al., 2022). Similarly, García-Panach et al. found widespread hypometabolism in UWS/VS and MCS patients with traumatic brain injury patients, especially in the thalamus and frontal cortex, which was linked to poorer neurological outcomes (García-Panach et al., 2011). Aubinet et al. added a nuanced layer by highlighting that MCS+ patients showed a metabolic functional disconnection between the angular gyrus and the

left prefrontal cortex in MCS− compared with MCS+ patients (Aubinet et al., 2020). This differentiation was not present in the other studies, which focused more broadly on metabolic impairment and did not delve into specific cognitive functions.

Overall, studies were heterogeneous in terms of population, with one study focusing on severe traumatic brain injury (García-Panach et al., 2011), while others examine hypoxic-ischemic injuries (He et al., 2022; Aubinet et al., 2020; Laureys et al., 1999) and the remaining studies including heterogeneous samples of patients of all etiologies. Furthermore, the methodologies vary across studies, with a focus on either regional metabolic activity or effective connectivity (Aubinet et al., 2020; Laureys et al., 1999).

In summary, a common thread emerges regarding the importance of PET functional and metabolic connectivity in understanding consciousness in severely brain-injured patients. Patients in MCS show greater neural responses and connectivity compared to those in UWS/VS, highlighting the role of specific brain structures in mediating conscious perception. The studies collectively illustrate the nuanced differences in brain activity and connectivity between varying states of consciousness and the potential of neuroimaging to inform clinical assessments and interventions for these patients.

4. Discussion

This scoping review highlights how molecular connectivity, often considered an early or "historical" approach in functional neuroimaging, is gaining renewed relevance in contemporary neuroscience. Although the concept originated decades ago with early PET studies, recent multimodal evidence strongly supports its critical role in the characterization of brain networks. In particular, the growing body of literature shows that task-induced changes in the BOLD signal within major networks are not consistently paralleled by corresponding variations in cerebral glucose or oxygen metabolism, implying that changes in BOLD signal not always accurately capture neural activity (Stiernman et al., 2021; Devor et al., 2008; Epp et al., 2025). These dissociations question the assumption of a uniform neurovascular coupling and underscore the added value of molecular imaging approaches. Techniques such as [^{15}O]H_2O-PET and [^{18}F]FDG-PET provide biologically grounded, complementary measures of brain's hemodynamic and metabolic state, suggesting that molecular connectivity should not be viewed as a legacy method, but rather as a integrative framework that can aid the interpretation of hemodynamic connectivity measures.

4.1. Perfusion vs. Metabolic Connectivity

Brain energetics rely on a delicate balance between glucose and oxygen supply, with neurons requiring disproportionately more oxygen relative to its modest excess in arterial blood. Because glucose uptake depends on ATP availability, which is oxygen-dependent, glucose metabolism may decline independently of perfusion, particularly in aging and neurodegeneration where mitochondrial dysfunction and NAD^+ depletion impair energy production despite preserved perfusion (Blaszczyk, 2020). Accordingly, perfusion PET with [^{15}O]H_2O captures transient hemodynamic responses, whereas [^{18}F]FDG-PET provides a more stable index of sustained neuronal energy consumption and network function (Jamadar et al., 2019).

Clinically, the divergence between perfusion and metabolic connectivity has significant implications. Perfusion imaging- closely linked to neurovascular coupling- has shown a close spatial and temporal relationship with neural activity (Girouard and Iadecola, 2006). Thus, perfusion PET has shown some utility in studying brain activation and networks recruited during cognitive or motor-related paradigms in HC and in disease conditions. Of note, early researches employed task-based approach to explore functional connectivity across cognitive domains such as language, memory, attention (Friston et al., 1993b; Schreckenberger et al., 1998; Severino et al., 2025). Interestingly, in psychiatric conditions, perfusion imaging has been employed to capture transient fluctuations associated with mood and cognitive states (Bolding et al., 2012). Conversely, [^{18}F]FDG-PET is independent from the vascular coupling and can provide a more stable marker, informative of altered neural and glial metabolism in different neurological conditions, such as AD (Minoshima et al., 1997) and other dementia (Perani et al., 2020), epilepsy (Eckert, 2008; Feigin, 2001), and movement disorders (Moeller, 1997; Schröter et al., 2023). In the context of movement disorders, both perfusion and glucose PET can estimate reliable covariance patterns as objective biomarkers able to differentiate patients from HC or other conditions.

To the best of our knowledge only one study provided a direct comparison between [^{18}F]FDG-PET and [^{15}O]H2O-PET for quantifying PDRP expression, showing a strong similarity between the two methods to detect elevated network activity in PD patients relative to HC (Ma et al., 2007). PDRP scores derived from [^{18}F]FDG-PET and [^{15}O]H_2O-PET were significantly correlated ($R^2 = 0.61$, $P < 0.001$), confirming that both glucose metabolism and perfusion data can capture disease-related network alterations with considerable fidelity. However, important methodological differences were also observed. [^{18}F]FDG-PET showed superior long-term test–retest reproducibility (ICC = 0.96–0.99 over up to 2 months), making it more suitable for longitudinal studies. In contrast, [^{15}O]H_2O-PET provided excellent short-term reliability (ICC = 0.94–0.96 within a 1-hour interval), while being more sensitive to dynamic, acute changes in cerebral function, such as those induced by therapeutic interventions. Notably, the correlation between the two tracers was lower in HC ($R^2 = 0.42$, $P = 0.05$), likely due to a narrower range of PDRP expression in non-diseased subjects. Despite these differences, both tracers support robust quantification of network expression, underscoring the validity of the PDRP as a biomarker across imaging modalities.

4.2. Multimodal approaches

Multimodal PET/MRI studies demonstrated that the strength and spatial distribution of network connections vary depending on whether metabolic or hemodynamic measures are used (Aiello et al., 2016; Sala, 2023). This confirms that these different modalities reflect partially different processes and underscores the importance of multimodal validation: BOLD response reflects the complex interactions of blood oxygenation, CBF and cerebral blood volume, while PET is an excellent tool for elucidating the metabolic basis of the fMRI signal.

The relationship between regional glucose metabolism and functional connectivity has been increasingly recognized as a key factor in understanding BOLD functional connectivity observed in fMRI studies. Simultaneous PET/fMRI studies have demonstrated that local neural activity in primary visual areas strongly determines functional connectivity within the visual network supporting previous findings of local neural activity–functional connectivity coupling in humans and animal models (Tomasi et al., 2013; Wehrl et al., 2013). At the whole-brain level, inter-individual correlations between metabolic and fMRI connectivity were found to be moderate (Di et al., 2017) but can improve substantially—with correlations reaching around 0.6—when data quality and preprocessing are optimized (Di et al., 2025).

The complementary information between PET and fMRI has also been more directly explored by using spatially constrained ICA approaches where fMRI resting networks are used as spatial priors in PET data (Saha, 2024). Importantly, PET data yields somewhat distinct patterns of covariation (i.e., molecular network covariation (MNC) relative to the fMRI functional network connectivity, this also being related to the specific tracer used in the analysis, reinforcing the complementarity of the PET and fMRI data. Building on this, tracer specific templates for use in constrained ICA (NeuroMark PET) have been developed (Eierud, 2025).

Additionally, multimodal integration offers valuable insight into how structural connectivity may shape functional connectivity patterns.

While structural networks are generally stable, functional connectivity—commonly assessed with fMRI—can fluctuate with behavioral state and does not always align with underlying anatomical pathways (Van Den Heuvel and Sporns, 2013; Honey et al., 2009). Although fMRI has been widely used to explore these types of dynamics, the potential of PET-based measures to inform connectivity analyses remains underexplored. Recent proposals suggest incorporating voxel-wise PET metrics alongside functional connectivity to better quantify how metabolic or neurochemical activity relates to structural and functional organization (Deco et al., 2013). For example, inter-regional covariance in [^{18}F]FDG-PET metabolism exhibits a spatial similarity to white-matter structural connectivity that is comparable to conventional fMRI-derived functional networks, indicating that PET metabolic networks can reflect aspects of underlying anatomy that are not fully captured by hemodynamic fluctuations alone (Lizarraga et al., 2024) and underscoring the value of metabolic connectivity as a complementary modality for mapping brain networks. Moreover, studies mapping FDG uptake covariance have identified coherent metabolic networks across subjects that parallel canonical functional networks, suggesting that PET-based connectivity estimates can reveal stable metabolic coupling patterns aligned with structural architecture even in the absence of dynamic BOLD signals (Yakushev et al., 2022).

Importantly, multimodal PET/fMRI studies offer the opportunity to clarify the neurophysiological mechanisms underlying anticorrelated BOLD functional connectivity, a phenomenon that has been the subject of considerable debate in functional neuroimaging research (Fox et al., 2009; Chai et al., 2012). While some researchers argue against anti-correlated BOLD functional connectivity since it is an artifact of fMRI preprocessing, others propose that it arises from true neuronal activity reductions in certain networks. The ability to simultaneously measure glucose metabolism and resting-state functional connectivity may help to disentangle these competing hypotheses. Furthermore, clinical neuroscience could benefit greatly from such integrative approaches, particularly in neuropsychiatric conditions where both metabolic and functional connectivity alterations have been observed but not yet fully understood in an integrated framework (Menon, 2011; Greicius, 2008).

Overall, multimodal PET/MRI approaches can provide complementary information for molecular, functional and structural brain connectivity assessment. More specifically, simultaneous PET/MRI acquisitions can reduce possible confounds related to inter-modal state variability and provide perfect spatial and temporal coregistration between scans. Such multi-dimensional connectome offers a biologically grounded framework to study network organization across spatial, temporal, and molecular scales, and may provide critical insight into disease-specific mechanisms that cannot be captured by single-modality approaches alone. Future studies should increasingly exploit these integrated acquisition and analysis strategies — such as simultaneous PET/MRI with multimodal data fusion — to systematically characterize cross-modal network interactions and to establish standardized multimodal connectivity frameworks that capture complementary metabolic, functional, and structural dimensions of brain organization across clinical and research settings (Savio et al., 2017b).

Recent advancements in PET neuroimaging suggest that dual-phase or early-phase imaging can provide perfusion-like information without requiring a separate perfusion scan. For example, dual-phase amyloid PET protocols capture both perfusion deficits and amyloid deposition in a single session (Valentina et al., 2016). This approach enhances clinical feasibility and reduces patient burden. Moreover, dynamic[^{11}C]PiB-PET scans have been used to derive rCBF images (e.g., R1 maps and early-frame averages, ePIB), which can be processed using multivariate techniques like SSM-PCA. These rCBF-derived ADRP show spatial and statistical similarity to canonical [^{18}F]FDG-PET metabolic patterns in distinguishing AD patients from HC (Peretti et al., 2022). In addition, pharmacokinetic modelling of non-specific brain tracers has shown feasibility of extracting perfusion-related patterns. Dynamic PIB data, for instance, can yield parametric images (such as R1, binding potential, standardized uptake value ratio; SUVR) that support disease pattern generation via SSM-PCA—again from a single PET acquisition (Peretti et al., 2021). Collectively, these findings underscore a promising methodological gap: it may be possible to derive robust perfusion and metabolic network information from existing dynamic PET protocols, obviating the need for dual scans. While the first studies are appearing — for example, recent work has begun to systematically quantify test-retest reproducibility of structural, functional and PET-based metabolic connectivity in the same cohort using simultaneous acquisitions and has shown that FDG-PET-derived metabolic covariance can be reliably estimated and compared with structural connectivity and fMRI networks (Lizarraga et al., 2025) — future works should systematically evaluate the reliability, biological specificity and test-retest reproducibility of these connectivity metrics in order to better characterize their sensitivity to disease-related network alterations and to support their integration within multimodal connectivity frameworks.

Beyond multimodal neuroimaging integration, recent advancements in imaging technologies and genome-wide studies have provided more opportunities to study brain complexity and its association with genetic risk factors. Some studies have investigated the genome-wide association to brain volume and structural changes in both physiological and pathological ageing (Wu et al., 2013b; Hibar et al., 2015; Stein et al., 2012). These findings indicate that genetic architecture substantially constrains macroscale brain organization and vulnerability to disease. However, the relationship between different genetic risk factors and brain molecular connectivity remains largely underexplored, with the exception of studies investigating the effect of APOE genotypes related to sporadic AD (Seo et al., 2013a; Didic et al., 2015; Yao et al., 2015). Future studies integrating genome-wide data with multimodal connectivity measures may help elucidate how genetic risk factors influence network-level metabolic alterations, providing a mechanistic bridge between molecular genetics and systems-level brain dysfunction.

4.3. *Methodological approaches*

IRCA has been widely used and validated to extract resting state networks from brain metabolism and perfusion (Schreckenberger et al., 1998; Di et al., 2019; Kim et al., 2018a; Sala et al., 2019; Biver et al., 1996; Benson et al., 2008; Yu et al., 2018). While effective for analysing well-characterized networks like the DMN, this method depends on a priori region selection, which may introduce bias and overlook hidden connectivity patterns (Sala et al., 2019). To overcome these limitations, data-driven multivariate approaches such as PCA and ICA have been increasingly applied. PCA has been particularly effective in metabolic PET studies, identifying covariance patterns associated with neurodegenerative diseases (Spetsieris and Eidelberg, 2023; Eckert et al., 2008), while ICA has demonstrated its utility in decomposing whole-brain PET signals into independent functional networks without requiring predefined ROIs (Yakushev et al., 2013).

Graph-theoretical methods and SICE have emerged as advanced techniques for quantifying network topology in both perfusion and metabolic imaging (Rus et al., 2022; Tang et al., 2013). These approaches conceptualize connectivity as an emergent property of complex brain networks, improving biological interpretability over traditional correlation-based analyses. For example, graph-based analyses have demonstrated progressive disruptions in connectivity efficiency and network reorganization in neurodegenerative diseases, while SICE enhances the estimation of direct network connections, reducing the influence of spurious correlations (Li et al., 2018b; Sala et al., 2017; Gupta et al., 2023). Longitudinal PET studies further support the role of metabolic connectivity in tracking disease progression in the prodromal phase of neurological disorders (Tang et al., 2013).

It is important to consider the influence of the mathematical formulation of functional connectivity itself as highlighted by Liu, 2025. Different methods yield markedly different network architectures, levels

of structure–function coupling (diffusion MRI tractography), and alignment with biological markers such as receptor similarity (PET), electrophysiological connectivity (Magnetoencephalography; MEG), gene expression (Allen Brain Atlas), and laminar similarity (BigBrain histology). Covariance- and precision-based approaches consistently perform best across multiple criteria, including individual fingerprinting and brain–behaviour prediction, compared to resting-state fMRI. However, no single method emerges as universally optimal, as each captures distinct aspects of inter-regional communication. These results highlight the importance of tailoring the choice of connectivity measure to the specific neurobiological question under investigation

In the case of single-subject (Devor et al., 2008) FDG-PET metabolic connectivity estimation, specifically, using Euclidean distance instead of Pearson's correlation for single-subject metabolic connectivity estimation leads to markedly different networks (Volpi et al., 2023). Using kinetic parameters rather than SUVR for individual metabolic connectivity estimation can yield markedly different brain networks. While SUVR correlates with ki, it is not identical and may be biased in pathological conditions. Moreover, the rate constants k1 and k3 capture distinct processes: glucose transport across the blood–brain barrier and its phosphorylation by hexokinase, the first step of glycolysis (Volpi et al., 2023).

4.4. Metabolic Connectivity as a Biomarker

Metabolic connectivity detects functionally direct or indirect interacting brain regions based on [^{18}F]FDG-PET imaging results and offers added value relative to conventional [^{18}F]FDG-PET univariate analyses (Yakushev et al., 2017). A growing body of evidence suggests that metabolic connectivity can track both normal and pathological cognitive function, particularly in neurodegenerative disorders. Unlike fMRI, PET connectivity derives from molecular and metabolic signals that are directly tied to disease mechanisms. This makes it inherently more specific and quantitative, two key features of a reliable biomarker. As such, PET connectivity may overcome some of the translational barriers faced by fMRI. However, the main limitation to validating its use as a biomarker is that it relies on across-subject measures, even though methods such as ICA and SSM-PCA can identify disease-specific pattern expression at the individual level (Eidelberg et al., 1994; Teune et al., 2013). The robustness and consistency of SSM-PCA has been demonstrated across studies in the field of neurodegenerative conditions (Blazhenets et al., 2020; Ma et al., 2007; Eidelberg et al., 1998). Of note, disease-specific covariance patterns have been associated with both motor and non-motor symptoms in PD with high reproducibility across different cohorts and PET scanners. These stable patterns can potentially serve as both diagnostic and prognostic markers, enabling the prediction of conversion from PD with MCI to dementia. Similarly, an AD conversion-related pattern has been identified as a valid predictor of conversion from MCI to dementia due to AD (Perovnik et al., 2023).

Beyond the established use of individual scores of SSM-PCA and ICA derived pattern expression, novel experimental approaches have been advanced to obtain measures of within-subjects connectivity directly from sPET images (Yao et al., 2016; Huang et al., 2010, 2020b). The reliability meaning and robustness of such measurements, including test–retest reproducibility, still needs to be fully interrogated for validation (Sala et al., 2022b). Wider availability of radiotracers, along with advances in denoising and image reconstruction algorithms for simultaneous PET/MRI, have now made it possible to study functional [^{18}F]FDG-PET with improved temporal resolution (Jamadar et al., 2019). fPET connectivity allows the construction of within-subjects connectivity matrices, holding the potential for its application as a biomarker at the single-subject level (Jamadar et al., 2019). However, functional PET signal remains susceptible to noise, thus new methods to improve signal-to-noise ratio, data accessibility and test-retest reproducibility need to be developed and tested (Sala et al., 2022b). A monotone property of SICE was further exploited to derive a quasi-measure of connection strength, allowing both the structure and relative weight of subject-level networks to be characterized (Huang et al., 2010). As this field matures, integrating viewpoints may help foster a more informative and nuanced approach: continued advancements in signal processing, scanner technology, and multimodal acquisition (e.g., PET/fMRI) are critical to resolving the methodological and conceptual challenges that currently limit the adoption of metabolic connectivity as a routine clinical tool.

4.5. Deep Learning Methods

The analysis of molecular connectivity is expected to benefit significantly from the shift towards deep learning (DL) methods. Classical approaches, such as SVMs, require handcrafted feature extraction and selection - a process that can be challenging and limiting for complex, high-dimensional data. In contrast, DL models, particularly 3D Convolutional Neural Networks (CNNs), are designed to automatically learn hierarchical and representative features directly from raw or minimally processed data. This allows 3D CNNs to simultaneously extract spectral and spatial features from the input data capturing complex, distributed pathophysiological patterns without relying on a priori design, often with superior diagnostic performance (Litjens et al., 2017; Lu et al., 2018). These features are particularly powerful for capturing the intricate, non-linear, and distributed patterns of pathophysiology that characterize neurodegenerative disorders.

Early applications of DL techniques demonstrated their potential for the study of neurological disorders. For instance, Stacked Auto-Encoders (SAEs) and Deep Belief Networks (DBNs) have been used to extract latent features from multi-modal data, including PET, for classifying neurological disorders, whereas 3D CNNs have been successfully applied to discriminate between conditions, paving the way to more objective, data-driven evaluations (Plis et al., 2014; Shi et al., 2018; Tufail et al., 2021). However, the application of DL methods raises two key concerns. First, the black-box nature of these methodologies hides the biological reason of their prediction, limiting the generation of new scientific insights. Furthermore, their performance is often constrained by the limited cohort sizes typical in clinical neuroimaging, raising concerns about applicability and generalizability. Achieving sufficiently large sample sizes usually requires community-wide efforts (see https://molecularconnectivity.com/resources/ for a non-exhaustive account) and multi-site data collection, which in turn introduces additional challenges related to data harmonization during implementation.

Explainable artificial intelligence (XAI) has been proposed as a potential strategy to address the interpretability limitations of DL models; however recent evidence indicate that XAI methods reliability cannot be assumed a priori. Widely used approaches, such as standard GradCAM and off-the-shelf Layer-wise Relevance Propagation rules, can fail systematically in structural neuroimaging, producing poor spatial localization and false-positive attributions to non-target structures when evaluated against validated anatomical references. This highlights that XAI is highly method- and domain-dependent, and that interpretations derived from unvalidated approaches may be misleading rather than informative (Siegel et al., 2025).

Thus, future studies should focus on the domain-specific validation of XAI techniques in neuroimaging to ensure that DL prediction is both interpretable and robust (Chaddad et al., 2025, 2023).

Overall, deep learning approaches offer a promising framework for multimodal integration, enabling the joint modeling of molecular connectivity with other imaging and non-imaging biomarkers, thereby facilitating a more comprehensive understanding of how metabolic, structural, and functional alterations interact within large-scale brain networks.

5. Conclusion

Molecular connectivity approaches in neuroimaging have greatly

advanced our understanding of brain function, revealing how perfusion and metabolic imaging complement each other in capturing transient functional changes and assessing network integrity. Future studies could benefit from standardizing methods and clarifying the biological meaning of metabolic connectivity, particularly by examining test–retest reliability and fostering harmonization across research centers. Transdiagnostic investigations will be essential to determine whether molecular connectivity patterns reflect shared mechanisms or disorder-specific processes. Moreover, leveraging [^{18}F]FDG-fPET to track dynamic connectivity—such as changes during cognitive tasks or following pharmacological interventions—may provide deeper insights into disease mechanisms and treatment responses. Understanding the organization of large-scale neural networks—how they interact to support cognition, emotion, and behavior—is central to progress in neuroscience. Multimodal approaches that combine imaging, electrophysiology, and molecular-level measures will increasingly be key to achieving a truly integrative view of brain function. Techniques with millisecond-level temporal resolution, such as MEG, can capture rapid neural oscillations and synchrony, bridging the gap between macroscale network architecture and microscale neurophysiological processes. A promising innovation on the horizon is total-body PET, which allows simultaneous imaging of the brain and peripheral organs. This technology opens exciting possibilities to explore how systemic physiology—including immune activity, endocrine signaling, and metabolic states—shapes brain connectivity and function. Despite these advances, challenges remain. Methodological variability, limited applicability in certain clinical populations, and a predominance of cross-sectional designs continue to constrain progress. Addressing these gaps through longitudinal, multimodal studies and advanced computational analyses will be critical. By overcoming these hurdles, molecular connectivity imaging could move beyond a research tool to become a clinically meaningful biomarker, enabling early diagnosis, patient stratification, and precision medicine interventions in neurological and psychiatric disorders.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

All authors have nothing to declare.

Acknowledgements

CC and SPC were supported by grants from the Italian Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A multiscale integrated approach to the study of the nervous system in healthy and disease (DN. 1553 11.10.2022).

JBP is supported by a Swedish Research Council grant (#2022–01108); Alzheimer Foundation; Brain Foundation (#2022–014); by European Union – NextGenerationEU and the Romanian Government, under National Recovery and Resilience Plan for Romania, contract no. 760250/28.12.2023, cod PNRR-C9-I8-CF109/31.07.2023, through the Romanian Ministry of Research, Innovation and Digitalization, within Component 9, Investment I8; KI Consolidator grant, Konung Gustaf V:s och Drottning Victorias Stiftelse; Gamla Tjänarinnor; and Stohnes Foundation. MV is supported by EU funding within the MUR PNRR "National Center for HPC, BIG DATA AND QUANTUM COMPUTING (Project no. CN00000013 CN1), the Ministry of University and Research within the Complementary National Plan PNC DIGITAL LIFELONG PREVENTION - DARE (Project no PNC0000002_DARE), and by Fondo per il Programma Nazionale di Ricerca e Progetti di Rilevante Interesse Nazionale (PRIN), (Project no 2022RXM3H7). MP was supported by The Slovenian Research Agency (ARRS) through grants P1–0389 and J3–60059.

We thank Maria Catanese for the valuable revision of the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2026.106623.

Data availability

N.A.

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