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Application of advanced brain positron emission tomography–based molecular imaging for a biological framework in neurodegenerative proteinopathies

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Abstract

Introduction: A rapid transition from a clinical-based classification to a pathology-based classification of neurodegenerative conditions, largely promoted by the increasing availability of imaging biomarkers, is emerging. The Framework for Innovative Multi-tracer molecular Brain Imaging, funded by the EU Joint Program - Neurodegenerative Disease Research 2016 "Working Groups for Harmonisation and Alignment in Brain Imaging Methods for Neurodegeneration," aimed at providing a roadmap for the applications of established and new molecular imaging techniques in dementia.
Methods: We consider current and future implications of adopting a pathology-based framework for the use and development of positron emission tomography techniques.
Results: This approach will enhance efforts to understand the multifactorial etiology of Alzheimer's disease and other dementias.
Discussion: The availability of pathology biomarkers will soon transform clinical and research practice. Crucially, a comprehensive understanding of strengths and caveats of these techniques will promote an informed use to take full advantage of these tools.
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1. Introduction

Ever since its introduction 40 years ago, molecular imaging with positron emission tomography (PET) techniques has revolutionized our ability to *in vivo* assess brain pathology and function. For years, the use of PET-based biomarkers, such as regional reductions in brain glucose metabolism or dopaminergic alterations, has been supportive for clinical practice and crucial in research [1,2]. Today, several PET biomarkers are fundamental tools in the diagnostic workup of different neurodegenerative conditions, including Alzheimer's disease (AD), the most common cause of dementia worldwide [3,4].

Concurrently, the clinical neuroscience field has been rapidly moving from essentially a clinical syndromic diagnosis, eventually corroborated by biomarkers, to a pathology-driven, biological definition of neurodegenerative conditions [5]. This shift was likely promoted by the

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increasing availability of both fluid- and imaging-based pathology biomarkers, as well as by increasing evidence of a sometimes-low specificity of clinical diagnosis in predicting pathology at autopsy [6]. It is now widely accepted that the same clinical syndrome, for example amnestic, can be associated with diverse underlying pathologies, ranging from AD to Lewy body disease or frontotemporal lobar degeneration spectrum, including tau and TAR DNA binding protein-43 pathologies. From another angle, it has been also shown that the same underlying pathology can trigger diverse clinical phenotypes. This is the case, among the others, of AD atypical variants, where the pathognomonic signature of plaques and tangles brain accumulation can distribute with different regional patterns and magnitude, triggering different clinical phenotypes (e.g., language-dominant, visual-dominant, frontal/dysexecutive dominant) [7]. In this framework, PET techniques provide a unique ability to *in vivo* evaluate underlying pathology, essentially pushing the field closer to the ultimate goal of a definite diagnosis in a living patient even at a preclinical stage. The importance of this paradigm shift is not limited to research. For instance, this is primarily important also for sound, informed and targeted clinical trials on possible disease-modifying treatments, where presence of disease must be ascertained to test drug efficacy. This is especially relevant as clinical trials are currently moving toward preclinical phases of AD, where subjects are asymptomatic and thus biomarkers play a central role in identifying the neuropathology in individuals at higher risk of clinical progression [8]. In addition, PET-based biomarkers in clinical trials can also be used longitudinally to investigate target engagement and assess whether a drug, for example amyloid-targeting, is actually able to engage and reduce detrimental proteinaceous accumulation.

1.1. PET-based pathology biomarkers

Two main PET techniques are currently available to investigate *in vivo* brain pathology, namely amyloid PET and tau PET [9,10]. The combination of the two, considering the respective properties and limitations (see in the following paragraphs), allows for the identification and tracking of AD course *in vivo*. Other than the diagnostic implications, brain imaging of amyloid and tau can provide unique insights into the AD pathophysiological cascade, for instance by allowing the evaluation of a sequence of pathological events and their interactions. Considering the original amyloid-cascade hypothesis, posing amyloid accumulation as the causative trigger in AD [11], PET molecular imaging techniques have recently allowed its more detailed scrutiny [11]. In addition, *in vivo* imaging of neuroinflammatory responses in the brain fostered the interest in these techniques by an increasingly recognized role of neuroinflammation in the pathophysiological cascade of multiple neurodegenerative conditions, including AD.

1.1.1. Amyloid PET

The term amyloid PET refers to all those PET procedures using radioligands that bind to amyloid plaques in the brain [10]. The first tracer to be introduced, more than a decade ago, was the carbon-labeled Pittsburgh Compound B, or ^{11}C-PiB, which is still the most used in research applications due to very favorable properties [10]. After several years, many other tracers have been developed and tested in humans [10]. Of these, three fluorinated radioligands have also been approved for clinical use by regulatory agencies such as the Food and Drug Administration and the European Medicines Agency, including the ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{18}F-flutemetamol [10]. The introduction of this technique revolutionized research in AD, being rapidly implemented into AD research diagnostic criteria [3,4]. The strength of this approach relies on the high consistency between amyloid PET evidence and autopsy tissue evaluation, as shown by multiple PET-to-autopsy studies [12]. This predictive potential is both positive, that is a positive amyloid PET is very likely to be associated with a positive neuropathology examination, and negative, that is a negative amyloid PET, especially in symptomatic phases, is likely to exclude a positive neuropathology examination. The ability to rule in/rule out AD can be particularly useful in specific clinical scenarios, as highlighted by the Appropriate Use Criteria, such as in very early symptomatic phases, in atypical cases, and in specific differential diagnostic settings [13]. One of the most remarkable outcomes of amyloid PET research was, however, the evidence for significant brain amyloid deposition in neurodegenerative conditions other than AD, such as in Lewy body disease, as well as in normal aging [14,15]. Overall, rates of amyloid positivity tend to increase with age, with estimates in cognitively normal subjects ranging from about 30% at age 70 to about 40% at age 80 [14]. This evidence has important implications for both early and differential diagnosis as well as for research practice, emphasizing how the same pathology can be observed across different conditions.

1.1.2. Tau PET

The investigation of brain tau protein accumulation *in vivo* has been available only for few years, but preliminary studies have already highlighted the groundbreaking potential of this technique [9,10]. A crucial difference between amyloid PET and tau PET is indeed the complexity and heterogeneity of the targets. Tau pathology can be extremely diverse, having different structures (e.g., 4-repeat/3-repeat) and conformations (e.g., paired helical filaments, straight filaments, and so forth) [10]. Different tau PET radioligands have been developed and tested in humans, most of which specifically designed to target the tauopathy observed in AD [16]. Preliminary studies with this technique have consistently shown a very significant and extensive cortical tracer

uptake in AD, with notably some variability considering clinical phenotypes and also the age of onset [9]. Consistently, postmortem autoradiographic studies have shown extensive and intense binding of tau PET ligands to paired helical filaments in AD brain tissue specimens [17]. Compared with amyloid PET, for which the available literature is less consistent, tau PET uptake has been shown to correlate with neurodegeneration and cognitive deficits, being also able to accurately track disease progression [9]. Possibly due to the pathological heterogeneity of tauopathies, that is a complex combination of isoforms and morphology, currently available tau PET techniques have provided rather underwhelming results in non-AD tauopathies, such as progressive supranuclear palsy and corticobasal degeneration. Several studies in these conditions have indeed shown significant tracer binding in biologically meaningful regions [18] but, nevertheless, postmortem autoradiographic studies have also shown overall weaker or null staining of the same tracers to non-AD tauopathies or other pathologies, such as TAR DNA binding protein-43 [17]. This discordance between *in vivo* regional patterns of meaningful uptake and *in vitro* weak/null binding of the tracer to the actual pathology is currently under investigation [17], especially in light of the known nonspecific binding some of these tracers show [19].

1.1.3. Neuroinflammation PET

Other than amyloid and tau PET, *in vivo* imaging of inflammatory responses in the brain has recently gained interest in clinical neuroscience research [20]. The majority of research in this field has focused on imaging of microglia activation, mostly targeting the 18 kDa translocator protein (TSPO), an outer mitochondrial membrane protein overexpressed by microglia during activation [20,21]. The application of these techniques has provided unique insights into *in vivo* dynamics of neuroinflammation in various neurodegenerative conditions, often showing significant microglia activation in biologically meaningful, disease-specific regions such as temporoparietal lobes in AD [20]. These techniques have also been used to delineate temporal trajectories of microglia activation along disease course [22], with preliminary applications also to test effects of immunomodulatory therapies, such as in Parkinson's disease and multiple system atrophy [23,24]. While compelling, these studies have nevertheless highlighted the limitations of these techniques. First, TSPO seems to be not an ideal target from the methodological standpoint, given its low-grade expression in the normal brain parenchyma and its endothelial binding, its expression to cell types other than microglia such as astrocytes, as well as a known genetic polymorphism modulating binding of some TSPO radioligands [25]. Additionally, microglia are known to show complex and dynamic types of activation, which can be both beneficial or detrimental [26]. As TSPO seems to be not able to differentiate functional phenotypes, new PET targets are currently under evaluation [27].

1.2. Relationships between pathology and topographical functional biomarkers

The availability of amyloid-, tau-, and neuroinflammation PET techniques has also enabled novel multimodal studies to evaluate *in vivo* the crucial relationships between pathology and functional/topographical markers of neurodegeneration. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG-PET) is the most widely used and validated *in vivo* biomarker of synaptic dysfunction, with a well-known diagnostic and prognostic value in neurodegenerative conditions [2,28]. ^{18}F-FDG-uptake is considered to reflect neuronal/synaptic activity and density [29-31], notwithstanding the possible contribution of other processes influencing the metabolic signal, such as astrocytes' activity [32]. Previous multimodal ^{18}F-FDG-PET/amyloid PET studies have provided evidence for an overall absent or weak relationship between amyloid plaques accumulation and colocalized synaptic dysfunction in AD (among the others, [33-37]). This evidence is consistent with other clinicopathology data showing that the burden of amyloid plaques postmortem correlates weakly with neurodegeneration and/or cognition [38,39]. This is supported by the considerable proportion of amyloid-positive cognitively normal elderly subjects [14]. The fundamental caveat of amyloid PET is that currently available radioligands target only the insoluble amyloid plaques and not the most toxic soluble oligomers. Thus, much of the toxic effects of the oligomers are underestimated. Compared with amyloid PET, preliminary data on tau PET otherwise showed a tight local association between neurofibrillary tau tangles accumulation and brain glucose hypometabolism in both typical and atypical AD [33,34,40-42]. This is also in keeping with the association between regional tau PET signal and clinical status/cognitive deficits found in the AD spectrum (among the others, [43-46]). Both tau PET and ^{18}F-FDG-PET represent crucial tools in providing *in vivo* biomarkers for neurodegeneration. As for neuroinflammation PET, only few studies have evaluated the *in vivo* relationships between microglia activation and brain glucose metabolism [47-49], mostly focusing on AD and on Parkinson's disease and dementia. Overall, the available data show topographical concordance between these biomarkers, with neuroimmune activation detected by PET in AD- and Parkinson's disease and dementia–associated hypometabolic regions and beyond [47-50], possibly predicting the severity of metabolic decline at follow-up [48]. On a technical note, multimodal neuroinflammation/glucose metabolism studies could be partially biased by the locally activated immune cells that by increasing their glucose utilization may attenuate the local cerebral hypometabolism detected by ^{18}F-FDG-PET [51].

1.3. Future applications and caveats

The adoption of a taxonomy of neurodegenerative conditions based on underlying pathology will in the future pave the way to a thorough consideration of PET molecular

imaging techniques as crucial tools. A similar approach will benefit both in clinical practice, for a more accurate early and differential diagnosis, and research, giving unique chances of testing pathophysiological models, comorbidity, and pathology/neuroinflammation dynamic interactions in neurodegeneration. One of the most remarkable implications will be the routine introduction of such pathology evaluations in clinical trials for not only accurate screening of eligible participants but also crucially evaluating whether tested drugs are having an actual effect on pathology burden. The adoption of a research framework for AD based on biological definitions has been just proposed [5], with PET- and fluid-based biomarkers playing a central role for the identification of underlying AD. Parallel to the future availability of new pathology tracers, such as targeting alpha-synuclein, 4R tau, or TAR DNA binding protein-43 pathology, the future holds promise for detailed investigations and redefinitions of the different neurodegenerative conditions. With different imaging markers available, future studies will be able to assess copathology distribution at the whole brain level, possibly tracking its time course and topography. A comprehensive understanding of pathology comorbidities, phenotype complexity, and limits of the available PET molecular imaging techniques, together with the adoption of well-validated quantification approaches, will allow an appropriate and fruitful use of these neuroimaging techniques.

RESEARCH IN CONTEXT

1. Systematic review: The authors referred to commonly used academic engines (PubMed, Google Scholar) to search relevant literature.

2. Interpretation: Strengths, weaknesses, and potentials of PET pathology biomarkers are recognized and discussed in relation to the study of neurodegenerative conditions and their classification.

3. Future directions: The availability of new PET pathology biomarkers, together with the validation of the currently available, will substantially transform the landscape of clinical and research practice. An informed and appropriate use of such tools will be quintessential to the advancement of the field.

References

[1] Brooks DJ. Molecular imaging of dopamine transporters. Ageing Res Rev 2016;30:114–21.

[2] Kato T, Inui Y, Nakamura A, Ito K. Brain fluorodeoxyglucose (FDG) PET in dementia. Ageing Res Rev 2016;30:73–84.

[3] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. 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 2011;7:263–9.

[4] Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. The Lancet Neurol 2014;13:614–29.

[5] Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018; 14:535–62.

[6] Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005- 2010. J Neuropathol Exp Neurol 2012; 71:266–73.

[7] Warren JD, Fletcher PD, Golden HL. The paradox of syndromic diversity in Alzheimer disease. Nat Rev Neurol 2012;8:451–64.

[8] Cummings J. Lessons learned from Alzheimer Disease: Clinical Trials with negative outcomes. Clin Transl Sci 2018;11:147–52.

[9] Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. Nat Rev Neurosci 2018;12:585.

[10] Villemagne VL, Doré V, Burnham SC, Masters CL, Rowe CC. Imaging tau and amyloid-β proteinopathies in Alzheimer disease and other conditions. Nat Rev Neurol 2018;14:225–36.

[11] Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 2016;8:595–608.

[12] Villeneuve S, Rabinovici GD, Cohn-Sheehy BI, Madison C, Ayakta N, Ghosh PM, et al. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation. Brain 2015;138:2020–33.

[13] Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. Alzheimer's Demen 2013;9:E1–16.

[14] Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FRJ, et al. Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia. JAMA 2015;313:1924–38.

[15] Ossenkoppele R, Jansen WJ, Rabinovici GD, Knol DL, van der Flier WM, van Berckel BNM, et al. Prevalence of Amyloid PET Positivity in Dementia Syndromes. JAMA 2015;313:1939–49.

[16] Villemagne VL, Fodero-Tavoletti MT, Masters CL, Rowe CC. Tau imaging: early progress and future directions. Lancet Neurol 2015; 14:114–24.

[17] Marquié M, Normandin MD, Vanderburg CR, Costantino IM, Bien EA, Rycyna LG, et al. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. Ann Neurol 2015;78:787–800.

[18] Saint-Aubert L, Lemoine L, Chiotis K, Leuzy A, Rodriguez-Vieitez E, Nordberg A. Tau PET imaging: present and future directions. Mol Neurodegener 2017;12:19.

[19] Lemoine L, Leuzy A, Chiotis K, Rodriguez-Vieitez E, Nordberg A. Tau positron emission tomography imaging in tauopathies: The added hurdle of off-target binding. Alzheimer's Demen Diagn Assess Dis Monit 2018;10:232–6.

[20] Jacobs AH, Tavitian B, INMiND consortium. Noninvasive molecular imaging of neuroinflammation. J Cereb Blood Flow Metab 2012; 32:1393–415.

[21] Hickman S, Izzy S, Sen P, Morsett L, Khoury El J. Microglia in neurodegeneration. Nat Neurosci 2018:1–11.

[22] Dupont A-C, Largeau B, Santiago Ribeiro MJ, Guilloteau D, Tronel C, Arlicot N. Translocator Protein-18 kDa (TSPO) Positron Emission Tomography (PET) Imaging and Its Clinical Impact in Neurodegenerative Diseases. Int J Mol Sci 2017;18:785. https://doi.org/10.3390/ijms18040785.

[23] Jucaite A, Svenningsson P, Rinne JO, Cselényi Z, Varnäs K, Johnström P, et al. Effect of the myeloperoxidase inhibitor AZD3241 on microglia: a PET study in Parkinson's disease. Brain 2015;138:2687–700.

[24] Dodel R, Spottke A, Gerhard A, Reuss A, Reinecker S, Schimke N, et al. Minocycline 1- year therapy in multiple-system-atrophy: effect on clinical symptoms and [(11)C] (R)- PK11195 PET (MEMSA-trial). Mov Disord 2010;25:97–107.

[25] Turkheimer FE, Rizzo G, Bloomfield PS, Howes O, Zanotti-Fregonara P, Bertoldo A, et al. The methodology of TSPO imaging with positron emission tomography. Biochem Soc Trans 2015; 43:586–92.

[26] Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. Nat Rev Immunol 2014;14:463–77.

[27] Tronel C, Largeau B, Santiago Ribeiro MJ, Guilloteau D, Dupont A-C, Arlicot N. Molecular Targets for PET Imaging of Activated Microglia: The Current Situation and Future Expectations. Int J Mol Sci 2017; 18:802. https://doi.org/10.3390/ijms18040802.

[28] Perani D. FDG-PET and amyloid-PET imaging: the diverging paths. Curr Opin Neurol 2014;27:405–13.

[29] Stoessl AJ. Glucose utilization: still in the synapse. Nat Neurosci 2017;20:382–4.

[30] Magistretti PJ, Pellerin L, Rothman DL, Shulman RG. Energy on demand. Science 1999;283:496–7.

[31] Rocher AB, Chapon F, Blaizot X, Baron J-C, Chavoix C. Resting-state brain glucose utilization as measured by PET is directly related to regional synaptophysin levels: a study in baboons. Neuroimage 2003;20:1894–8.

[32] Zimmer ER, Parent MJ, Souza DG, Leuzy A, Lecrux C, Kim H-I, et al. [18F]FDG PET signal is driven by astroglial glutamate transport. Nat Neurosci 2017;20:393–5.

[33] Bischof GN, Jessen F, Fliessbach K, Dronse J, Hammes J, Neumaier B, et al. Impact of tau and amyloid burden on glucose metabolism in Alzheimer's disease. Ann Clin Transl Neurol 2016;3:934–9.

[34] Ossenkoppele R, Schonhaut DR, Schöll M, Lockhart SN, Ayakta N, Baker SL, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 2016;139:1551–67.

[35] Lehmann M, Ghosh PM, Madison C, Laforce R, Corbetta-Rastelli C, Weiner MW, et al. Diverging patterns of amyloid deposition and hypometabolism in clinical variants of probable Alzheimer's disease. Brain 2013;136:844–58.

[36] Altmann A, Ng B, Landau SM, Jagust WJ, Greicius MD, Alzheimer's Disease Neuroimaging Initiative. Regional brain hypometabolism is unrelated to regional amyloid plaque burden. Brain 2015; 138:3734–46.

[37] La Joie R, Perrotin A, Barré L, Hommet C, Mézenge F, Ibazizene M, et al. Region-specific hierarchy between atrophy, hypometabolism, and 2-amyloid (Aβ) load in Alzheimer's disease dementia. J Neurosci 2012;32:16265–73.

[38] Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J Neuropathol Exp Neurol 2012; 71:362–81.

[39] Murray ME, Lowe VJ, Graff-Radford NR, Liesinger AM, Cannon A, Przybelski SA, et al. Clinicopathologic and 11C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum. Brain 2015;138:1370–81.

[40] Schöll M, Lockhart SN, Schonhaut DR, O'Neil JP, Janabi M, Ossenkoppele R, et al. PET Imaging of Tau Deposition in the Aging Human Brain. Neuron 2016;89:971–82.

[41] Dronse J, Fliessbach K, Bischof GN, Reutern von B, Faber J, Hammes J, et al. In vivo patterns of tau pathology, amyloid-β burden, and neuronal dysfunction in clinical variants of Alzheimer's disease. J Alzheimers Dis 2017;55:465–71.

[42] Sintini I, Schwarz CG, Martin PR, Graff-Radford J, Machulda MM, Senjem ML, et al. Regional multimodal relationships between tau, hypometabolism, atrophy, and fractional anisotropy in atypical Alzheimer's disease. Hum Brain Mapp 2019;40:1618–31.

[43] Bejanin A, Schonhaut DR, La Joie R, Kramer JH, Baker SL, Sosa N, et al. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. Brain 2017;140:3286–300.

[44] Ossenkoppele R, Smith R, Ohlsson T, Strandberg O, Mattsson N, Insel PS, et al. Associations between tau, Aβ, and cortical thickness with cognition in Alzheimer disease. Neurology 2019;92:e601–12.

[45] Johnson KA, Schultz A, Betensky RA, Becker JA, Sepulcre J, Rentz D, et al. Tau positron emission tomographic imaging in aging and early Alzheimer disease. Ann Neurol 2016;79:110–9.

[46] Cho H, Choi JY, Hwang MS, Lee JH, Kim YJ, Lee HM, et al. Tau PET in Alzheimer disease and mild cognitive impairment. Neurology 2016; 87:375–83.

[47] Femminella GD, Ninan S, Atkinson R, Fan Z, Brooks DJ, Edison P. Does microglial activation influence hippocampal volume and neuronal function in Alzheimer"s disease and Parkinson"s disease dementia? J Alzheimers Dis 2016;51:1275–89.

[48] Fan Z, Aman Y, Ahmed I, Chetelat G, Landeau B, Ray Chaudhuri K, et al. Influence of microglial activation on neuronal function in Alzheimer"s and Parkinson"s disease dementia. Alzheimers Dement 2015;11:608–621.e7.

[49] Kreisl WC, Lyoo CH, Liow J-S, Snow J, Page E, Jenko KJ, et al. Distinct patterns of increased translocator protein in posterior cortical atrophy and amnestic Alzheimer's disease. Neurobiol Aging 2017; 51:132–40.

[50] Fan Z, Okello AA, Brooks DJ, Edison P. Longitudinal influence of microglial activation and amyloid on neuronal function in Alzheimer's disease. Brain 2015;138:3685–98.

[51] Backes H, Walberer M, Ladwig A, Rueger MA, Neumaier B, Endepols H, et al. Glucose consumption of inflammatory cells masks metabolic deficits in the brain. Neuroimage 2016;128:54–62.