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Sleep and EEG Power Spectral Analysis in Three Transgenic Mouse Models of Alzheimer's Disease: APP/PS1, 3xTgAD, and Tg2576

Brianne A. Kent^a, Stephen M. Strittmatter^b, and Haakon B. Nygaard^{a,*}

^aDivision of Neurology and Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, Canada

^bCellular Neuroscience, Neurodegeneration and Repair Program, Yale University School of Medicine, New Haven, CT, USA

Abstract

Background: Sleep disturbances have long been associated with Alzheimer's disease (AD), and there is a growing interest in how these disturbances might impact AD pathophysiology. Despite this growing interest, surprisingly little is known about how sleep architecture and the broader neuronal network are affected in widely used transgenic mouse models of AD.

Objective: We analyzed sleep and electroencephalography (EEG) power in three transgenic mouse models of AD, using identical and commercially available hardware and analytical software. The goal was to assess the suitability of these mouse lines to model sleep and the broader neuronal network dysfunction measured by EEG in AD.

Methods: Tg2576, APP/PS1, and 3xTgAD transgenic AD mice were studied using *in vivo* EEG recordings for sleep/wake time and power spectral analysis.

Results: Both the APP/PS1 model at 8–10 months and the Tg2576 model at 12 months of age exhibited stage-dependent decreases in theta and delta power, and shifts in the power spectra toward higher frequencies. Stage-dependent power spectral analyses showed no changes in the 3xTgAD model at 18 months of age. The percentage of time spent awake, in non-rapid eye movement sleep (NREM), or in rapid-eye-movement sleep (REM) was not different between genotypes in any of the transgenic lines.

Conclusion: Our findings are consistent with data from several other transgenic AD models as well as certain studies in patients with mild cognitive impairment. Further studies will be needed to better understand the correlation between EEG spectra and AD pathophysiology, both in AD models and the human condition.

Keywords

Alzheimer's disease; dementia; EEG; sleep; transgenic mice

*Correspondence to: Haakon B. Nygaard, MD, PhD, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, 2215 Westbrook Mall, Vancouver, BC V6T 1Z3, Canada., haakon.nygaard@ubc.ca.

SUPPLEMENTARY MATERIAL

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INTRODUCTION

The majority of patients with Alzheimer's disease (AD) exhibit some form of clinical sleep disturbance, representing a leading cause of institutionalization [1, 2]. The most common sleep disturbances in AD include nocturnal sleep fragmentation, increased daytime napping, decreased non-rapid eye movement (NREM) slow-wave sleep (SWS, stage N3), and decreased rapid-eye-movement sleep (REM) (reviewed by [3, 4]). Importantly, sleep disturbances appear to precede cognitive decline in the progression of AD, beginning during the asymptomatic or pre-clinical stages, and are associated with a rise in brain amyloid- β (A β) as measured by Pittsburgh Compound B positron emission tomography (PiB-PET) imaging and cerebrospinal fluid (CSF) analysis [5, 6]. Poor sleep quality is also thought to independently increase the risk of dementia in older individuals [7]. Clinical sleep disruptions are closely related to pathological changes in the broader neuronal network. Using electroencephalography (EEG) there is a general consensus that the resting, awake EEG profile of AD patients is represented by a non-specific increase in diffuse, low amplitude slow wave activity (reviewed by [8] and [9]). However, using spectral analysis through quantitative EEG (qEEG), which provides objective measures of the frequency bands of interest, the findings are more nuanced, correlating with disease stage. In patients with established AD, the awake EEG profile generally shows increased power in the lower frequencies (delta and theta), with a decrease in fast-wave activity (alpha and beta) [10–16]. These increases in posterior delta and theta power have been reported to predict conversion of mild cognitive impairment (MCI) to dementia [13, 17–19], although these findings are not uniform in all stages of MCI. Several studies in MCI have shown *decreased* posterior delta power in this population, indicating a dynamic pathophysiologic process along the AD spectrum [10, 12].

The potential importance of sleep and neuronal network abnormalities in the pathophysiology of AD has prompted the modeling of these processes in murine AD models, which express a combination of human transgenes associated with familial AD (e.g., amyloid precursor protein (*APP*), or presenilin 1 and 2 (*PS1/2*)). Although none of the models fully recapitulate the human disease, they are thought to best model the earliest stages of AD prior to widespread synaptic loss [20]. Using chronic *in vivo* EEG monitoring, sleep and/or power spectra have been assessed across AD mouse models, including Tg2576 (APP_{SWE}) [21, 22], APP_{SWE}/PS1_{A264E} [23,24], PSAPP (APP_{SWE}/PS1_{M146L}) [25], mixed background APP_{SWE}/PS1_{dE9} [26], PLB1_{Triple} (APP_{LON,SWE}/PS1_{A246E}/MAPT_{P301L,R406W}) [27, 28], TgCRN D8 (APP_{SWE,IND}) [29], APP_{SWE,IND}/TTA [30], APP23 (APP_{SWE}) [31], and 5xFAD (APP_{SWE,FLO,LON}/PS1_{M146L,L286V}) [32]. Given the phenotypic heterogeneity within these models with respect to amyloid and tau deposition, and degree of cognitive deficits, as well as a multitude of experimental techniques, it is not surprising that a uniform shift in sleep and qEEG has not been identified. Even within the same mouse model, conflicting results have been reported [23, 24] highlighting the critical need for a standardized methodological approach to improve consistency and the translational potential of sleep and qEEG analysis in AD mice.

To address these current shortcomings, we investigated sleep and qEEG in three widely used transgenic mouse models of AD, Tg2576 (APP_{SWE}), APP/PS1 (APP_{SWE}/PS1_{dE9}), and 3xTgAD (APP_{SWE}/PS1_{M146V}/MAPT_{P301L}), using commercially available EEG hardware and analytical software. We chose a single time point when behavioral abnormalities were comparable between models based on previously published data [33]. To our knowledge, this is the first study of qEEG in the 3xTgAD (APP_{SWE}/PS1_{M146V}/MAPT_{P301L}) model of AD.

MATERIALS AND METHODS

Animals

The Yale Institutional Animal Care and Use Committee approved these experiments. Three strains of mice and littermate controls were used: Tg2576 (APP_{SWE}), APP/PS1 (APP_{SWE}/PS1_{dE9}), and 3xTgAD (APP_{SWE}/PS1_{M146V}/MAPT_{P301L}). The Tg2576 mice were on the C57BL/6/SJL background and were obtained from Taconic Biosciences [34]. The APP/PS1 transgenic mice were obtained from the Jackson Laboratory and maintained on a pure C57BL/6J background [35]. The 3xTgAD mice were a gift from Dr. Paul Lombroso (Yale University). The 3xTgAD mice express the mutated knock-in gene PS1_{M146V}, as well as APP_{SWE} and MAPT_{P301L}, at the same locus, both under control of the mouse Thy1.2 regulatory element [36]. 3xTgAD mice were on a mixed C57BL/6J × 129/Sv background as previously described [36]. Tg2576 mice were studied at the age of 12 months, APP/PS1 at 8–10 months, and 3xTgAD mice at 18 months. The ages were chosen to approximate an emerging or mild behavioral phenotype seen in our laboratory using the Morris Water maze [33], recognizing some degree of inter-laboratory variability associated with behavioral and histologic phenotypes in transgenic mice [33, 37]. At 18 months, cortical A β plaque burden remains lower in 3xTgAD mice compared to either Tg2576 or APP/PS1 at the ages used in this study, with the latter two displaying comparable soluble brain A β _{1–42} levels, but higher burden of cortical plaque in APP/PS1 mice compared to Tg2576 [33]. The sample sizes used in the experiments were: Tg2576 $n = 13$ (Tg = 8 (4 females/4 males), WT = 5 (2 females/3 males)), APP/PS1 $n = 17$ (Tg = 12 (5 females/7 males), WT = 5 (3 females/2 males)), 3xTgAD $n = 16$ (Tg = 8 (4 females/4 males), WT = 8 (4 females/4 males)).

Mouse genotyping

Mouse genotyping was performed using the RedExtract-N-Amp Tissue PCR kit (Sigma, St. Louis, MO, USA) according to manufacturer instructions.

Surgery

To implant dural electrodes, the mice were anesthetized and maintained with inhaled isoflurane and mounted in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA). A midline incision was made, and four burr holes were manually drilled through the skull at the following coordinates relative to bregma: AP +2 mm, ML $\pm$ 1.5 mm, and AP -4 mm, ML $\pm$ 1.5 mm. Four stainless steel screw electrodes were inserted through holes of a prefabricated EEG headmount (catalog number 8201; Pinnacle Technology) and manually rotated into the pre-drilled burr holes. The headmount was secured with a layer of

dental cement (catalog number 526000; A-M Systems, Sequim, WA, USA). All mice were allowed to recover for at least 7 days prior to chronic EEG recordings.

EEG

Mice were transferred to EEG recording cages and attached to recording cables. Mice were recorded using an *in vivo* EEG monitoring system (8200-K1-SE3, 8236; Pinnacle Systems). EEGs were sampled at 400 Hz with $100\times$ preamplifier gain and filtered at 30 Hz. Each mouse underwent 72 h of continuous EEG video recording and was maintained on a regular 12-h light/12-h dark cycle with full access to food and water.

Data analysis

Sleep/wake analysis and power spectral analysis were completed on the final 24 hours of the EEG recordings. EEG traces were scored manually for wake, NREM, and REM states by an investigator, blinded to genotype, using a 10 s epoch duration and Sirenia Sleep Pro software (Pinnacle Technology). Specifically, the data were first analyzed using cluster scoring, evaluating power by specific frequency bands (e.g., delta, theta, alpha, beta, and low gamma) for both EEG channels, to identify bouts of sleep and wake, as well as the transition periods. The scoring of each 10 s epoch was then confirmed through visual inspection by evaluating the recording and corresponding spectral plot. Wake was defined by low-amplitude EEG and dominant frequency > 4 Hz. NREM was defined by high-amplitude EEG and dominant frequency < 4 Hz. REM was defined by a dominant frequency between 4–8 Hz in the parietal EEG recording, uniform EEG waveforms, and occurring at a transition from NREM to wake. An epoch was defined according to which state was $>50\%$ of the 10 s epoch. EEG channels were scored for reliability by an experimenter blind to genotype. Channels without clear recordings (i.e., flat line) or high levels of artifact were removed from the analysis of sleep estimates and power spectra. In total, $n = 5$ APP/PS1 and $n = 5$ Tg2576 mice were not scored and excluded from the analyses (original sample size of APP/PS1 was $n = 22$ APP/PS1 and the original sample of the Tg2576 was $n = 18$). Percentage of time spent in each sleep/wake state was calculated by dividing by total time (24 h) subtracted by the time unscored due to artifact $[(\text{time spent in state}) / (24 \text{ h} - \text{time unscored})]$. Bouts unscored due to artifact amounted to 0.08–1.9% of the total bouts, depending on the genotype (Supplementary Figure 1). Percentage of time spent in wake, NREM, and REM stages for the TG and WT of each mouse line was compared using a two-tail unpaired *t*-test. Statistical significance was set at $p = 0.05$. Power spectral analysis was completed by using Fast Fourier Transform (FFT) to decompose the EEG time series into a voltage by frequency spectral graph, with power being the square of the EEG magnitude, and magnitude being the integral average of the amplitude of the EEG signal. Power data was normalized as a percentage of the accumulated power from 0.1–30 Hz. All statistics were performed in Graphpad Prism 7.0a (GraphPad Software Inc., La Jolla, CA USA). Statistical significance was determined by two-way analysis of variance (ANOVA) and followed by *post hoc t*-tests using the Bonferroni correction to compare specific frequency bands when a significant interaction was observed. All data are expressed as mean $\pm$ standard error of the mean (SEM).

RESULTS

Time spent in wake, NREM, or REM does not differ in Tg2576, APP/PS1 and 3xTgAD transgenic AD mice compared to wildtype control animals

The final 24 h of EEG recordings were analyzed for time spent asleep and awake. There were no statistically significant differences between the TG and WT littermate controls for the amount of time spent in wake, NREM, or REM for the 3xTgAD, Tg2576, or APP/PS1 mouse lines (Fig. 1). To evaluate the effects of the light-dark (LD) phase, percentage of time spent in wake, NREM, and REM during the 12 h dark phase, as well as the nocturnality ratios (calculated as amount of time spent awake during the 12 h dark phase, divided by total time spent awake throughout the total 24 h) were assessed. There was a nominally significant difference between the 3xTgAD and WT in the amount of time spent in NREM during the 12 h dark phase ($p = 0.045$, independent t -test), such that the WT mice spent a greater percent of time in NREM sleep during the 12 h dark phase, and less percent time in NREM during the 12 h light phase; however, this difference was not statistically significant when correcting for multiple comparisons (Supplementary Figure 4). There were no other statistically significant differences between TG and WT for time spent in wake, NREM, or REM, or for nocturnality in any of the mouse lines (Supplementary Figure 4).

Frontal and parietal EEG recordings in Tg2576 and APP/PS1, but not 3xTgAD mice, show shifts in the power spectra

Once the final 24 h of EEG recordings were scored for sleep-wake states, state-dependent power spectral analysis was conducted. The raw and normalized power spectra for wake, NREM, and REM for the 24 h period were compared between genotypes (Figs. 2 and 3, Supplementary Figures 2 and 3). Two-way ANOVAs confirmed statistically significant interactions between genotype and power spectra for both the Tg2576 and APP/PS1 models (Figs. 2 and 3, Supplementary Figures 2 and 3). There was no effect of genotype on the power spectra in the 3xTgAD mouse line for the frontal or parietal EEG for wake, NREM, or REM (Figs. 2 and 3, Supplementary Figures 2 and 3).

The power spectra of the Tg2576 showed an interaction with genotype in the frontal EEG during wake ($p < 0.0001$, $F(30,341) = 2.265$, Fig. 2D), NREM ($p = 0.0154$, $F(30,341) = 1.687$, Fig. 2E), and REM ($p = 0.0037$, $F(30,341) = 1.902$, Fig. 2F), with the power spectra generally showing a shift to higher frequencies. The power spectra of the APP/PS1 showed an interaction with genotype in the frontal EEG during NREM ($p < 0.0001$, $F(30,310) = 13.22$, Fig. 2H), exhibiting a shift to higher frequencies.

Parietal power spectra of the Tg2576 showed an interaction with genotype in the parietal EEG during wake ($p < 0.0001$, $F(30,341) = 4.797$, Fig. 3D), and a trend toward significance in NREM ($p = 0.0564$), both power spectra exhibiting a shift to higher frequencies. The power spectra of the APP/PS1 showed an interaction with genotype in the parietal EEG during wake ($p = 0.0004$, $F(30,310) = 2.206$, Fig. 3G) and NREM ($p < 0.0001$, $F(30,310) = 3.986$, Fig. 3H), exhibiting a shift to higher frequencies. Power spectra across vigilance stages did not differ in 3xTgAD mice compared to wildtype littermates.

To examine which frequency bands were specifically affected in the Tg2576 and APP/PS1 mouse lines, the power spectra from the 24 h recording was binned into delta (0.1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–20 Hz), and low gamma (20–30 Hz) frequency bands. Only power spectra that showed a statistically significant interaction between genotype and frequency were evaluated further at specific frequency bands.

For the Tg2576 mouse line, the power spectra for the frontal EEG were evaluated by frequency band for wake, NREM, and REM states (Fig. 4A–O). The power spectra for the parietal EEG were evaluated by frequency band for only the wake state (Fig. 4P–T). Two-tailed *t*-tests revealed a statistically significant difference between the Tg2576 and WT in the power spectra from the frontal EEG during wake for the theta (reduced) ($p = 0.0239$, $t = 2.619$, $df = 11$), beta (increased) ($p = 0.0142$, $t = 2.908$, $df = 11$), and low gamma (increased) ($p = 0.0221$, $t = 2.662$, $df = 11$) frequency bands, and during REM for the beta (increased) ($p = 0.0084$, $t = 3.201$, $df = 11$) and low gamma (increased) ($p = 0.0042$, $t = 3.594$, $df = 11$) frequency bands. Two-tailed *t*-tests revealed a statistically significant difference between the Tg2576 and WT in the power spectra from the parietal EEG during wake for the delta (decreased) ($p = 0.0116$, $t = 2.977$, $df = 12$), beta (increased) ($p = 0.0209$, $t = 2.657$, $df = 12$), and low gamma (increased) ($p = 0.0485$, $t = 2.196$, $df = 12$) frequency bands. There were no statistically significant differences between Tg2576 and WT in the other frequency bands ($p > 0.05$).

For the APP/PS1 mouse line, the power spectra for the frontal EEG were evaluated by frequency bands for NREM and the parietal EEG power spectra were evaluated by frequency bands for wake and NREM states (Fig. 5). Two-tailed *t*-tests revealed statistically significant differences between APP/PS1 and WT mice in the power spectra from the frontal EEG during NREM for the beta frequency band (increased) ($p = 0.0492$, $t = 2.238$, $df = 10$) and low gamma frequency band (increased) ($p = 0.0430$, $t = 2.317$, $df = 10$). Two-tailed *t*-tests revealed statistically significant differences between the TG and WT in the power spectra from the parietal EEG during wake in the theta frequency band (decreased) ($p = 0.0091$, $t = 3.228$, $df = 10$) and beta frequency bands (increased) ($p = 0.0377$, $t = 2.394$, $df = 10$), and during NREM in the delta frequency band (decreased) ($p = 0.0363$, $t = 2.416$, $df = 10$) and beta frequency band (increased) ($p = 0.0341$, $t = 2.452$, $df = 10$). There were no statistically significant differences between APP/PS1 and WT mice in the other frequency bands ($p > 0.05$).

DISCUSSION

Sleep abnormalities have been observed for decades in neurodegenerative disorders, but only recently have these changes been linked experimentally to the pathophysiology of AD and other dementias. To optimize reproducibility and the translational potential of preclinical modeling of sleep and brain network changes in AD, we quantified sleep parameters and qEEG in three widely used transgenic mouse models using commercially available, and fully integrated EEG hardware and analysis software. We demonstrate that the percentage of time spent awake, in NREM, or in REM states was not different between genotypes in Tg2576, APP/PS1, or 3xTgAD transgenic AD mice compared to non-transgenic littermate control animals. However, despite the time spent in each state being similar between genotypes,

both the Tg2576 and APP/PS1 transgenic mouse AD models exhibited stage-dependent shifts in EEG power spectra. Specifically, compared to littermate controls, the Tg2576 and APP/PS1 mice showed an overall trend towards reduced power in the lower frequencies (delta and theta) and higher power in the faster frequencies (alpha and beta). These spectral changes depended on both vigilance stage and EEG electrode placement. In Tg2576 animals, spectral changes were most pronounced during the awake state, with lower theta power seen over the frontal lobe and lower delta power over the parietal lobe (mouse hippocampus). Beta power was increased in all vigilance stages over the frontal lobe in the Tg2576 model, but only during the awake state when recording over the parietal lobe. In APP/PS1 mice there was also reduced delta and increased beta power over the frontal lobe during NREM sleep. In these mice, spectral changes during the awake state is only seen over the parietal lobe, with decreased theta power and increased beta power. The 3xTgAD mouse model did not exhibit genotype-dependent shifts in the power spectra during wake, NREM, or REM states.

Similar to our findings, the Tg2576 mouse model of AD has previously been shown to exhibit lower delta power during NREM sleep in two independent studies, with mice ranging from 6–15 months of age [21, 22]. These findings were complicated by a trend towards a reverse pattern (higher delta power) in older (17-month-old) female transgenic mice, which could be related to the more aggressive amyloid pathology related to sex [21]. Reduced delta power during awake states has been observed in TgCRND8, APP23, APP^{swe}/PS1A264E, and PDAPP mouse models, although in the studies that incorporated vigilance staging there was either no change or an increase in higher frequencies in the power spectra during NREM or REM sleep [24, 25, 29, 31]. 5xFAD mice also show decreased theta and delta power at 6 months, although vigilance stage was not considered [32]. Similar to our findings, power in higher frequency spectral bands (alpha, beta, gamma) are generally increased in both NREM sleep and awake states across AD models, with the notable exception of 5xFAD mice which show decreases in alpha and beta power at 6 months of age [32]. A single study of congenic, 4-month-old APP/PS1 mice (the model used in the present study) reported higher cortical EEG power in the 5–100 Hz frequency range in all vigilance stages [38]. Despite several studies using EEG in transgenic AD mice, to our knowledge qEEG has not been previously performed at an older age in two of the strains used here, congenic APP^{SWE}/PS1^{DE9} or 3xTgAD mice. The lack of an EEG phenotype in 18-month-old 3xTgAD mice may in part be related to a relatively mild brain amyloid pathology at the time when subtle behavioral deficits emerge, compared to APP/PS1 and Tg2576 AD mice [33], although other models with similarly low plaque loads nevertheless display changes in sleep and qEEG [27]. Future studies are required to delineate the AD-associated pathology, including tau, that is most relevant to changes in sleep and power spectra in AD.

qEEG analysis in human AD has remained relatively sparse, but the accumulating evidence suggests a dynamic process across the AD spectrum, eventually leading to sustained elevations in theta and delta power in the awake state, and a decrease in higher frequency bands (alpha and beta) [10–19]. Through advancements in AD biomarkers, particularly using amyloid and fluorodeoxyglucose (FDG) PET imaging, it is now well established that the pathologic changes in the brain leading to AD start at least 15–20 years prior to clinical symptoms [39]. The EEG signature of subjects destined to get AD would be expected to

evolve along the same continuum. Interestingly, two independent studies of patients with MCI, totaling 137 subjects, found decreased delta power over the temporal regions during awake states [10, 12]. While this has not been replicated in all MCI studies, with some reporting either no change or increased theta and delta power [13, 14, 17, 40, 41], these findings nevertheless suggest that there may be a window along the AD spectrum where a decrease in lower frequency power spectra predominate. In further support of these findings, amnesic MCI patients may have lower delta and theta power during sleep, compared to age-matched controls [42]. Moreover, advancing age is associated with a decrease in delta, theta, and sigma power during sleep [43–45] and delta and theta power during sleep were found to be positively correlated with memory recall in amnesic MCI patients, suggesting that the reduced slow wave power is associated with cognitive decline [42].

The underlying mechanisms linking qEEG findings in AD transgenic mice and patients with MCI are not fully elucidated. Reduced delta power in MCI has been hypothesized to involve a period of enhanced cholinergic output in the brain, perhaps as a compensatory response to ongoing neurodegeneration [10]. This is further supported by findings in an autopsy series from MCI and AD patients showing increased acetylcholine transferase, an enzyme responsible for the synthesis of acetylcholine, in MCI compared to AD [46]. Moreover, administering the anticholinergic drug scopolamine to healthy individuals leads to an increase in EEG delta power [47], and boosting acetylcholine through the use of cholinesterase inhibitors for the treatment of AD decreases EEG slow-wave power in this patient group [48–50]. While these findings are of great interest, similar increases in cholinergic transmission have not been demonstrated across AD transgenic mice [51–54], and thus the spectral changes reported in the present work likely involve mechanisms beyond the cholinergic system. Future studies will be required to further elucidate these mechanisms, with a particular focus on those that are shared between preclinical models and human subjects.

While we report relatively robust and consistent transgene-dependent changes in the power spectra across several AD mouse models, total time spent awake, or in NREM or REM sleep did not differ in transgenic mice compared to wildtype littermates. This contrasts with increased wakefulness and/or decreased REM/NREM sleep reported in other models, including Tg2576 [21, 22], APP_{SWE}/PS1_{A264E} [24], mixed background APP_{SWE}/PS1_{ΔE9} [26], TgCRND8 [29], PLB1_{Triple} [27], 5xFAD [32], and PDAPP [55]. Sleep architecture has not previously been studied in congenic APP_{SWE}/PS1_{ΔE9} or 3xTgAD mice, so a direct comparison to our results is not possible. In a study of Tg2576 mice up to 17 months of age, no changes were seen in total time spent awake or in NREM or REM sleep, which is consistent with our findings. However, in female Tg2576 mice, REM sleep quantity was reportedly decreased at 22 months of age. Another study of Tg2576 mice showed isolated decreases in REM sleep starting at 6 months of age [22]. Similar to varying qEEG results even within the same mouse model, the difference in sleep staging across AD models is likely in part due to different methodologies. One potential limitation of the present study is REM sleep scoring was conducted without EMG data, although rigorous manual scoring of an entire 24-h period in each mouse also strengthens our results. In contrast to qEEG, we conclude that with the standardized methods used here, APP/PS1, Tg2576, or 3xTgAD mouse models of AD do not have a robust deficit in relative time spent awake or in REM/

NREM sleep at an age where both behavioral impairment and AD-like pathology have emerged.

There are several limitations to the present study. First, we did not conduct a prospective qEEG analysis at different ages, which could potentially miss a phenotype only emerging at a later age. Our study was not designed to fully assess sex-specific differences in sleep and EEG power, and whether one sex drives the phenotypes reported here. We also recognize that a direct comparison between the models used here is challenging given their differences in genetic background and transgenes.

In summary, we report a comprehensive assessment of sleep and qEEG in three commonly used mouse models of AD using readily available EEG hardware and analytical software. These measures have not previously been shown in congenic APP/PS1 and 3xTgAD mice, while several findings in Tg2576 reported here are consistent with previous work in this model. Given the wide availability of the methods and equipment used in this study, we anticipate better consistency of results across research laboratories if using the same approach. Sleep and qEEG analysis are promising translational measures in AD, and future work will further delineate their value as outcome measures in both AD animal studies and therapeutic clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Percentage of time spent awake, in NREM, or in REM in transgenic AD mice. No differences between the transgenic AD mice compared to wildtype control animals were seen in the percentage of time spent in awake, in NREM, or in REM sleep over a 24 h period for the 3xTgAD (A-C), Tg2576 (D-F), or APP/PS1 (G-I) mouse models of AD. All data are expressed as mean $\pm$ SEM.

Fig. 2.

Frontal EEG power spectra for 3xTgAD (A-C), Tg2576 (D-F), and APP/PS1 (G-I) mouse models. Normalized power for the 24 h EEG recording during wake (left column), NREM (middle column), and REM (right column). The Tg2576 mice exhibit shifts in the frontal EEG power spectra during wake, NREM, and REM. The APP/PS1 mice show a shift in the frontal EEG power spectra during NREM. Data expressed as percent of total power across frequencies 0.1–30 Hz. All data are expressed as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$ interaction, two-way ANOVA.

Fig. 3.

Parietal EEG power spectra for 3xTgAD (A-C), Tg2576 (D-F), and APP/PS1 (G-I) mouse models. Normalized power for the 24 h EEG recording during wake (left column), NREM (middle column), and REM (right column). The Tg2576 exhibit a shift in the parietal EEG power spectra during wake. The APP/PS1 exhibit a shift in the parietal EEG power spectra during wake and NREM. Data expressed as percent of total power across frequencies 0.1–30 Hz. All data are expressed as mean $\pm$ SEM. *** $p < 0.001$, **** $p < 0.0001$ interaction, two-way ANOVA.

Fig. 4.

Binned, stage-dependent power spectra in Tg2576 mice. Tg2576 power comparison for delta (0.1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–20 Hz), and low gamma (20–30 Hz) frequency bands for the frontal EEG during wake (A–E), NREM (F–J), and REM (K–O), and for the parietal EEG during wake (P–T). In the frontal EEG, the Tg2576 mice exhibited lower power in the theta (B) frequency band and higher power in the beta (D) and low gamma (E) frequency bands during wake and higher power in the beta (N) and low gamma (O) frequency bands during REM, compared to the WT mice. In the parietal EEG, the Tg2576 mice exhibited lower power in the delta (P) frequency band and higher power in the beta (S) and low gamma (T) frequency bands during wake, compared to the WT mice. All data are expressed as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$ independent t -test.

Fig. 5.

Binned, stage-dependent power spectra in APP/PS1 mice. APP/PS1 power band comparisons for delta (0.1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–20 Hz), and low gamma (20–30 Hz) frequencies for the frontal EEG during NREM (A-E) and the parietal EEG during wake (F-J) and NREM (K-O). The APP/PS1 mice exhibited higher beta (D) and gamma (E) frequency band power during NREM in the frontal EEG and higher beta power during wake in the parietal EEG (I). During NREM the APP/PS1 exhibit less power in the delta (K) frequency band and higher power in the beta frequency band (N) in the parietal EEG. All data are expressed as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$ independent t -test.