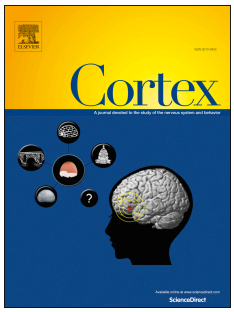

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ABSTRACT

FDG-PET is a useful paraclinical exam for the diagnosis of Alzheimer's disease (AD). In this narrative review, we report seminal studies in clinically probable AD that have shown the importance of posterior brain metabolic decrease and the paradoxical variability of the hippocampal metabolism. The FDG-PET pattern was a sensitive indicator of AD in pathologically confirmed cases and it was used for differential diagnosis of dementia conditions. In prodromal AD, the AD FDG-PET pattern was observed in converters and predicted conversion. Automated data analysis techniques provided variable accuracy according to the reported indices and machine learning methods showed variable reliability of results. FDG-PET could confirm AD clinical heterogeneity and image data driven analyses identified hypometabolic subtypes with variable involvement of the hippocampus, reminiscent if the paradoxical FDG uptake. In studies dedicated to clinical and metabolic correlations, episodic memory was related to metabolism in the default mode network (and Papez's circuit) in prodromal and mild AD stages, and specific cognitive processes were associated to precisely distributed brain metabolism. Cerebral metabolic correlates of anosognosia could also be related to current neuropsychological models. AD FDG-PET pattern was reported in preclinical AD stages and related to cognition or to conversion to mild cognitive impairment (MCI). Using other biomarkers, the AD FDG-PET pattern was confirmed in AD participants with positive PET-amyloid. Intriguing observations reported increased metabolism related to brain amyloid and/or tau deposition. Preserved glucose metabolism sometimes appear as a compensation, but it was frequently detrimental and the nature of such a preservation of glucose metabolism remains an open question. Limbic metabolic involvement was frequently related to non-AD biomarkers profile and clinical stability, and it was reported in non-AD pathologies, such as the limbic predominant age-

related encephalopathy (LATE). FDG-PET abnormalities observed in the absence of classical AD proteinopathies can be useful to search for pathological mechanisms and differential diagnosis of AD.

Key words: brain metabolism, FDG-PET, dementia, mild cognitive impairment, memory.

1. Introduction

Alzheimer's disease (AD) is a common neurocognitive disorder. It represents a serious medical and socioeconomic problem. It is considered as a heterogenous neurodegenerative disease, frequently evolving over decades, mainly characterized from a pathological viewpoint by abnormal amyloid and hyperphosphorylated tau cerebral deposits, amyloid angiopathy and synaptic loss (Jellinger, 2020). The early damage of synapses, inducing network dysfunction, is the best correlate of the cognitive impairment in patients with AD (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011). Importantly, there are frequent non-AD, age-related associated pathologies (such as hippocampal sclerosis, limbic-predominant age-related TDP-43 encephalopathy, argyrophilic grain disease and aging-related tau astrogliopathy) that may influence the clinical picture and the disease progression (Jellinger, 2020; Trejo-Lopez, Yachnis, & Prokop, 2022).

Positron emission tomography (PET) has a poor spatial resolution compared to MRI, but a high sensitivity (it detects photons from trace quantity of radioligand, in nanomolar to picomolar range) to demonstrate regional patterns of impaired cerebral biological processes likely to correspond to different stages or different types of degenerative dementia. The study of regional cerebral glucose metabolism through 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) plays a leading role in early detection of AD because the decrease of cerebral metabolism precedes the onset of conspicuous AD symptoms, and occurs even in a preclinical stage (Mosconi et al., 2010). A dementia of the Alzheimer type cannot be diagnosed until obvious symptoms appear in the patient. Brain AD pathologies have been shown to occur decades before dementia is diagnosed (Jack et al., 2013), and studies have found that patients with AD show abnormalities in regional metabolism before the occurrence of brain structure changes, that are downstream of the pathological event

(De Santi et al., 2001; Ibanez et al., 1998; Jagust et al., 2006). Moreover, the pattern of regional hypometabolism is related to clinical symptoms and disease evolution. Accordingly, FDG-PET was better than MRI for detecting participants with early onset mild cognitive impairment (MCI) and a rapid conversion to AD (Dukart et al., 2013).

This narrative review will report the progressive demonstration of impaired cerebral metabolism for the diagnosis and the prognosis of dementia and prodromal stages of AD along with methodological considerations, the observation of subgroups with different metabolic patterns, and studies dedicated to clinical correlates of reduced regional metabolism, with a focus on episodic memory. We will present examples of the occurrence of brain metabolic disturbances in preclinical stages of AD and report interactions between glucose metabolism and other biomarkers in different stages and subgroups of AD and in other age-associated neurodegenerative brain pathologies.

2. Patterns of impaired metabolism in typical AD

In the typical form of AD characterized by initial memory deficits, impaired metabolism was first reported in the parietal regions of clinically probable AD participants (Chase, Foster, & Mansi, 1983). A seminal observation in AD was the importance of hypometabolism in the posterior cingulate cortex (PCC), a posterior medial region included in Papez's circuit (Minoshima, Foster, & Kuhl, 1994). Metabolic impairment has also been observed in hippocampal structures, but not as consistently as neocortical hypometabolism (Mosconi, 2005). Glucose metabolism was paradoxically less impaired or even relatively preserved compared to atrophy in the hippocampus, while FDG uptake was clearly reduced in the precuneus of AD participants (Chetelat et al., 2008; Ishii et al., 1998; Tahmasian et al., 2015). Involvement of frontal associative cortices was often observed during the progression of AD

dementia, including not only lateral prefrontal regions, but also the ventromedial prefrontal cortex (Herholz et al., 2002). Accordingly, a meta-analysis reported that early AD affected functionally the inferior parietal lobules and precuneus, while fully developed AD involved additionally a medial frontal and thalamic network (Schroeter, Stein, Maslowski, & Neumann, 2009). Likewise, a recent multivariate (principal components) analysis including patients with cerebrospinal fluid AD biomarkers reported a pattern of decreased metabolism in temporoparietal cortices, PCC, precuneus and in a posterior portion of the thalami (Perovnik et al., 2022). The brain regions metabolically impaired in AD form a signature of the disease and they were reported to belong to the « default mode network » (DMN), involved in episodic memory and self-reference (Buckner et al., 2005). Hypometabolism is actually observed in several networks with the progression of AD, but the DMN is more impaired than other cognitive networks, such as the frontoparietal network, involved in executive control (Grothe, Teipel, & Alzheimer's Disease Neuroimaging, 2016).

Importantly, it was rapidly emphasized that hypometabolism in the hippocampus, PCC and medial prefrontal cortex is not specific for typical AD. It was reported in other types of global amnesia (Perani et al., 1993) and memory impairment was related to disturbed metabolism in regions of Papez's circuit, consistently with the importance of this circuit for episodic memory.

A seminal clinical study demonstrated that the regional brain metabolism studied with FDG-PET was a sensitive indicator of AD and other neurodegenerative diseases in patients presenting cognitive symptoms (Silverman et al., 2001). The authors presented a multicentre group with pathologically confirmed diagnoses, where AD was identified in 70% (97/138) of histopathologically examined cases. FDG-PET correctly identified the presence or absence of AD in 88% of the cases, with a sensitivity of 94% and a specificity of 73%. In a group with a 3

years longitudinal clinical follow-up, a progressive course was documented in 59% (86/146) of the participants. FDG-PET correctly predicted an ensuing progressive evolution with a sensitivity of 91% and predicted a nonprogressive course with a specificity of 75%.

The accuracy of visual analysis of FDG-PET was shown to decrease in elderly participants, justifying the use of quantitative analyses (Ng et al., 2007). Among the many quantification methods, statistical parametric mapping (SPM) and three-dimensional stereotactic surface projection (3D-SSP) have been widely used in research to statistically analyze brain FDG-PET images (Friston, Frith, Liddle, & Frackowiak, 1991; Minoshima, Frey, Koeppe, Foster, & Kuhl, 1995). The two methods were shown to provide similar patterns of hypometabolism in AD, but with some differences in the extent, severity, and location of metabolic changes, suggesting that potential artifacts introduced by stereotactic anatomic standardization of atrophied brains had to be taken into account (Ishii et al., 2001). The cerebral global mean or few regions (cerebellum, pons, primary sensorimotor cortex, white matter) considered to be less affected by the disease, can be used as reference for voxel or region-of-interest normalization in the analysis (Yakushev et al., 2008).

FDG-PET was shown to be useful in differentiating AD from frontotemporal dementia (Foster et al., 2007) and this diagnostic contribution was subsequently recognized by the Food and Drug Administration. A multicenter study examined FDG-PET as a tool for the differential diagnosis of AD, frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB). The researchers examined FDG-PET scans of 548 subjects collected from seven participating centers, including 110 healthy individuals (normal control [NC]), 114 participants with mild cognitive impairment (MCI), 199 with AD, 98 with FTD, and 27 participants with DLB (Mosconi, Tsui, et al., 2008). Standardized disease-specific PET patterns were developed using 3D-SSP and correctly classified 95% AD, 92% DLB, 94% FTD and 94% NC. AD FDG-PET

pattern was observed in 79% of MCI patients with deficits in multiple cognitive domains and in 31% of amnestic MCI (aMCI). FDG-PET variability in MCI with nonmemory deficits ranged from absent hypometabolism to FTD and DLB patterns. The usefulness of FDG-PET to provide support to the differential diagnosis of AD, FTD and LBD was confirmed in a recent meta-analysis (Na et al., 2024).

The Alzheimer's Disease Neuroimaging Initiative (ADNI) project has clearly confirmed the feasibility and utility of multicentre PET studies in the evaluation of prodromal and mild stages of dementia (Jagust et al., 2010). For example, such a study described 12-month declines of brain FDG uptake in 69 probable AD patients, 154 amnestic MCI patients, and 79 cognitively normal participants from ADNI using SPM. The authors used an empirically predefined statistical region-of-interest (sROI) to characterize declines of FDG uptake. The AD and MCI groups each had significant 12-month declines of FDG uptake bilaterally in PCC, medial and lateral parietal, medial and lateral temporal, frontal and also occipital cortices, that were significantly greater than those in the NC group and that correlated with measures of cognitive decline (Chen et al., 2010).

Concerning prodromal AD, a meta-analysis of baseline FDG-PET identified hypometabolism in PCC/precuneus (the most robust difference), and also in the anterior cingulate cortex (ACC), the left middle temporal gyrus and the left middle frontal gyrus (the later associated to longer follow up duration) in aMCI converters compared to non-converters (Ma et al., 2018). A longitudinal study in aMCI suggested that hippocampal atrophy progressively leads to disruption of the cingulum bundle and uncinate fasciculus, which in turn leads to glucose hypometabolism respectively in the PCC and in the subgenual ACC (Villain et al., 2010). Both ventral and dorsal PCC actually showed decreased glucose metabolism in aMCI (Mutlu et al., 2016), but the most consistently hypometabolic region in individual MCI participants was a

subregion of the posterior cingulate, the retrosplenial cortex (Nestor, Fryer, Ikeda, & Hodges, 2003).

From a clinical viewpoint, in a 5 years longitudinal study, FDG-PET visual assessment showed high performance for predicting conversion to AD from MCI (Inui, Ito, Kato, & Group, 2017) and a typical AD FDG-PET pattern analyzed with a voxel-based (SPM) method predicted conversion to AD dementia in MCI participants (Caminiti et al., 2018). An expert paper emphasized the high negative predictive value of a normal FDG-PET in participants with MCI who will not subsequently decline (Arbizu et al., 2018). Automated data analysis techniques have been developed to help detecting the AD-related pattern of hypometabolism in a single index (Caroli et al., 2012). A systematic review of the accuracy of such indices to detect MCI participants who will convert to dementia showed quite variable results (Smailagic, Lafortune, Kelly, Hyde, & Brayne, 2018). In this review, best sensitive and specific values were reported with the single case SPM analysis (Presotto et al., 2017).

A systematic review of machine learning (ML) methods applied to neuroimaging data emphasized that the ADNI dataset was most commonly used (Borchert et al., 2023) which might introduce selection bias. ML methods using FDG-PET allowed to distinguish MCI and AD participants from controls (accuracy >78% and 86% respectively) and to predict MCI conversion at different time periods (accuracies 72% to 80%). The authors emphasized methodological variability and proposed consideration about reliability of results, the differential diagnosis requiring multi-class classifiers was recognized as a hard problem, and the importance of validation on independent datasets was addressed. Some more recent models can identify patients with AD at different stages with high sensitivity and specificity, and distinguish patients at the early MCI or late MCI stage (Duan et al., 2023). Accordingly, deep learning has been reported to very accurately classify stable MCI versus progressive

MCI using ADNI FDG-PET images (Kishore & Goel, 2023), while a 3D convolutional neural network provided a FDG-PET derived probability score able to predict conversion of MCI participants to AD dementia (Yee, Popuri, Beg, & Alzheimer's Disease Neuroimaging, 2020). In connection with the limited specificity of ML models (Aberathne, Kulasiri, & Samarasinghe, 2023), a 3D neural network was also successfully used for classification of AD, FTD or cognitively normal subjects based on brain glucose metabolism (Rogeau et al., 2024). ML methods such as clustering analysis have also been used to differentiate subgroups of AD participants with different clinical presentations and evolutions (see below).

3. Metabolic patterns and subgroups of AD

It is well recognized from a clinical viewpoint that AD does not present a unitary pattern of symptoms in all patients (McKhann et al., 2011). Atypical presentations comprise visuospatial (or posterior), logopenic and frontal variants of AD. Early FDG-PET studies already emphasized that metabolic asymmetries were greater in patients with AD than in controls and correlated with neuropsychological discrepancies between visuospatial and language abilities (Haxby et al., 1990). FDG-PET was shown to provide different metabolic patterns corresponding to the clinical variants in participants with AD positive cerebrospinal fluid biomarkers (Sala et al., 2020). The frontal variant of AD has been characterized by predominant medial and orbital frontal hypometabolism (Woodward, Rowe, Jones, Villemagne, & Varos, 2015), but compared to an FTD group, AD frontal variant was characterized by hypometabolism in dorsolateral prefrontal cortex, and also in precuneus and lateral temporoparietal regions (Sala et al., 2020).

In amyloid-positive patients with AD type dementia, image data driven analyses identified three main hypometabolic subtypes: “typical” (49%), showing a classic posterior

temporoparietal hypometabolic pattern, “limbic-predominant” (44%), characterized a memory-predominant cognitive profile, and a “cortical-predominant” (or hippocampal sparing) subtype (7%) mainly characterized by “atypical” clinical presentations (Levin et al., 2021). The variable involvement of the medial temporal lobe was not surprising, considering the hippocampal metabolic paradox observed in previous studies of probable AD participants. Diagnostic information provided by brain imaging methods on early stage AD subtypes was recently reviewed (Herholz, 2022).

Two forms of AD onset have been defined based on the age: early-onset AD (EOAD) defined as AD with clinical onset occurring in patients younger than 65 years and late-onset AD (LOAD) defined as patients older than 65 years. In amnestic EOAD and LOAD, hypometabolism was observed in the bilateral temporoparietal junction and the PCC (Aziz et al., 2017). However, EOAD participants were shown to have lower metabolism in the precuneus and the angular gyrus than LOAD ones (Tanner et al., 2022). Concerning patients with familial AD, a study reported greater metabolic decrease in the PCC, parahippocampal, and occipital cortex as compared to patients with sporadic AD (Mosconi et al., 2003).

4. Clinical correlates of decreased brain glucose metabolism

Correlation analyses between FDG-PET regional uptake and cognitive measures have been key in unraveling the neural correlates of cognitive and clinical symptoms in AD, supporting the refinement of theoretical neuropsychological models as will be illustrated below for memory and anosognosia. Very recently, subscores of the Addenbrooke’s Cognitive Examination were related to cerebral FDG-PET of participants with AD (Cabrera-Martin et al., 2023). The language domain was associated with left hemisphere metabolism, within

temporoparietal regions and left inferior and middle frontal gyri. The visuospatial domain was correlated with metabolism in a large set of posterior brain regions, comprising bilateral temporal lobe and inferior parietal lobule, angular and supramarginal gyri, precuneus, PCC, lingual gyrus, and middle occipital gyrus. The memory domain was correlated with bilateral superior, middle, and inferior temporal gyri, left parahippocampal gyrus and hippocampus, posterior and middle cingulate gyri, precuneus, and inferior parietal lobule. Another study correlated principal component analysis of neuropsychological tests and different naming errors produced in different subgroups of AD patients to FDG-PET (Isella et al., 2022). A factor grouping language tests and anomia or circumlocutions errors correlated with left basal temporal hypometabolism. A visual processing factor clustering visuospatial tests, visual and visual-semantic errors was associated with right parieto-occipital hypometabolism. A phonology factor including the digit span and phonological errors was linked with hypometabolism in the left temporo-parietal cortex, previously reported as subserving a phonological store.

Studies on the neural correlates of memory impairment have been the most frequent ones. In sporadic forms of EOAD, episodic memory impairment was correlated to hypometabolism in the bilateral hippocampi and amygdala, entorhinal and parahippocampal cortices, PCC, insula, lateral and medial orbitofrontal, the left frontal pole and the right superior temporal cortex, taking regional atrophy as covariate (Vanhoutte et al., 2017). In MCI, episodic memory scores were found to correlate with hypometabolism in a circumscribed bilateral network encompassing the hippocampus, medial septum, PCC, retrosplenial cortex, ventral precuneus, and the inferior parietal cortex, most regions belonging to Papez's circuit. A further cluster was located in the left dorsolateral prefrontal cortex (Grothe, Heinsen, Amaro, Grinberg, & Teipel, 2016).

Studies on memory in AD using neuropsychological evaluation showed that different systems may become dysfunctional at specific stages of AD. In a mild stage of AD, episodic memory performance was related to the level of glucose metabolism in medial temporal structures and PCC (Desgranges, Baron, Lalevee, et al., 2002). In a recent memory model, the medial temporal region is involved in representation of information, and the PCC subserves the integration of memory-related operations and contents (Bastin et al., 2019). In a moderate stage of AD, a correlation was observed between memory scores and the left temporal cortex, known to be involved in semantic memory (Desgranges, Baron, Lalevee, et al., 2002). Accordingly, semantic memory was positively correlated with left posterior middle temporal metabolism, and it was more impaired in LOAD than in EOAD (Joubert et al., 2016). Scores for recent autobiographical memories were correlated to metabolism in PCC, medial temporal, medial orbitofrontal and ventrolateral prefrontal cortex in participants with amnestic MCI (Tomadesso et al., 2015). The medial orbitofrontal cortex would determine the current individual significance of the information, while the ventrolateral prefrontal cortex participates in cue specification for memory retrieval (Bastin et al., 2019).

Among studies exploring more specific mechanisms of episodic memory, a correlation was reported between recognition of novel words and metabolism in right hippocampus involved in recollection, whereas recognition of familiar words was related to metabolic activity in the posterior orbitofrontal cortex more involved in a selection process (Lekeu, Van der Linden, Degueldre, et al., 2003). The controlled free recall process was related to lateral prefrontal metabolism involved in searching strategies, while cued recall was correlated with glucose uptake in the medial temporal lobe, that would subserve the association between category and item (Lekeu, Van der Linden, Chicherio, et al., 2003). Similar correlations were previously observed for intrusions in free and cued recall respectively (Desgranges, Baron,

Giffard, et al., 2002). In another neuropsychological study, mild AD patients and controls had to remember item-color associations by imagining color either as a feature of the item to be encoded (conjunctive memory) or as a contextual association (relational memory), depending on binding capacities (Bastin et al., 2014). Partial Least Square analyses revealed that poor conjunctive memory was related to hypometabolism in an anterior temporal and posterior fusiform brain network, involved in entity representation. Decreased relational memory in AD participants correlated with metabolism in regions of the default mode network, comprising the retrosplenial cortex, that enables the reinstatement of the content of episodic memories and also the temporoparietal cortex , the anterior medial prefrontal and the dorsomedial prefrontal cortex (Bastin et al., 2014). The temporoparietal cortex is involved in attention to memory (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). The medial prefrontal regions participate to an attribution system, and they are respectively involved in self-referencing and metacognitive operations (Bastin et al., 2019). Voxel-based cognitive and metabolic correlations showed that a decrease in controlled memory processes in very early AD patients was preferentially correlated with lower activity in the dorsomedial prefrontal cortex, included in a metacognitive DMN subsystem, and in the PCC, included in the DMN core system (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Bastin et al., 2010).

In participants with MCI and AD, impaired executive functioning was associated with reduced parietotemporal metabolism (Habeck et al., 2012). In another study, a significant positive correlation was observed between an inhibition factor (Hayling, delayed alternation and phonemic fluency tasks) and an area including the left middle and superior frontal gyrus. With regard to a coordination factor (dual-task paradigm, alpha-span and self-ordering tasks), significant negative correlations were observed with three different regions: a

cingulate area (BA 31) spreading to the right inferior parietal region, a right middle temporal region, and finally with a left-sided area including the cingulate gyrus and a region at the junction of the inferior and superior parietal gyrus (Collette, Van der Linden, & Salmon, 1999).

Consistent with the neuropsychological studies, a principal component analysis has been applied on a large sample of FDG-PET images obtained in 225 patients with probable AD (Salmon et al., 2009). One functional ensemble included structures from Papez's circuit (medial temporal regions, posterior and anterior cingulate cortex, thalamus) and scores in AD patients were related to episodic memory impairment. Another principal component showed major metabolic variance in posterior cerebral cortices, and patients' scores were correlated to instrumental functions (language and visuospatial abilities). A third component comprised frontal, parietal, temporal and posteromedial (posterior cingulate and precuneus) cortices, and patients' scores for this anterior-posterior brain network were related to executive dysfunction and global cognitive impairment. The three main metabolic covariance networks converged in the posterior cingulate area, the most frequently affected connectivity hub in AD, capable of integrating multiple data.

Another important symptom in AD, anosognosia for cognitive impairment, was associated to hypometabolism in the PCC (Gerretsen et al., 2017) and in the dorsal ACC (Guerrier et al., 2018). In cognitively normal older adults, subjective memory complaints were associated to reduced FDG uptake in the posteromedial cortex, that would allow integrated access to current and past information on memory functioning (Vannini et al., 2017). Anosognosia of AD participants for personality traits was related to metabolism in the dorsomedial prefrontal cortex (dMPFC) that is involved in processing inferences regarding complex enduring dispositions of self and others (Jedidi et al., 2013). The dorsomedial frontal regions

would subserve metacognitive processes important for self-assessment (Salmon, Meyer, Genon, Collette, & Bastin, 2024). Impaired connectivity between frontal and posterior medial brain regions in resting state is consistently correlated to the degree of anosognosia in AD (Antoine et al., 2019; Perrotin et al., 2015).

Impaired self-evaluation of cognitive capacities was related to a decrease in brain glucose metabolism in medial temporal structures and in orbital prefrontal cortex (Salmon et al., 2006). In a cognitive model of anosognosia, medial temporal dysfunction might impair a relational mechanism between current information on cognition and personal knowledge, while hypoactivity in the orbitofrontal cortex may not allow AD patients to select the judgment adapted to their currently impaired cognitive abilities. Both medial temporal and orbitofrontal metabolic decrease would impair updating of personal knowledge in AD (Salmon et al., 2024). A discrepancy score between caregiver's and patient's evaluation measuring anosognosia was negatively related to metabolic activity located in the temporoparietal junction, consistent with an impairment of self-referential processes and perspective taking in AD (Salmon et al., 2006).

5. Brain metabolism in preclinical stages of AD

PET has a high sensitivity since it reveals the molecular level changes prior to the onset of structural changes in brain regions even in the preclinical stage of AD. In a 3-year longitudinal study of 48 normal elderly individuals, 25% of subjects demonstrated cognitive decline. At baseline, metabolic reductions in the entorhinal cortex accurately predicted the conversion from normal to MCI. Among those who had declined, the baseline FDG uptake reduction in the entorhinal cortex predicted subsequent memory and temporal neocortex metabolism

reduction (de Leon et al., 2001). Cognitively normal, late-middle aged carriers of the apolipoprotein E epsilon 4 allele (APO-E4), a common susceptibility gene for LOAD, were shown to have abnormally low FDG uptake in the same brain regions as patients with probable AD (Reiman et al., 1996). Similarly, healthy APO-E4 carriers had reduced metabolism within the left anterior medial temporal lobe, and a correlation was observed between metabolism in this area and performance on a memory test (delayed matching to sample-48 items), in line with converging evidence involving the perirhinal cortex in entity-based memory (Didic et al., 2015).

In autosomal dominant AD, a significant decrease of glucose metabolism was observed in the precuneus approximately 10 years before the expected onset of symptoms (Bateman et al., 2012). However, in a sample of participants of the Dominantly Inherited Alzheimer Network (DIAN) initiative, symptomatic mutation carriers had significantly lower levels of glucose metabolism in isthmus cingulate and inferior parietal regions (and smaller hippocampal volume) compared to non-carriers while there were neither metabolic nor volumetric differences between non-carriers and asymptomatic mutation carriers, suggesting possible compensation mechanisms (McKay et al., 2023).

The hypometabolic profile in AD-related regions has been observed at the group level in subjects with subjective cognitive decline and it involves the parietotemporal cortex, precuneus and parahippocampal gyri (Mosconi, De Santi, et al., 2008; Song, Choi, Oh, Chung, & Chung, 2016). An association was reported in this syndrome between hypometabolism in the right precuneus at baseline and the degree of longitudinal memory decline (Scheef et al., 2012). However, single-subject SPM analysis of FDG-PET in a group of SCD participants revealed quite heterogeneous patterns, comprising normal and frontal-like distribution, and

about 10% only of AD-like or LBD-like or limbic predominant patterns (Tondo et al., 2022). In the entire group, memory performance correlated with a typical AD-like FDG pattern.

6. AD and associated age-related pathologies

The ATN classification (amyloid, tau and neurodegeneration) has been extremely interesting to further discuss AD and non-AD pathologies (Jack et al., 2018). Abnormal amyloid deposit with or without tau proteinopathy is mandatory to define the Alzheimer's continuum, while it was reminded that FDG-PET is a measure of neurodegeneration that is not specific for AD. It was confirmed that AD participants with positive amyloid-PET had reduced FDG uptake in AD related associative cortices and in the hippocampus (Yang, Cummings, Kinney, Cordes, & Alzheimer's Disease Neuroimaging, 2023). At two-year follow up, those AD subjects showed significant decrease of metabolism in PCC, precuneus, parietal and temporal associative cortices, but not in the hippocampus. In MCI participants with brain amyloid, a normal FDG-PET at baseline was confirmed to predict clinical stability (Iaccarino, Sala, Perani, & Alzheimer's Disease Neuroimaging, 2019). In cognitively normal older adults with positive brain amyloid load (at-risk for AD), subjective memory complaints were associated to reduced FDG uptake in the hippocampus (Vannini et al., 2017), that would progressively impair the dynamic update of episodic memory.

An intriguing observation was that normal or even increased glucose metabolism could be related to cerebral AD proteinopathy. Accordingly, in normal elderly subjects with variable brain amyloid deposition, precuneus amyloidopathy was positively related to posterior cingulate FDG uptake (Ossenkoppele et al., 2014). Participants with higher glucose metabolism in a composite ROI comprising PCC, angular and inferior temporal cortices had higher verbal episodic memory performance, suggesting that asymptomatic elderly controls

at risk for AD can maintain their memory efficiency through increased regional metabolism. In another sample of normal elderly participants with low amyloid load, higher inferior temporal tau accumulation was related to higher PCC metabolism, while it was associated to PCC hypometabolism in participants with high amyloid load (Hanseeuw et al., 2017). PCC and entorhinal hypometabolism predicted subsequent memory decline in subjects with high amyloid load. Among participants with high amyloid load, while amyloid deposition and FDG uptake negatively correlated in precuneus and parietal cortex of the AD group, there was a positive correlation in the MCI group (Cohen et al., 2009). In amyloid negative subgroups of MCI participants, hypermetabolism was measured in several cortical regions (Ashraf, Fan, Brooks, & Edison, 2015) and higher cortical tau was associated to higher FDG uptake (Rubinski, Franzmeier, Neitzel, Ewers, & Alzheimer's Disease Neuroimaging, 2020). High right frontal glucose metabolism was detrimental since it was associated with worse episodic memory performance. When brain amyloid was increased in MCI subgroups, higher tau levels were associated to lower FDG uptake in typical AD related regions (Rubinski et al., 2020) and absolute values of glucose metabolism were decreased in the hippocampus (Ashraf et al., 2015). Importantly, no causal relationship between AD proteinopathy and cerebral glucose metabolism can be derived from those studies.

In a subgroup of aMCI participants with hippocampal sparing, FDG-PET pattern, amyloid and tau-PET were positive and cognitive decline was fast (Boccalini et al., 2024). A variable degree of tau accumulation was observed in the hippocampus and the nature of the preserved medial temporal metabolism in MCI-AD remains an open question. It was considered to be detrimental in MCI subjects with different etiologies since it was negatively correlated with verbal fluency performance (Apostolova et al., 2018). A relatively preserved glucose metabolism in the hippocampal formation was also observed in participants with

Lewy Body Disease and it was negatively correlated with cognition or with episodic verbal memory performance (Jeong et al., 2024; Kang, Jeon, Lee, & Ye, 2024).

In a population of normal adults, a group with only neurodegenerative abnormalities (hippocampal atrophy and hypometabolism of AD-type) did not show any group differences compared to a preclinical AD group (showing brain amyloid and subtle cognitive changes) on measures of FDG-PET regional hypometabolism, MR regional brain volume loss and cerebrovascular imaging lesions (Knopman et al., 2013). The concept of suspected non-Alzheimer pathology has led to the hypothesis that AD-like neuronal injury may be independent from brain amyloid proteinopathy (Chetelat, 2013). Accordingly, in a subgroup of amnestic amyloid-negative participants with subtle atrophy and hypometabolism restricted to the retrosplenial/posterior cingulate cortex, the clinical presentation and follow-up remained consistent with AD (Chetelat et al., 2016). However, in another study, two subgroups of amnestic MCI participants were defined by their FDG-PET pattern: a limbic predominant and a typical AD metabolic distribution (Tondo et al., 2021). While the “typical AD” subgroup had a high rate of progression to dementia, the “limbic predominant” subgroup showed clinical stability over a mean duration of 8 years and only 7% conversion to dementia. According to the ATN classification based on cerebrospinal fluid AD biomarkers, 46% of the limbic predominant group had a non-AD profile. A similar medial temporal hypometabolic subgroup of aMCI participants was characterized by variable brain amyloid deposit, no significant or MTL limited tau deposit and stable evolution, suggesting again a non-AD pathology (Boccalini et al., 2024).

Large-scale autopsy series have estimated that approximately 15% to 30% of clinically diagnosed probable AD patients do not meet neuropathologic criteria for AD (Mehta & Schneider, 2021). For example, a distinct disease entity is called limbic predominant age-

related TDP-43 encephalopathy or LATE (Nelson et al., 2019). Elderly participants with amnestic cognitive impairment, hippocampal atrophy and negative brain tau-PET had reduced FDG uptake limited to MTL and PCC/precuneus compared to more extensive hypometabolism in tau positive subjects (Botha et al., 2018). A similar FDG pattern was observed in a group with autopsy proven TDP-43 positive hippocampal sclerosis compared to subjects with Alzheimer's pathology. Patients with a clinical diagnosis of AD dementia showing this "LATE-NC-like" pattern had an older age at evaluation, a memory-dominant cognitive impairment profile, a slower clinical course and lower AD biomarkers levels (Grothe et al., 2023). Compared to AD, patients with autopsy proven association of AD- and LATE-NC showed a FDG-PET pattern characterized by a much more pronounced involvement of the medial temporal lobe and related limbic areas (such as insula and fronto-opercular cortex) and less pronounced involvement of inferior temporal and lateral parietal areas (Corriveau-Lecavalier et al., 2023). An inferior-to-medial temporal metabolism ratio was proposed as a simplified biomarker metric to capture the LATE pattern (Botha et al., 2018). One cannot exclude that other age-related pathologies that preferentially target the medial temporal lobe, such as primary age-related tauopathy, argyrophilic grain disease, or limbic-predominant AD, may also be present in subsets of these patients, especially given that these pathologies often overlap with LATE.

7. Conclusions

FDG-PET remains a highly valuable technique to study regional modifications of brain glucose metabolism in AD and associated forms of dementia. Although not specific, FDG-PET is quite sensitive to early pathological changes in cerebral networks. Functional modifications are related to the diverse clinical symptoms observed at different disease

stages and with different pathologies. Accordingly, for some authors, an increase in cerebral FDG uptake is considered as decisive evidence for a favorable effect of disease modifying treatment (Hoilund-Carlsen, Alavi, & Revheim, 2023; Khosravi et al., 2019).

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The authors have no disclosure and they have no conflict of interest

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References

Aberathne, I., Kulasiri, D., & Samarasinghe, S. (2023). Detection of Alzheimer's disease onset using MRI and PET neuroimaging: longitudinal data analysis and machine learning. *Neural Regen Res, 18*(10), 2134-2140. doi: 10.4103/1673-5374.367840

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron, 65*(4), 550-562. doi: 10.1016/j.neuron.2010.02.005

Antoine, N., Bahri, M. A., Bastin, C., Collette, F., Phillips, C., Balteau, E., . . . Salmon, E. (2019). Anosognosia and default mode subnetwork dysfunction in Alzheimer's disease. *Hum Brain Mapp, 40*(18), 5330-5340. doi: 10.1002/hbm.24775

Apostolova, I., Lange, C., Maurer, A., Suppa, P., Spies, L., Grothe, M. J., . . . Alzheimer's Disease Neuroimaging, I. (2018). Hypermetabolism in the hippocampal formation of cognitively impaired patients indicates detrimental maladaptation. *Neurobiol Aging, 65*, 41-50. doi: 10.1016/j.neurobiolaging.2018.01.002

Arbizu, J., Festari, C., Altomare, D., Walker, Z., Bouwman, F., Rivolta, J., . . . Disorders, E.-E. T. F. f. t. P. o. F.-P. f. D. N. (2018). Clinical utility of FDG-PET for the clinical diagnosis in MCI. *Eur J Nucl Med Mol Imaging, 45*(9), 1497-1508. doi: 10.1007/s00259-018-4039-7

Ashraf, A., Fan, Z., Brooks, D. J., & Edison, P. (2015). Cortical hypermetabolism in MCI subjects: a compensatory mechanism? *Eur J Nucl Med Mol Imaging, 42*(3), 447-458. doi: 10.1007/s00259-014-2919-z

Aziz, A. L., Giusiano, B., Joubert, S., Duprat, L., Didic, M., Gueriot, C., . . . Ceccaldi, M. (2017). Difference in imaging biomarkers of neurodegeneration between early and late-onset amnestic Alzheimer's disease. *Neurobiol Aging, 54*, 22-30. doi: 10.1016/j.neurobiolaging.2017.02.010

Bastin, C., Bahri, M. A., Mievis, F., Lemaire, C., Collette, F., Genon, S., . . . Salmon, E. (2014). Associative memory and its cerebral correlates in Alzheimers disease: Evidence for distinct deficits of relational and conjunctive memory. *Neuropsychologia, 63*, 99-106. doi: 10.1016/j.neuropsychologia.2014.08.023

Bastin, C., Besson, G., Simon, J., Delhaye, E., Geurten, M., Willems, S., & Salmon, E. (2019). An integrative memory model of recollection and familiarity to understand memory deficits. *Behav Brain Sci, 42*, e281. doi: 10.1017/S0140525X19000621

Bastin, C., Kerrouche, N., Lekeu, F., Adam, S., Guillaume, B., Lemaire, C., . . . Salmon, E. (2010). Controlled memory processes in questionable Alzheimer's disease: a view from neuroimaging research. *J Alzheimers Dis, 20*(2), 547-560.

Bateman, R. J., Xiong, C., Benzinger, T. L., Fagan, A. M., Goate, A., Fox, N. C., . . . Dominantly Inherited Alzheimer, N. (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med, 367*(9), 795-804. doi: 10.1056/NEJMoa1202753

Boccalini, C., Caminiti, S. P., Chiti, A., Frisoni, G. B., Garibotto, V., Perani, D., & Alzheimer's Disease Neuroimaging, I. (2024). The diagnostic and prognostic value of tau-PET in amnestic MCI with different FDG-PET subtypes. *Ann Clin Transl Neurol, 11*(5), 1236-1249. doi: 10.1002/acn3.52039

Borchert, R. J., Azevedo, T., Badhwar, A., Bernal, J., Betts, M., Bruffaerts, R., . . . Rittman, T. (2023). Artificial intelligence for diagnostic and prognostic neuroimaging in dementia: A systematic review. *Alzheimers Dement, 19*(12), 5885-5904. doi: 10.1002/alz.13412

Botha, H., Mantyh, W. G., Murray, M. E., Knopman, D. S., Przybelski, S. A., Wiste, H. J., . . . Jones, D. T. (2018). FDG-PET in tau-negative amnestic dementia resembles that of autopsy-proven hippocampal sclerosis. *Brain, 141*(4), 1201-1217. doi: 10.1093/brain/awy049

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., . . . Mintun, M. A. (2005). Molecular, structural, and functional characterization of Alzheimer's disease:

evidence for a relationship between default activity, amyloid, and memory. *J Neurosci, 25*(34), 7709-7717.

Cabeza, R., Ciaramelli, E., Olson, I. R., & Moscovitch, M. (2008). The parietal cortex and episodic memory: an attentional account. *Nat Rev Neurosci, 9*(8), 613-625.

Cabrera-Martin, M. N., Nespral, P., Valles-Salgado, M., Bascunana, P., Delgado-Alonso, C., Delgado-Alvarez, A., . . . Matias-Guiu, J. A. (2023). FDG-PET-based neural correlates of Addenbrooke's cognitive examination III scores in Alzheimer's disease and frontotemporal degeneration. *Front Psychol, 14*, 1273608. doi: 10.3389/fpsyg.2023.1273608

Caminiti, S. P., Ballarini, T., Sala, A., Cerami, C., Presotto, L., Santangelo, R., . . . Project, B. (2018). FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort. *Neuroimage Clin, 18*, 167-177. doi: 10.1016/j.nicl.2018.01.019

Caroli, A., Prestia, A., Chen, K., Ayutyanont, N., Landau, S. M., Madison, C. M., . . . Alzheimer's Disease Neuroimaging, I. (2012). Summary metrics to assess Alzheimer disease-related hypometabolic pattern with 18F-FDG PET: head-to-head comparison. *J Nucl Med, 53*(4), 592-600. doi: 10.2967/jnumed.111.094946

Chase, T. N., Foster, N. L., & Mansi, L. (1983). Alzheimer's disease and the parietal lobe. *Lancet, 2*(8343), 225. doi: 10.1016/s0140-6736(83)90211-8

Chen, K., Langbaum, J. B., Fleisher, A. S., Ayutyanont, N., Reschke, C., Lee, W., . . . Alzheimer's Disease Neuroimaging, I. (2010). Twelve-month metabolic declines in probable Alzheimer's disease and amnestic mild cognitive impairment assessed using an empirically pre-defined statistical region-of-interest: findings from the Alzheimer's Disease Neuroimaging Initiative. *Neuroimage, 51*(2), 654-664. doi: 10.1016/j.neuroimage.2010.02.064

Chetelat, G. (2013). Alzheimer disease: Abeta-independent processes-rethinking preclinical AD. *Nat Rev Neurol, 9*(3), 123-124. doi: 10.1038/nrneurol.2013.21

Chetelat, G., Desgranges, B., Landeau, B., Mezenge, F., Poline, J. B., de la Sayette, V., . . . Baron, J. C. (2008). Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. *Brain, 131*(Pt 1), 60-71. doi: 10.1093/brain/awm288

Chetelat, G., Ossenkoppele, R., Villemagne, V. L., Perrotin, A., Landeau, B., Mezenge, F., . . . Rabinovici, G. D. (2016). Atrophy, hypometabolism and clinical trajectories in patients with amyloid-negative Alzheimer's disease. *Brain, 139*(Pt 9), 2528-2539. doi: 10.1093/brain/aww159

Cohen, A. D., Price, J. C., Weissfeld, L. A., James, J., Rosario, B. L., Bi, W., . . . Klunk, W. E. (2009). Basal cerebral metabolism may modulate the cognitive effects of Abeta in mild cognitive impairment: an example of brain reserve. *J Neurosci, 29*(47), 14770-14778. doi: 10.1523/JNEUROSCI.3669-09.2009

Collette, F., Van der Linden, M., & Salmon, E. (1999). Executive dysfunction in Alzheimer's disease. *Cortex, 35*(1), 57-72 (http://hdl.handle.net/2268/3743).

Corriveau-Lecavalier, N., Botha, H., Graff-Radford, J., Switzer, A. R., Przybelski, S. A., Wiste, H. J., . . . Jones, D. T. (2023). A limbic-predominant amnestic neurodegenerative syndrome associated with TDP-43 pathology. *medRxiv*. doi: 10.1101/2023.11.19.23298314

de Leon, M. J., Convit, A., Wolf, O. T., Tarshish, C. Y., DeSanti, S., Rusinek, H., . . . Fowler, J. (2001). Prediction of cognitive decline in normal elderly subjects with 2-[(18)F]fluoro-2-deoxy-D-glucose/poitron-emission tomography (FDG/PET). *Proc Natl Acad Sci U S A, 98*(19), 10966-10971. doi: 10.1073/pnas.191044198

De Santi, S., de Leon, M. J., Rusinek, H., Convit, A., Tarshish, C. Y., Roche, A., . . . Fowler, J. (2001). Hippocampal formation glucose metabolism and volume losses in MCI and AD. *Neurobiol Aging, 22*(4), 529-539. doi: 10.1016/s0197-4580(01)00230-5

Desgranges, B., Baron, J. C., Giffard, B., Chetelat, G., Lalevee, C., Viader, F., . . . Eustache, F. (2002). The neural basis of intrusions in free recall and cued recall: a PET study in Alzheimer's disease. *Neuroimage, 17*(3), 1658-1664.

Desgranges, B., Baron, J. C., Lalevee, C., Giffard, B., Viader, F., de La Sayette, V., & Eustache, F. (2002). The neural substrates of episodic memory impairment in Alzheimer's disease as revealed by FDG-PET: relationship to degree of deterioration. *Brain, 125*(Pt 5), 1116-1124.

Didic, M., Felician, O., Gour, N., Bernard, R., Pecheux, C., Mundler, O., . . . Guedj, E. (2015). Rhinal hypometabolism on FDG PET in healthy APO-E4 carriers: impact on memory function and metabolic networks. *Eur J Nucl Med Mol Imaging, 42*(10), 1512-1521. doi: 10.1007/s00259-015-3057-y

Duan, J., Liu, Y., Wu, H., Wang, J., Chen, L., & Chen, C. L. P. (2023). Broad learning for early diagnosis of Alzheimer's disease using FDG-PET of the brain. *Front Neurosci, 17*, 1137567. doi: 10.3389/fnins.2023.1137567

Dukart, J., Mueller, K., Villringer, A., Kherif, F., Draganski, B., Frackowiak, R., . . . Alzheimer's Disease Neuroimaging, I. (2013). Relationship between imaging biomarkers, age, progression and symptom severity in Alzheimer's disease. *Neuroimage Clin, 3*, 84-94. doi: 10.1016/j.nicl.2013.07.005

Foster, N. L., Heidebrink, J. L., Clark, C. M., Jagust, W. J., Arnold, S. E., Barbas, N. R., . . . Minoshima, S. (2007). FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain, 130*(Pt 10), 2616-2635. doi: 10.1093/brain/awm177

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. (1991). Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab, 11*(4), 690-699. doi: 10.1038/jcbfm.1991.122

Gerretsen, P., Chung, J. K., Shah, P., Plitman, E., Iwata, Y., Caravaggio, F., . . . Alzheimer's Disease Neuroimaging, I. (2017). Anosognosia Is an Independent Predictor of Conversion From Mild Cognitive Impairment to Alzheimer's Disease and Is Associated With Reduced Brain Metabolism. *J Clin Psychiatry, 78*(9), e1187-e1196. doi: 10.4088/JCP.16m11367

Grothe, M. J., Heinsen, H., Amaro, E., Jr., Grinberg, L. T., & Teipel, S. J. (2016). Cognitive Correlates of Basal Forebrain Atrophy and Associated Cortical Hypometabolism in Mild Cognitive Impairment. *Cereb Cortex, 26*(6), 2411-2426. doi: 10.1093/cercor/bhv062

Grothe, M. J., Moscoso, A., Silva-Rodriguez, J., Lange, C., Nho, K., Saykin, A. J., . . . Alzheimer's Disease Neuroimaging, I. (2023). Differential diagnosis of amnestic dementia patients based on an FDG-PET signature of autopsy-confirmed LATE-NC. *Alzheimers Dement, 19*(4), 1234-1244. doi: 10.1002/alz.12763

Grothe, M. J., Teipel, S. J., & Alzheimer's Disease Neuroimaging, I. (2016). Spatial patterns of atrophy, hypometabolism, and amyloid deposition in Alzheimer's disease correspond to dissociable functional brain networks. *Hum Brain Mapp, 37*(1), 35-53. doi: 10.1002/hbm.23018

Guerrier, L., Le Men, J., Gane, A., Planton, M., Salabert, A. S., Payoux, P., . . . Pariente, J. (2018). Involvement of the Cingulate Cortex in Anosognosia: A Multimodal Neuroimaging Study in Alzheimer's Disease Patients. *J Alzheimers Dis, 65*(2), 443-453. doi: 10.3233/JAD-180324

Habeck, C., Risacher, S., Lee, G. J., Glymour, M. M., Mormino, E., Mukherjee, S., . . . Alzheimer's Disease Neuroimaging, I. (2012). Relationship between baseline brain metabolism measured using [(1)(8)F]FDG PET and memory and executive function in prodromal and early Alzheimer's disease. *Brain Imaging Behav, 6*(4), 568-583. doi: 10.1007/s11682-012-9208-x

Hanseeuw, B. J., Betensky, R. A., Schultz, A. P., Papp, K. V., Mormino, E. C., Sepulcre, J., . . . Johnson, K. A. (2017). Fluorodeoxyglucose metabolism associated with tau-amyloid interaction predicts memory decline. *Ann Neurol, 81*(4), 583-596. doi: 10.1002/ana.24910

Haxby, J. V., Grady, C. L., Koss, E., Horwitz, B., Heston, L., Schapiro, M., . . . Rapoport, S. I. (1990). Longitudinal study of cerebral metabolic asymmetries and associated neuropsychological patterns in early dementia of the Alzheimer type. *Arch Neurol, 47*(7), 753-760. doi: 10.1001/archneur.1990.00530070043010

Herholz, K. (2022). Imaging Clinical Subtypes and Associated Brain Networks in Alzheimer's Disease. *Brain Sci, 12*(2). doi: 10.3390/brainsci12020146

Herholz, K., Salmon, E., Perani, D., Baron, J. C., Holthoff, V., Frolich, L., . . . Heiss, W. D. (2002). Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. *Neuroimage, 17*(1), 302-316.

Hoilund-Carlsen, P. F., Alavi, A., & Revheim, M. E. (2023). Re: Aducanumab-Related ARIA: Paean or Lament? *Clin Nucl Med, 48*(6), 505-506. doi: 10.1097/RLU.0000000000004509

Iaccarino, L., Sala, A., Perani, D., & Alzheimer's Disease Neuroimaging, I. (2019). Predicting long-term clinical stability in amyloid-positive subjects by FDG-PET. *Ann Clin Transl Neurol, 6*(6), 1113-1120. doi: 10.1002/acn3.782

Ibanez, V., Pietrini, P., Alexander, G. E., Furey, M. L., Teichberg, D., Rajapakse, J. C., . . . Horwitz, B. (1998). Regional glucose metabolic abnormalities are not the result of atrophy in Alzheimer's disease. *Neurology, 50*(6), 1585-1593. doi: 10.1212/wnl.50.6.1585

Inui, Y., Ito, K., Kato, T., & Group, S.-J. S. (2017). Longer-Term Investigation of the Value of 18F-FDG-PET and Magnetic Resonance Imaging for Predicting the Conversion of Mild Cognitive Impairment to Alzheimer's Disease: A Multicenter Study. *J Alzheimers Dis, 60*(3), 877-887. doi: 10.3233/JAD-170395

Isella, V., Rosazza, C., Ferri, F., Gazzotti, M., Impagnatiello, V., Mapelli, C., . . . Ferrarese, C. (2022). Learning From Mistakes: Cognitive and Metabolic Correlates of Errors on Picture Naming in the Alzheimer's Disease Spectrum. *J Alzheimers Dis, 87*(3), 1033-1053. doi: 10.3233/JAD-220053

Ishii, K., Sasaki, M., Yamaji, S., Sakamoto, S., Kitagaki, H., & Mori, E. (1998). Relatively preserved hippocampal glucose metabolism in mild Alzheimer's disease. *Dement Geriatr Cogn Disord, 9*(6), 317-322. doi: 10.1159/000017083

Ishii, K., Willoch, F., Minoshima, S., Drzezga, A., Ficaro, E. P., Cross, D. J., . . . Schwaiger, M. (2001). Statistical brain mapping of 18F-FDG PET in Alzheimer's disease: validation of anatomic standardization for atrophied brains. *J Nucl Med, 42*(4), 548-557.

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., . . . Contributors. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement, 14*(4), 535-562. doi: 10.1016/j.jalz.2018.02.018

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., . . . Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol, 12*(2), 207-216. doi: 10.1016/S1474-4422(12)70291-0

Jagust, W., Bandy, D., Chen, K., Foster, N. L., Landau, S. M., Mathis, C. A., . . . Alzheimer's Disease Neuroimaging, I. (2010). The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. *Alzheimers Dement, 6*(3), 221-229. doi: 10.1016/j.jalz.2010.03.003

Jagust, W., Gitcho, A., Sun, F., Kuczynski, B., Mungas, D., & Haan, M. (2006). Brain imaging evidence of preclinical Alzheimer's disease in normal aging. *Ann Neurol, 59*(4), 673-681. doi: 10.1002/ana.20799

Jedidi, H., Feyers, D., Collette, F., Bahri, M. A., Jaspar, M., d'Argembeau, A., . . . Bastin, C. (2013). Dorsomedial prefrontal metabolism and unawareness of current characteristics of personality traits in Alzheimer's disease. *Soc Cogn Affect Neurosci*. doi: 10.1093/scan/nst132

Jellinger, K. A. (2020). Neuropathological assessment of the Alzheimer spectrum. *J Neural Transm (Vienna), 127*(9), 1229-1256. doi: 10.1007/s00702-020-02232-9

Jeong, S. H., Cha, J., Yoo, H. S., Chung, S. J., Jung, J. H., Sohn, Y. H., & Lee, P. H. (2024). Different effect of hypo- and hypermetabolism on cognition in dementia with Lewy bodies: are they coupled or independent? *NPJ Parkinsons Dis, 10*(1), 4. doi: 10.1038/s41531-023-00622-w

Joubert, S., Gour, N., Guedj, E., Didic, M., Gueriot, C., Koric, L., . . . Ceccaldi, M. (2016). Early-onset and late-onset Alzheimer's disease are associated with distinct patterns of memory impairment. *Cortex, 74*, 217-232. doi: 10.1016/j.cortex.2015.10.014

Kang, S., Jeon, S., Lee, Y. G., & Ye, B. S. (2024). Alteration of medial temporal lobe metabolism related to Alzheimer's disease and dementia with lewy bodies. *Alzheimers Res Ther, 16*(1), 89. doi: 10.1186/s13195-024-01429-4

Khosravi, M., Peter, J., Wintering, N. A., Serruya, M., Shamchi, S. P., Werner, T. J., . . . Newberg, A. B. (2019). 18F-FDG Is a Superior Indicator of Cognitive Performance Compared to 18F-Florbetapir in Alzheimer's Disease and Mild Cognitive Impairment Evaluation: A Global Quantitative Analysis. *J Alzheimers Dis, 70*(4), 1197-1207. doi: 10.3233/JAD-190220

Kishore, N., & Goel, N. (2023). Deep learning based diagnosis of Alzheimer's disease using FDG-PET images. *Neurosci Lett, 817*, 137530. doi: 10.1016/j.neulet.2023.137530

Knopman, D. S., Jack, C. R., Jr., Wiste, H. J., Weigand, S. D., Vemuri, P., Lowe, V. J., . . . Petersen, R. C. (2013). Brain injury biomarkers are not dependent on beta-amyloid in normal elderly. *Ann Neurol, 73*(4), 472-480. doi: 10.1002/ana.23816

Lekeu, F., Van der Linden, M., Chicherio, C., Collette, F., Degueldre, C., Franck, G., . . . Salmon, E. (2003). Brain correlates of performance in a free/cued recall task with semantic encoding in Alzheimer disease. *Alzheimer Dis Assoc Disord, 17*(1), 35-45.

Lekeu, F., Van der Linden, M., Degueldre, C., Lemaire, C., Luxen, A., Franck, G., . . . Salmon, E. (2003). Effects of Alzheimer's disease on the recognition of novel versus familiar words: neuropsychological and clinico-metabolic data. *Neuropsychology, 17*(1), 143-154.

Levin, F., Ferreira, D., Lange, C., Dyrba, M., Westman, E., Buchert, R., . . . Alzheimer's Disease Neuroimaging, I. (2021). Data-driven FDG-PET subtypes of Alzheimer's disease-related neurodegeneration. *Alzheimers Res Ther, 13*(1), 49. doi: 10.1186/s13195-021-00785-9

Ma, H. R., Sheng, L. Q., Pan, P. L., Wang, G. D., Luo, R., Shi, H. C., . . . Zhong, J. G. (2018). Cerebral glucose metabolic prediction from amnestic mild cognitive impairment to Alzheimer's dementia: a meta-analysis. *Transl Neurodegener, 7*, 9. doi: 10.1186/s40035-018-0114-z

McKay, N. S., Gordon, B. A., Hornbeck, R. C., Dincer, A., Flores, S., Keefe, S. J., . . . Dominantly Inherited Alzheimer, N. (2023). Positron emission tomography and magnetic resonance

imaging methods and datasets within the Dominantly Inherited Alzheimer Network (DIAN). *Nat Neurosci, 26*(8), 1449-1460. doi: 10.1038/s41593-023-01359-8

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263-269. doi: 10.1016/j.jalz.2011.03.005

Mehta, R. I., & Schneider, J. A. (2021). What is 'Alzheimer's disease'? The neuropathological heterogeneity of clinically defined Alzheimer's dementia. *Curr Opin Neurol, 34*(2), 237-245. doi: 10.1097/WCO.0000000000000912

Minoshima, S., Foster, N. L., & Kuhl, D. E. (1994). Posterior cingulate cortex in Alzheimer's disease. *Lancet, 344*(8926), 895.

Minoshima, S., Frey, K. A., Koeppe, R. A., Foster, N. L., & Kuhl, D. E. (1995). A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. *J Nucl Med, 36*(7), 1238-1248.

Mosconi, L. (2005). Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. FDG-PET studies in MCI and AD. *Eur J Nucl Med Mol Imaging, 32*(4), 486-510. doi: 10.1007/s00259-005-1762-7

Mosconi, L., Berti, V., Glodzik, L., Pupi, A., De Santi, S., & de Leon, M. J. (2010). Pre-clinical detection of Alzheimer's disease using FDG-PET, with or without amyloid imaging. *J Alzheimers Dis, 20*(3), 843-854. doi: 10.3233/JAD-2010-091504

Mosconi, L., De Santi, S., Brys, M., Tsui, W. H., Pirraglia, E., Glodzik-Sobanska, L., . . . de Leon, M. J. (2008). Hypometabolism and altered cerebrospinal fluid markers in normal apolipoprotein E E4 carriers with subjective memory complaints. *Biol Psychiatry, 63*(6), 609-618. doi: 10.1016/j.biopsych.2007.05.030

Mosconi, L., Sorbi, S., Nacmias, B., De Cristofaro, M. T., Fayyaz, M., Cellini, E., . . . Pupi, A. (2003). Brain metabolic differences between sporadic and familial Alzheimer's disease. *Neurology, 61*(8), 1138-1140. doi: 10.1212/01.wnl.0000086816.30011.75

Mosconi, L., Tsui, W. H., Herholz, K., Pupi, A., Drzezga, A., Lucignani, G., . . . de Leon, M. J. (2008). Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. *J Nucl Med, 49*(3), 390-398. doi: 10.2967/jnumed.107.045385

Mutlu, J., Landeau, B., Tomadesso, C., de Flores, R., Mezenge, F., de La Sayette, V., . . . Chetelat, G. (2016). Connectivity Disruption, Atrophy, and Hypometabolism within Posterior Cingulate Networks in Alzheimer's Disease. *Front Neurosci, 10*, 582. doi: 10.3389/fnins.2016.00582

Na, S., Kang, D. W., Kim, G. H., Kim, K. W., Kim, Y., Kim, H. J., . . . Korean Dementia, A. (2024). The Usefulness of (18)F-FDG PET to Differentiate Subtypes of Dementia: The Systematic Review and Meta-Analysis. *Dement Neurocogn Disord, 23*(1), 54-66. doi: 10.12779/dnd.2024.23.1.54

Nelson, P. T., Dickson, D. W., Trojanowski, J. Q., Jack, C. R., Boyle, P. A., Arfanakis, K., . . . Schneider, J. A. (2019). Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain, 142*(6), 1503-1527. doi: 10.1093/brain/awz099

Nestor, P. J., Fryer, T. D., Ikeda, M., & Hodges, J. R. (2003). Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). *Eur J Neurosci, 18*(9), 2663-2667. doi: 10.1046/j.1460-9568.2003.02999.x

Ng, S., Villemagne, V. L., Berlangieri, S., Lee, S. T., Cherk, M., Gong, S. J., . . . Rowe, C. C. (2007). Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. *J Nucl Med, 48*(4), 547-552. doi: 10.2967/jnumed.106.037762

Ossenkoppele, R., Madison, C., Oh, H., Wirth, M., van Berckel, B. N., & Jagust, W. J. (2014). Is verbal episodic memory in elderly with amyloid deposits preserved through altered neuronal function? *Cereb Cortex, 24*(8), 2210-2218. doi: 10.1093/cercor/bht076

Perani, D., Bressi, S., Cappa, S. F., Vallar, G., Alberoni, M., Grassi, F., . . . et al. (1993). Evidence of multiple memory systems in the human brain. A [18F]FDG PET metabolic study. *Brain, 116 (Pt 4)*, 903-919. doi: 10.1093/brain/116.4.903

Perovnik, M., Tomse, P., Jamsek, J., Emersic, A., Tang, C., Eidelberg, D., & Trost, M. (2022). Identification and validation of Alzheimer's disease-related metabolic brain pattern in biomarker confirmed Alzheimer's dementia patients. *Sci Rep, 12*(1), 11752. doi: 10.1038/s41598-022-15667-9

Perrotin, A., Desgranges, B., Landeau, B., Mezenge, F., La Joie, R., Egret, S., . . . Chetelat, G. (2015). Anosognosia in Alzheimer disease: Disconnection between memory and self-related brain networks. *Ann Neurol, 78*(3), 477-486. doi: 10.1002/ana.24462

Presotto, L., Ballarini, T., Caminiti, S. P., Bettinardi, V., Gianolli, L., & Perani, D. (2017). Validation of (18)F-FDG-PET Single-Subject Optimized SPM Procedure with Different PET Scanners. *Neuroinformatics, 15*(2), 151-163. doi: 10.1007/s12021-016-9322-9

Reiman, E. M., Caselli, R. J., Yun, L. S., Chen, K., Bandy, D., Minoshima, S., . . . Osborne, D. (1996). Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med, 334*(12), 752-758. doi: 10.1056/NEJM199603213341202

Rogeau, A., Hives, F., Bordier, C., Lahousse, H., Roca, V., Lebouvier, T., . . . Lopes, R. (2024). A 3D convolutional neural network to classify subjects as Alzheimer's disease, frontotemporal dementia or healthy controls using brain 18F-FDG PET. *Neuroimage, 288*, 120530. doi: 10.1016/j.neuroimage.2024.120530

Rubinski, A., Franzmeier, N., Neitzel, J., Ewers, M., & Alzheimer's Disease Neuroimaging, I. (2020). FDG-PET hypermetabolism is associated with higher tau-PET in mild cognitive impairment at low amyloid-PET levels. *Alzheimers Res Ther, 12*(1), 133. doi: 10.1186/s13195-020-00702-6

Sala, A., Caprioglio, C., Santangelo, R., Vanoli, E. G., Iannaccone, S., Magnani, G., & Perani, D. (2020). Brain metabolic signatures across the Alzheimer's disease spectrum. *Eur J Nucl Med Mol Imaging, 47*(2), 256-269. doi: 10.1007/s00259-019-04559-2

Salmon, E., Kerrouche, N., Perani, D., Lekeu, F., Holthoff, V., Beuthien-Baumann, B., . . . Herholz, K. (2009). On the multivariate nature of brain metabolic impairment in Alzheimer's disease. *Neurobiol Aging, 30*(2), 186-197.

Salmon, E., Meyer, F., Genon, S., Collette, F., & Bastin, C. (2024). Neural correlates of impaired cognitive processes underlying self-unawareness in Alzheimer's disease. *Cortex, 171*, 1-12. doi: 10.1016/j.cortex.2023.10.009

Salmon, E., Perani, D., Herholz, K., Marique, P., Kalbe, E., Holthoff, V., . . . Garraux, G. (2006). Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Hum Brain Mapp, 27*(7), 588-597.

Scheef, L., Spottke, A., Daerr, M., Joe, A., Striepens, N., Kolsch, H., . . . Jessen, F. (2012). Glucose metabolism, gray matter structure, and memory decline in subjective memory impairment. *Neurology, 79*(13), 1332-1339. doi: 10.1212/WNL.0b013e31826c1a8d

Schroeter, M. L., Stein, T., Maslowski, N., & Neumann, J. (2009). Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. *Neuroimage, 47*(4), 1196-1206. doi: 10.1016/j.neuroimage.2009.05.037

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med, 1*(1), a006189. doi: 10.1101/cshperspect.a006189

Silverman, D. H., Small, G. W., Chang, C. Y., Lu, C. S., Kung De Aburto, M. A., Chen, W., . . . Phelps, M. E. (2001). Positron emission tomography in evaluation of dementia: Regional brain metabolism and long-term outcome. *Jama, 286*(17), 2120-2127.

Smailagic, N., Lafortune, L., Kelly, S., Hyde, C., & Brayne, C. (2018). 18F-FDG PET for Prediction of Conversion to Alzheimer's Disease Dementia in People with Mild Cognitive Impairment: An Updated Systematic Review of Test Accuracy. *J Alzheimers Dis, 64*(4), 1175-1194. doi: 10.3233/JAD-171125

Song, I. U., Choi, E. K., Oh, J. K., Chung, Y. A., & Chung, S. W. (2016). Alteration patterns of brain glucose metabolism: comparisons of healthy controls, subjective memory impairment and mild cognitive impairment. *Acta Radiol, 57*(1), 90-97. doi: 10.1177/0284185114566088

Tahmasian, M., Pasquini, L., Scherr, M., Meng, C., Forster, S., Mulej Bratec, S., . . . Drzezga, A. (2015). The lower hippocampus global connectivity, the higher its local metabolism in Alzheimer disease. *Neurology, 84*(19), 1956-1963. doi: 10.1212/WNL.0000000000001575

Tanner, J. A., Iaccarino, L., Edwards, L., Asken, B. M., Gorno-Tempini, M. L., Kramer, J. H., . . . Rabinovici, G. D. (2022). Amyloid, tau and metabolic PET correlates of cognition in early and late-onset Alzheimer's disease. *Brain, 145*(12), 4489-4505. doi: 10.1093/brain/awac229

Tomadesso, C., Perrotin, A., Mutlu, J., Mezenge, F., Landeau, B., Egret, S., . . . Chetelat, G. (2015). Brain structural, functional, and cognitive correlates of recent versus remote autobiographical memories in amnestic Mild Cognitive Impairment. *Neuroimage Clin, 8*, 473-482. doi: 10.1016/j.nicl.2015.05.010

Tondo, G., Boccalini, C., Vanoli, E. G., Presotto, L., Muscio, C., Ciullo, V., . . . Network, A. D. p. (2022). Brain Metabolism and Amyloid Load in Individuals With Subjective Cognitive Decline or Pre-Mild Cognitive Impairment. *Neurology, 99*(3), e258-e269. doi: 10.1212/WNL.0000000000200351

Tondo, G., Carli, G., Santangelo, R., Mattoli, M. V., Presotto, L., Filippi, M., . . . Alzheimer's Disease Neuroimaging, I. (2021). Biomarker-based stability in limbic-predominant amnestic mild cognitive impairment. *Eur J Neurol, 28*(4), 1123-1133. doi: 10.1111/ene.14639

Trejo-Lopez, J. A., Yachnis, A. T., & Prokop, S. (2022). Neuropathology of Alzheimer's Disease. *Neurotherapeutics, 19*(1), 173-185. doi: 10.1007/s13311-021-01146-y

Vanhoutte, M., Semah, F., Rollin Sillaire, A., Jaillard, A., Petyt, G., Kuchcinski, G., . . . Lopes, R. (2017). (18)F-FDG PET hypometabolism patterns reflect clinical heterogeneity in sporadic forms of early-onset Alzheimer's disease. *Neurobiol Aging, 59*, 184-196. doi: 10.1016/j.neurobiolaging.2017.08.009

Vannini, P., Hanseeuw, B., Munro, C. E., Amariglio, R. E., Marshall, G. A., Rentz, D. M., . . . Sperling, R. A. (2017). Hippocampal hypometabolism in older adults with memory complaints and increased amyloid burden. *Neurology, 88*(18), 1759-1767. doi: 10.1212/WNL.0000000000003889

Villain, N., Fouquet, M., Baron, J. C., Mezenge, F., Landeau, B., de La Sayette, V., . . . Chetelat, G. (2010). Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease. *Brain, 133*(11), 3301-3314.

Woodward, M. C., Rowe, C. C., Jones, G., Villemagne, V. L., & Varos, T. A. (2015). Differentiating the frontal presentation of Alzheimer's disease with FDG-PET. *J Alzheimers Dis, 44*(1), 233-242. doi: 10.3233/JAD-141110

Yakushev, I., Landvogt, C., Buchholz, H. G., Fellgiebel, A., Hammers, A., Scheurich, A., . . . Bartenstein, P. (2008). Choice of reference area in studies of Alzheimer's disease using positron emission tomography with fluorodeoxyglucose-F18. *Psychiatry Res, 164*(2), 143-153. doi: 10.1016/j.pscychresns.2007.11.004

Yang, Z., Cummings, J. L., Kinney, J. W., Cordes, D., & Alzheimer's Disease Neuroimaging, I. (2023). Accelerated hypometabolism with disease progression associated with faster cognitive decline among amyloid positive patients. *Front Neurosci, 17*, 1151820. doi: 10.3389/fnins.2023.1151820

Yee, E., Popuri, K., Beg, M. F., & Alzheimer's Disease Neuroimaging, I. (2020). Quantifying brain metabolism from FDG-PET images into a probability of Alzheimer's dementia score. *Hum Brain Mapp, 41*(1), 5-16. doi: 10.1002/hbm.24783