

FDG-PET imaging, EEG and sleep phenotypes as translational biomarkers for research in Alzheimer's disease

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Abstract

The lack of reliable translational procedures applicable to both patients and experimental models are a major obstacle for the advancement of basic research as well as for the development of therapeutics. This is particularly relevant to neurodegenerative disorders such as AD (Alzheimer's disease), where the predictive validity of animal models and procedures applied preclinically have met with little success. Two approaches available for human diagnostics are currently experiencing major advancements in preclinical research: *in vivo* imaging using MRI (magnetic resonance imaging) or PET (positron-emission tomography) and recordings of brain electrical activity via surface EEG (electroencephalogram). The present paper reviews the results obtained so far in rodent AD models, and summarizes advantages and disadvantages of such procedures.

Introduction

Translational research requires biomarkers that (i) can be obtained both in clinic and preclinic; (ii) are reproducible, graded and sensitive (>80%) indicators of the individual's health status; and (iii) are disease specific (>80%). Additionally, it is desirable that methods of biomarker quantification are affordable, non-invasive or at least low risk, and samples are easily accessible and quantifiable. Disease biomarkers are classified as antecedent (predicting the risk of developing a disease), diagnostic (identifying an existing condition) or prognostic (detecting the course of a disease and therapeutic success). The mutual dependence between efficient translational research, early diagnosis and treatment must be recognized, along with their implications for patients: treatment benefits would be greatest in early stages of the disease, but reliable detection is ethically difficult to justify if no therapy can be offered.

Despite its high prevalence, reliable translational biomarkers for dementia, and AD (Alzheimer's disease) in particular, are still elusive. In humans, cognitive testing is commonly administered (e.g. mini mental state examination), but cannot reliably identify prodromal stages and provide prognostic value. Importantly, tasks probing for episodic memory, a cognitive function most characteristically diminished in AD patients, have proven difficult to implement in rodents [1]. Thus forward translation (from animal to patient) cannot be readily achieved. Advancements are further complicated by the non-standardized,

idiosyncratic approaches between laboratories with regard to both choice of animal models (see below) and paradigms used.

For AD, current biomarker research focuses on molecules identifiable in blood (plasma) or cerebrospinal fluid [2], by and large those related to the main risk genes, i.e. APP (amyloid precursor protein), microtubule-associated protein tau, presenilin and apolipoprotein E [3]. To date, however, no single parameter reliably serves as a prognostic or diagnostic marker, and even combinational approaches have insufficient sensitivity, specificity and reproducibility. The hunt for disease-specific biomarkers thus now includes genomic and proteomic analyses, as well as large-scale neuroimaging initiatives such as the multi-centre ADNI (Alzheimer's disease neuroimaging initiative, [4]) which if successful hopes to back-translate results to the preclinic.

Animal models

In its traditional form, effective translational research and treatment development hinge on experimental models that reliably mimic at least some aspects of the disease under scrutiny ('face validity'), and allow assessments of potential treatments that can be brought forward to the clinic ('predictive validity'). A variety of vertebrate and invertebrate experimental models exist that mimic some aspects of AD pathology by overexpression of APP and/or tau [5,6]. Human, mutated APP-expressing mice show heightened levels of β A (β -amyloid) protein, plaque-like depositions, inflammation and occasionally synapse reduction and dystrophic neurites. Deficits in learning and memory are reported, but are not specific for domains typically impaired in AD. Early tau-based models, on the other hand, generated by introduction of familial mutations associated with frontotemporal dementia [7,8], often presented with severe sensory-motor deficits due to wide-spread tau pathology in motor areas, limiting the use of these rodent models. Generation of advanced, bi- or tri-genic mice overexpressing

Key words: Alzheimer's disease (AD), imaging, positron-emission tomography (PET), power spectrum, quantitative electroencephalogram, sleep.

Abbreviations used: AD, Alzheimer's disease; APP, amyloid precursor protein; β A, β -amyloid; EEG, electroencephalogram; FDG, 2-[¹⁸F]fluoro-2-deoxy-D-glucose; MRI, magnetic resonance imaging; PET, positron-emission tomography; PIB, Pittsburgh compound B; qEEG, quantitative EEG; REM, rapid eye movement.

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both APP, tau and/or PS1 transgenes induced accelerated and more aggressive brain pathology [9,10] reminiscent of late-stage AD. A clear mismatch with familial AD patients is the required hyperexpression of transgenes in rodents to achieve plaque and tangle-like pathologies [6]. Such expression rates cause histopathological changes in young adults (3–6 months, see Table 1), useful for quantification of plaque/tangle burden. Animals, however, are often developmentally affected and devoid of a slow progression into prodromal AD/mild cognitive impairment, which would be the desired time point for dementia classification and therapeutic intervention. More importantly, aggregated β A/tau and cognitive decline do not correlate in many mouse models. Instead, cognitive deficits develop in parallel with intracellular β A, prior to extracellular plaque formation [9,10], implying soluble protein as the cause of neuronal malfunction and toxicity [11]. Equally, a significant proportion of elderly people have β A deposits but are not demented; whereas some AD patients present with severely impaired cognition but relatively few plaques. Thus cytosolic prefibrillary β A mono- or oligo-mers are sufficient for early pathological events [12,13]. Similarly, oligomeric tau proteins confer higher toxicity than fibrils and tangles (e.g. [14]) and granular oligomers are already present in AD patients at Braak stage 0; these intensify progressively and are inducible in transgenic animal models and cell culture (e.g. [15]).

Most mouse models of AD tested to date were created by pronuclear injection of mutant transgenic material under regulatory elements driving strong overexpression. As a corollary, it proved difficult to avoid compensatory processes (genetically/physiologically), a random number of (unstable) insertion sites with uncertainties of gene dosing and location, or making transgene expression region-, cell-type- and age-specific [16]. To avoid such problems, better regulated transgenic models are now emerging, for example, via selective expression of intracellular APP [13] or by inducible suppression of tau transgenes [17]. To model both APP- and tau-related pathologies in a controlled manner, we have recently developed a knock-in AD mouse (termed PLB1), which carries single-copy-mutated human APP (Swedish and London) and human tau (301L/406W) constructs. Both transgenes were fused and expressed under the control of the mouse α CaMKII (α -Ca²⁺/calmodulin-dependent protein kinase) promoter [18] to ascertain postnatal forebrain and neuron specificity of APP and tau expression. In addition, cross breeding with an existing (asymptomatic) PS1 line [19] resulted in PLB1_{Triple} mice [20], which presented with an age-related pathology of intraneuronal amyloid and hyperphosphorylated tau accumulation in hippocampus and cortex from 6 months of age.

***In vivo* FDG (2-[¹⁸F]fluoro-2-deoxy-D-glucose)-PET (positron-emission tomography) imaging as an emerging translational tool**

Functional neuroimaging is now routinely applied in clinical diagnosis and great strides are being made to implement

the technique as a modern translational tool in drug discovery. Although MRI (magnetic resonance imaging) is most widely used, others including PET, photon emission tomography, and dual-modality imaging (e.g. MRI/PET) have made considerable progress [4,21]. They provide high spatial resolution of altered neural activity during resting or event-related activation. In patients, amyloid tracers such as [¹¹C]PIB (Pittsburgh compound B) as well as [¹⁸F]florbetapir (AV-45) have enabled labelling of aggregated β A and provide a functional index for plaque development, but at the same time showed high levels of non-specific white matter retention and only detect grey matter plaque load, thus lacking sensitivity for early stages of AD (see also comments above regarding the relevance of plaque load as a biomarker in humans). Unclear is also the observation that PIB failed to detect plaques in high APP expression murine models ([22], but see [23]), for which conformational differences in fibrillary proteins have been advocated. Novel tracers may achieve better results (e.g. [³H]AZD2184; [24]), but have not yet been tested with *in vivo* imaging.

In comparison, metabolic imaging with radio-labelled FDG used as a standard in cancer diagnosis, lacks the desired disease specificity, but regional metabolic patterns enable its use as a diagnostic tool in CNS (central nervous system) disorders, and it is suitable and directly translatable for experimental purposes, where disease-specific models are available, thus not requiring specific ligands.

Advantages of *in vivo* FDG-PET imaging comprise its non-invasive nature, provision of physiological/functional information, and the possibility for repeat scans enabling longitudinal studies and within-subject comparisons. Disadvantages and challenges must however also be recognized: the size of the mouse brain (~3000 times smaller than human brain) makes accurate registration essential and, together with the lack of anatomical detail and limits of resolution, region-specific effects difficult to decipher. For animal studies, anaesthesia is generally administered during image acquisition, therefore precluding the recording of functional information arising from a behavioural context (e.g. during cognitive task performance). Devices such as the 'RatCap' aim at addressing this issue [25], but are not providing genuine unrestricted conditions and are not suitable for mice.

Sensitive, disease-specific PET signatures from patients that map on to animals still need to be determined and validated, notwithstanding the high costs associated with purchase and maintenance of suitable facilities, and image analyses that require specialist knowledge and are at present not standardized. The application of an *a priori* defined seed voxel analysis provides a powerful tool, but exploratory or data-driven approaches such as independent or principal component analysis may reveal changes in metabolism that are not immediately intuitive [26]. For example, areas of apparent hypermetabolism in the diseased brain can be the results of the normalization process (e.g. compared with whole brain or cerebellum), metabolic phenotypes can emerge as the consequence of confounding factors (e.g. the

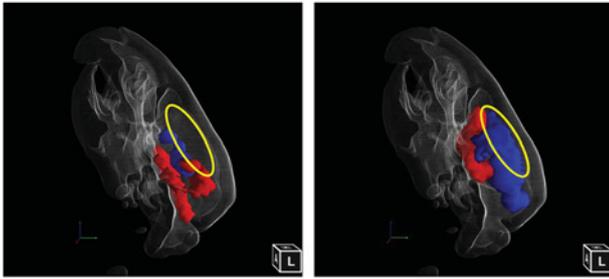
Table 1 | Overview of FDG-PET, EEG and sleep phenotypes reported in rodent AD models

Unless indicated otherwise, models are transgenic mice. No studies based on these technologies have yet been published in tau models. PS, presenilin; ICV, intracerebroventricular; NA, not analysed.

Model	Transgenes	Procedure	Histopathological phenotype	Cognitive phenotype	Increased wakefulness	Sleep fragmentation	EEG power spectra shifts	FDG-PET phenotype	Reference(s)
Tg2576	APP _{Swe} (KM670/ 671NL)	Pronuclear, random integration	Onset: ~9 months, moderate, no tau pathology, no cell loss	Cognitive deficit from ~9 months	No (reduced REM)	No	Yes, but not AD-like	No phenotype or hyper-metabolism only in young mice	[30,31,40,41,43]
PSAPP (Tg2576×PS1)	APP _{Swe} PS1 _{M146L}	Pronuclear, random integration	Early onset (2–3 months), very aggressive, no tau pathology, no cell loss	Variable, non-progressive	Yes (young only)	No	Yes, but not AD-like	Central hypo-metabolism, ventral hyper-metabolism, autoradiography: global and early hypo-metabolism	Present paper; [44]
APP×PSEN	APP _{Swe} PS1 _{A246E}	Pronuclear, random integration	Onset: ~6 months, aggressive, no tau pathology, no cell loss	Variable, progressive	Yes	No	Yes, but not AD-like and not age-dependent	No	Present paper; [39,45]
APP×PSEN	APP _{Swe810n} PS1 _{M146V}	Pronuclear, random integration	Early onset (2–3 months)	Cognitive deficit from ~10 months	NA	NA	NA	No PET study, three-dimensional autoradiography: hyper- and hypo-metabolism detected in AD-relevant areas	[46]
PDAPP	APP (V717F)	Pronuclear, random integration	Onset: ~6 months, aggressive, no tau pathology, cell loss from 3 months?	Early onset (3 months), variable, non-progressive	Yes (only dark period)	Yes (REM)	NA	No PET study, autoradiography: early hypo-metabolism (2 months)	[27,47]
3×Tg	APP _{Swe} Tau _{301L} PS1 _{M146V}	Pronuclear (APP and tau) and knock-in (PS1)	Onset: amyloid ~6 months, tau: delayed, aggressive, no cell loss	Early onset (pre-plaque), progressive	Some circadian abnormalities	NA	NA	No PET study, autoradiography: global and early hypometabolism (2 months)	[29,48]
Aβ ₂₅₋₃₅ infused rats	NA	ICV infusions	NA	Spatial memory impaired 1 month post-perfusion	NA	NA	Yes	NA	[49]
PLB1 _{Triple}	APP _{Swe810n} Tau _{301L/406W} PS1 _{A246E}	Knock-in, targeted insertion	Onset: ~6 months, subtle amyloid and tau pathol, no cell loss	Moderate, progressive	Yes	Yes (NREM)	Yes	Onset: 6 months, cortical hypometabolism, ventral hypermetabolism	Present paper; [50]

Figure 1 | FDG–PET phenotypes in (A) PSAPP (14 months) and (B) PLB1_{Triple} (18 months) mice

Group comparisons with age-matched wild-type controls are depicted for lateral (L, lateral; A, anterior; H, horizontal) views of three-dimensional images; areas of significant increase (red) and decrease (blue) are illustrated based on SPM (statistical parametric mapping) at $P < 0.01$. A surface render of a CT (computed tomography) image provides the anatomical reference. Cortical areas (indicated by a yellow ellipse) are most affected by amyloid plaque build-up, but appear metabolically unchanged in PSAPP mice while PLB1_{Triple} mice display cortical hypometabolism.



transgene or genetic background may have affected general growth [27]), changes can occur as a result of inflammation and metabolic activity of glia [28] or display compensatory neuronal activity.

In a recent pilot study, we compared FDG–PET phenotypes in cohorts of three young (4–5 months) and aged (17–10 months) transgenic mice (PSAPP, APP/PS1 and PLB1_{Triple}). Data were pooled for each genotype, and compared with age-matched wild-type litter mates using voxel-based statistical parametric mapping (two-step analyses, voxel threshold: $P < 0.01$, cluster threshold: $P < 0.05$). Parametric maps of changes in FDG uptake displayed significant differences (hypermetabolism: red, hypometabolism: blue) between genotypes (Figure 1 and Table 1). No significant differences were detected in any of the young mice and in aged APP/PS1 mice, but metabolic activity was reliably compromised in both aged PSAPP and PLB1_{Triple} transgenic mice cf. controls. Interestingly, cortical areas, severely affected by plaque load, showed no evidence of metabolic change in PSAPP mice, while PLB1_{Triple} mice displayed cortical hypometabolism and basal hypermetabolism.

Compared with data from other AD models acquired by FDG-based autoradiography (see Table 1), metabolic changes were, for example, also reported in the 3×Tg mouse [29], but AD-relevant brain region specificity was poor. The observation that more aggressive AD pathology led to impaired metabolism at a preplaque age of 2 months in PDAPP mice [27] may be interpreted as a developmental phenotype and, owing to the poor overall health of such models, also indicated by lower body weights intrinsic to these lines, and not as an age-related decline in cognition and corresponding brain activation. As for the limited number of *in vivo* FDG–PET studies available to date (Table 1), APP overexpressing mice have so far not presented with

AD-like FDG–PET phenotypes [30,31]. For example, FDG–PET studies conducted in Tg2576 mice identified areas of hypermetabolism in young adult (7-month-old) transgenic mice cf. wild-types, but no differences were revealed in older mice [31].

Overall, altered glucose metabolism does not appear to correlate with plaque load, this is in agreement with evidence from a number of studies negating plaques as reliable biomarker linked with cognition (see above). Nevertheless, PLB1_{Triple} mice displayed a robust age-dependent, bi-directional change in metabolic activity compared with their wild-type counterparts. With respect to transgene expression in AD-relevant brain regions, the observed hypometabolism goes some way in matching the human endophenotype.

EEG (electroencephalogram), sleep and circadian activity

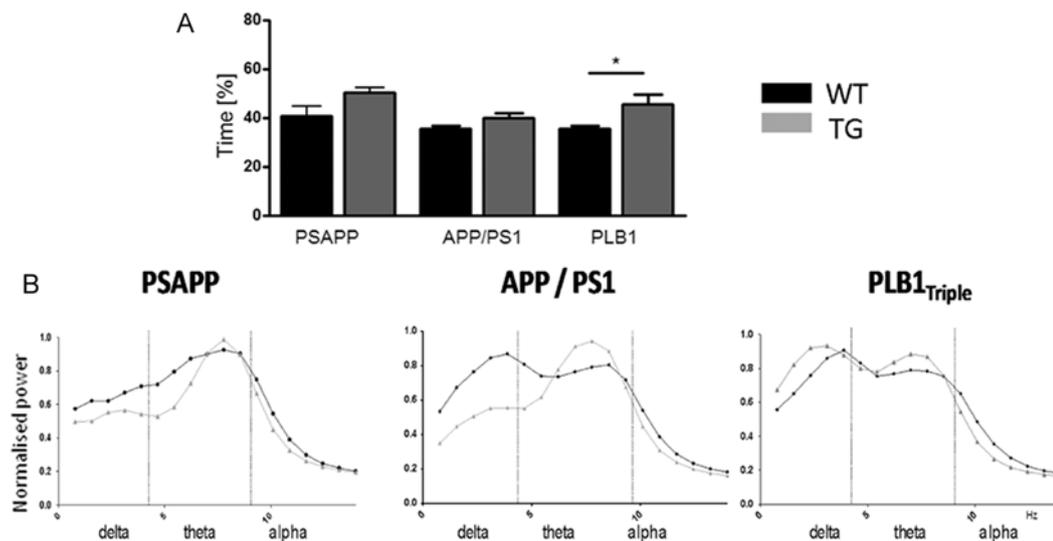
In contrast with neuroimaging, EEG has been conducted for over 100 years and serves as a diagnostic tool for a number of conditions, such as sleep disorders and epilepsy [32]. EEG is a relatively inexpensive procedure and available to smaller clinics and research groups, making it an attractive diagnostic and research tool. Superior to imaging is the high temporal resolution, since sample rates in the kHz range can be achieved. Some spatial information is provided by multiple recordings sites, but activity is captured from superficial areas only. As for imaging, the complexity of data analyses using linear and non-linear algorithms created uncertainties *vis-à-vis* reliability of results, but more fully automated and standardized procedures are currently in development, aided by internet platforms and novel computational tools.

EEG and sleep research complement each other, as typical EEG signatures are highly dependent on vigilance stages, motor activity and sleep phases, and thus used in sleep research and clinics. Sleep phenotypes are determined by circadian and ultradian cycles of three main vigilance stages: wakefulness, paradoxical or REM (rapid eye movement) sleep, and slow wave or NREM (non-REM) sleep [33]. Sleep function remains elusive despite an increasing comprehension of cellular and physiological processes underlying both the generation and modulation of sleep stages and its involvement in memory consolidation [34]. Sleep disturbances and altered circadian/ultradian patterns (such as frequent daytime naps) are commonly observed in AD patients, and positively correlate with the EEG power spectrum shift to lower frequencies, and incoherent fast rhythms, likely to arise from failing cholinergic transmission [35]. Recent evidence suggests that sleep disturbances precede overt degenerative events in AD [36], and EEG could be a more sensitive diagnostic tool for early degeneration than cognition [37]. Novel approaches in qEEG (quantitative EEG) have high prediction accuracy (95%) for conversion from mild cognitive impairment to dementia [38].

By comparison, preclinical studies applying qEEG have so far rarely been conducted. We have recently performed a comprehensive analysis of sleep patterns, vigilance staging

Figure 2 | Changes in wakefulness and EEG spectra as a prodromal markers in young-adult transgenic compared with wild-type mice

(A) A trend for increased wakefulness (illustrated as percentage of time, during light phase) was observed in PSAPP and APP/PS1 mice, but only reached significance in PLB1_{Triple} mice. (B) Normalized power spectra (δ - α bands) recorded during wakefulness from PSAPP, PLB1_{Triple} ($n = 5$ per group) and APP/PS1 mice [39] at 4–5 months of age, recorded above the parietal cortex. A loss of δ power was observed in the aggressively overexpressing models, an AD-like shift towards lower frequencies only occurred in PLB1 mice. WT, wild-type controls; TG, transgenic mice.



and qEEG changes at rest in APP/PS1-overexpressing mice (Table 1) using wireless microchip technologies and observed elevated wakefulness pre-plaque, and a genotype- and age-dependent decline in low and an increase in high-frequency spectral EEG power [39]. Other plaque-bearing mice (Tg2576) also presented with reduced REM sleep at 6 and 12 months, but sleep fragmentation and AD-like shifts in spectral power (recorded above the parietal cortex) have so far only been observed in a pilot study conducted in our PLB1_{Triple} mice [40–42] (see Figure 2 and Table 1), and showed congruency with FDG hypometabolism maps (Figure 1). Intriguing is the vast difference in experimental acquisition time (minutes in PET, 24 h in qEEG), lending compelling support to the notion that PLB1_{Triple} mice express robust translational biomarkers accessible to both metabolic and physiological imaging.

What remains to be determined is whether shifts in spectral power and altered vigilance staging correlate with cognition and histopathology in PLB1 mice and is sensitive to therapeutic intervention. Initial data indicate that they precede the emergence of cognitive decline by several months, and thus may serve as convenient and reliable prognostic biomarkers that enable accurate prediction of onset and monitoring of progression of AD-like symptomatology [32].

Conclusions

Preclinical *in vivo* imaging is still in its infancy and lags behind its clinical counterpart. However, growing demand for translational applications in conjunction with advancements in imaging technology and tracer development make this approach a prime candidate for future research. In

comparison, EEG recordings have a long-standing history in clinical diagnosis and are more readily available. This field is currently experiencing a revival in translational research, due to novel recording devices and advanced computational abilities. It will be important in the near future to seek harmonization of recording and analysis techniques between human and rodent/monkey applications to foster a more direct comparison between the different disciplines.

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