

Supplementary Information

Supplementary Figure 1: Stereotaxic EEG electrode placement. **A)** One epidural, differential electrode is placed on the motor cortex (M1), an additional intrahippocampal differential electrode is placed in the CA1 region of the hippocampus. Both pseudoreference electrodes are localized on the cerebellum. **B)** Coronal section (scheme) illustrating the localisation of the deep, intracranial electrode for recording the electrohippocampogram. **C)** Close-up of the deep EEG electrode, the sensing lead of the radiofrequency transmitter and their arrangement on top of the murine skull.

Supplementary Figure 2: Characteristics of theta amplitude in control and 5XFAD mice. The theta-alpha band was analyzed using a time-frequency approach. Behavioral artefacts were removed using an algorithm as described above. Amplitude was calculated for both genotypes for the total observation period (**A**) and the light (**B**) and dark (**C**) phase, respectively. Total and phase-specific analysis was also done for non-motor activity (**D-F**) and motor activity (not shown). No difference was observed between both genotypes.

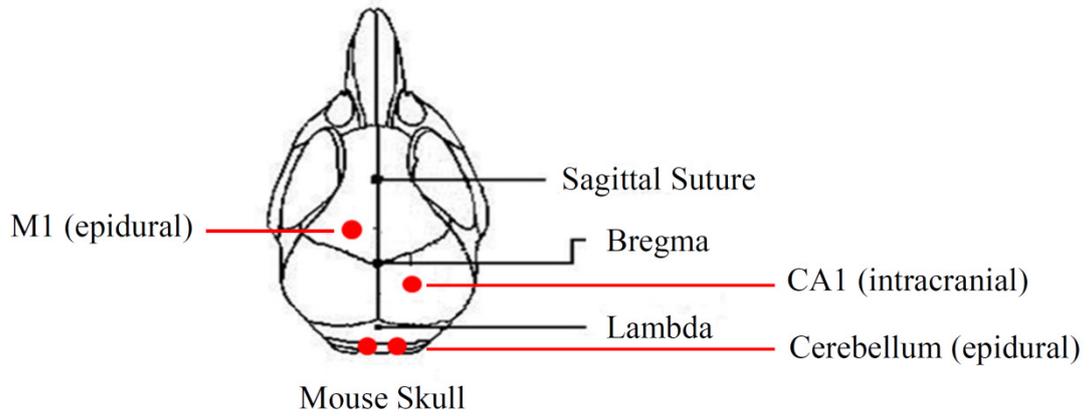
Supplementary Figure 3: Functional integration of seizure activity and theta oscillations. Time-frequency analysis in 5XFAD mice revealed changes in theta duration and theta frequency which are not related to motor activity, particularly during the dark phase. Under these conditions, animals are either at sleep or at rest. Hippocampal activity during the state of alert immobility is characterized by atropine-sensitive type II theta, which is related to the muscarinic signal transduction pathway. Activation of PLC was shown to enhance Ca^{2+} influx via $\text{Ca}_v2.3$ R-type Ca^{2+} channels which can lead to the generation of

epileptiform burst activity via CNG mediated plateau potentials. However, Ca_v2.3 R-type Ca²⁺ channels were also shown to be involved in the generation of hippocampal theta oscillations.

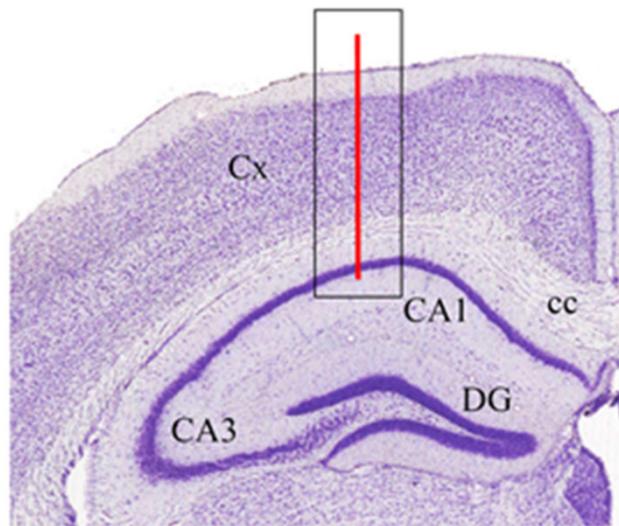
Supplementary Table 1: Representation of interesting candidate genes based on microarray analysis. The absolute fold change (AFC) between transgenic 5XFAD (TG) mice and WT control littermates.

Supplementary Table 2: Presentation of candidate genes based on microarray analysis with absolute fold change (AFC) > 2 between transgenic 5XFAD (TG) mice and WT control littermates (WT). Gene ontology analysis revealed that the strongest transcriptional alterations belong to immune-response and inflammation related genes observed in the context of late-stage cerebral amyloidosis.

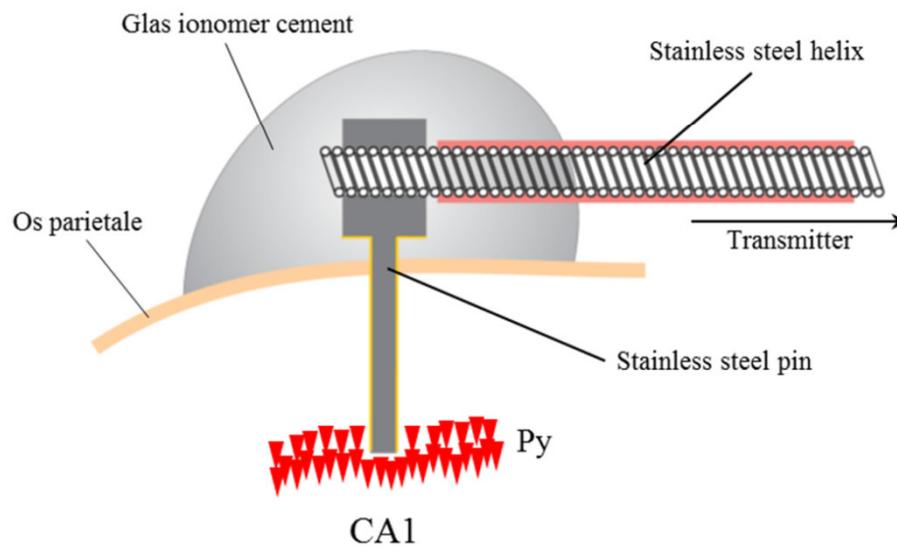
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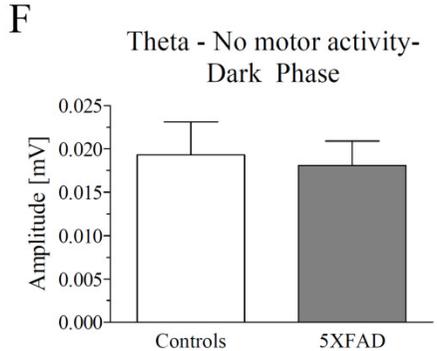
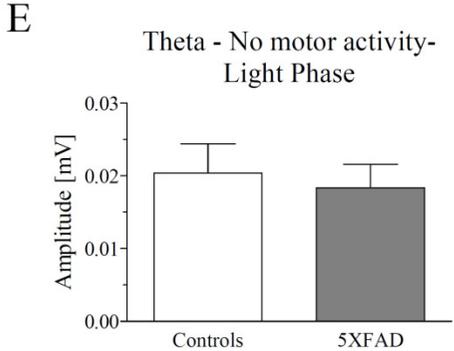
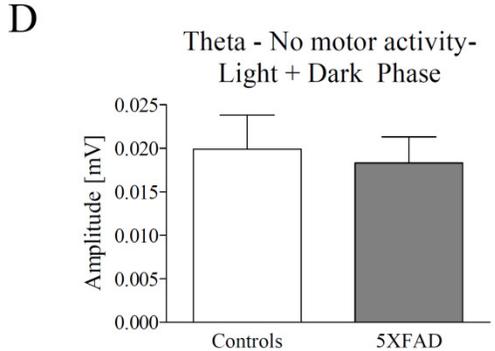
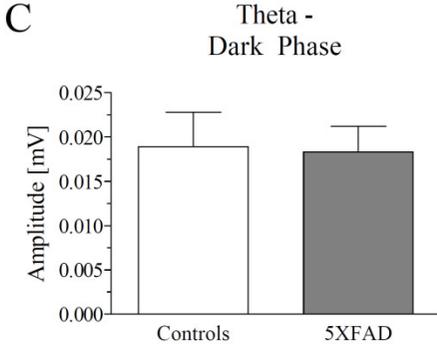
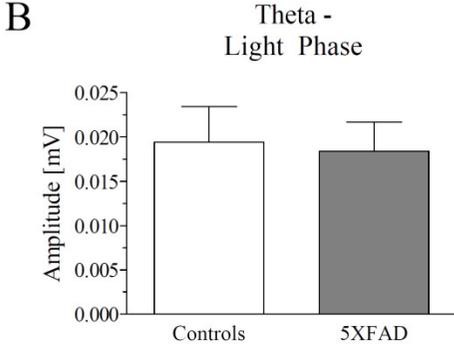
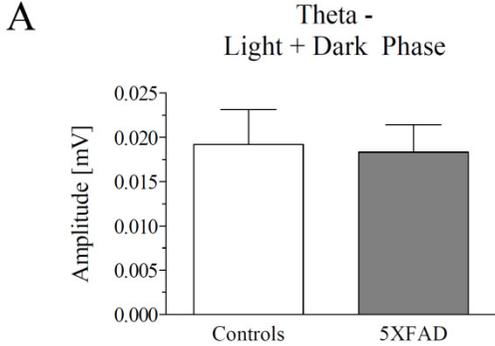


B



C





Supplementary Table 1:

Representation of interesting candidate genes revealed from microarray analysis. Absolute fold change (AFC) between transgenic Alzheimer's 5XFAD mice (TG) and wild type control littermates (WT).

AFC TG vs WT	Regulation	Candidate Genes
1.1079566	down	Cacna2d1, Calcium Channel, L Type, Alpha
1.1112925	down	Cacna1e, Cav2.3 calcium channel
1.1162357	up	Cacng5, calcium channel, voltage-dependent, gamma subunit 5
1.2483352	down	Cacng2, calcium channel, voltage-dependent, gamma subunit 2
1.2776582	down	Kcna4, potassium voltage-gated channel
1.1231822	down	Kcnab1, potassium voltage-gated channel
1.0865682	down	Kcne4, potassium voltage-gated channel, Isk-related family, member 4
1.3661991	down	Kcnh5, potassium voltage-gated channel, subfamily H (eag-related), member 5
1.4835429	down	Kcnh7, potassium voltage channel, subfamily H, member 7
1.1978878	down	Kcnip4, potassium channel interacting protein
1.1670644	down	Kcnj11, potassium inwardly-rectifying channel, subfamily J, member 11
1.0783806	down	Kcnma1, potassium large conductance calcium-activated channel, subfamily M, α 1
1.2284602	down	Kcnn2, potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2
1.2311752	down	Kcnq3, potassium voltage-gated channel, KQT-like subfamily, member 3
1.1255795	down	Scn8a, sodium channel, voltage-gated, type VIII, alpha
1.0604281	up	Ank, progressive ankylosis protein
1.1039068	down	Ankra2, ankyrin repeat, family A (RFXANK-like), 2
1.2761725	up	Ankrd13a, ankyrin repeat domain 13A
1.7455606	down	Ankrd34c, ankyrin repeat domain 34C
1.1975257	down	Ankrd43, ankyrin repeat domain-containing protein 43
1.1477777	down	Ankzf1, ankyrin repeat and zinc finger domain containing 1
1.1017654	up	Aplp2, amyloid beta (A4) precursor-like protein 2
1.0611709	down	Calm2, calmodulin 2
1.4713943	up	Chrm5, cholinergic receptor, muscarinic 5
1.158719	up	Eef1b2, eukaryotic translation elongation factor 1 beta 2
1.1446922	down	Gabra4, gamma-aminobutyric acid (GABA) A receptor, subunit alpha 4
1.2972732	down	Gabbr2, gamma-aminobutyric acid (GABA) A receptor, subunit beta 2
1.0849586	down	Gabbr3, gamma-aminobutyric acid (GABA) A receptor, subunit beta 3

1.0767342	down	Gria3, AMPA-selective glutamate receptor 3
1.185587	down	Gria4, AMPA-selective glutamate receptor 4
1.1791353	down	Grid1 Mir346, gluR delta-1 subunit
1.1244333	down	Grin2a, N-methyl D-aspartate receptor subtype 2A
1.1251612	down	Grin2b, N-methyl D-aspartate receptor 2B
1.0896682	down	Kank3, KN motif and ankyrin repeat domains 3
1.1632725	down	Negr1, neuronal growth regulator 1
1.1632118	down	Pde1b, phosphodiesterase 1B, Ca ²⁺ -calmodulin dependent
1.149241	down	Plcb1, phospholipase C, beta 1
1.1644183	up	Plcb3, phospholipase C, beta 3
1.2514523	up	Plcd4 Zfp142, phospholipase C, delta 4, PLC-delta-4
1.9414148	up	Plce1, phospholipase C, epsilon
1.2460053	up	Plcg2, phospholipase C, gamma 2
1.1797961	down	Prkar2b, protein kinase, cAMP dependent regulatory, type II beta
1.1495365	down	Prkcb, protein kinase C, beta
1.1005048	up	Prkx, protein kinase PKX1
1.1885214	up	Rapgef3, Rap1 guanine-nucleotide-exchange factor directly activated by cAMP
1.2769251	down	Scg2, secretogranin II
1.1976677	down	Stx1b, syntaxin-1B
1.5812538	up	Syng2, synaptogyrin 2
1.2852507	down	Trank1, tetratricopeptide repeat and ankyrin repeat containing 1
1.5507693	up	Vamp8, vesicle-associated membrane protein 8
1.5849916	up	Casp8, Caspase 8
1.4427319	up	Cflar, Casp8 and FADD-like apoptosis regulator

Supplementary Table 2:

Presentation of candidate genes revealed from microarray analysis with absolute fold change (AFC) ≥ 2 between transgenic Alzheimer's 5XFAD (TG) mice and wild type control littermates (WT).

AFC TG vs WT	Regulation	Candidate Genes
30,691187	up	Cst7, cystatin F (leukocystatin); 2310001A20Rik, RIKEN cDNA 2310001A20 gene
25,800545	up	Cst7, cystatin F (leukocystatin); 2310001A20Rik, RIKEN cDNA 2310001A20 gene
11,236571	up	Ccl3, chemokine (C-C motif) ligand 3
6,5900187	up	Gpnmb, glycoprotein (transmembrane) nmb
6,0320563	up	Olf111, olfactory receptor 111; Olf110, olfactory receptor 110
4,5509095	up	Lyz2, lysozyme 2; Lyz1, lysozyme 1
4,509695	up	Tyrobp, TYRO protein tyrosine kinase binding protein
4,4565377	up	CD68 antigen
4,2304597	up	Serpina3nm, serine (or cysteine) peptidase inhibitor, clade A, member 3N
4,0053725	up	Osmr, oncostatin M receptor
3,980827	up	Trem2, triggering receptor expressed on myeloid cells 2
3,9256482	up	Gfap, glial fibrillary acidic protein
3,8248506	up	C3ar1, complement component 3a receptor 1
3,6593776	up	Ly86, lymphocyte antigen 86; Igsf21, immunoglobulin superfamily, member 21
3,6451392	up	Clec7a, C-type lectin domain family 7, member a
3,6262984	up	C4b, complement component 4B (Childo blood group); C4a, complement component 4A (Rodgers blood group)
3,5611908	up	Itgax, integrin alpha X; Mcart1, mitochondrial carrier triple repeat 1; Itgad, integrin, alpha D
3,4145424	up	Lilrb4, leukocyte immunoglobulin-like receptor, subfamily B, member 4; Gp49a, glycoprotein 49 A
3,4005163	up	CD180 antigen
3,2523582	up	CD84 antigen
3,074628	up	Ctss, cathepsin S
3,0741098	up	Fcer1g, Fc receptor, IgE, high affinity I, gamma polypeptide
3,0641675	up	Fcgr3, Fc receptor, IgG, low affinity III
3,0616438	up	Lgals3bp, lectin, galactoside-binding, soluble, 3 binding protein
3,0302508	up	C1qc, complement component 1, q subcomponent, C chain
2,9237657	up	C1qb, complement component 1, q subcomponent, beta polypeptide
2,905447	up	Laptm5, lysosomal-associated protein transmembrane 5
2,8482487	up	C1qa, complement component 1, q subcomponent, alpha polypeptide
2,8451812	up	Fcgr2b, Fc receptor, IgG, low affinity IIb

2,8256595	up	Ctsd, cathepsin D
2,8111982	up	Plek, pleckstrin
2,8064747	up	Ctsz, cathepsin Z
2,7769005	up	Hexb, hexosaminidase B
2,7556384	up	Tlr7, toll-like receptor 7
2,615431	up	Bcl2a1d, B-cell leukemia/lymphoma 2 related protein A1d; Bcl2a1b, B-cell leukemia/lymphoma 2 related protein A1b; Bcl2a1a, B-cell leukemia/lymphoma 2 related protein A1a
2,543658	up	Slc11a1, solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1
2,4172409	up	CD52 antigen
2,4062214	up	CD9 antigen
2,3877494	up	Slc14a1, solute carrier family 14 (urea transporter), member 1
2,385867	up	CD53 antigen
2,3474405	up	Cybb, cytochrome b-245, beta polypeptide
2,3225377	up	Lcn2, lipocalin 2
2,3032408	up	Hvcn1, hydrogen voltage-gated channel 1; Tctn1, tectonic family member 1
2,2871568	up	Gp49a, glycoprotein 49 A; AB056442, cDNA sequence AB056442; Lilrb4, leukocyte immunoglobulin-like receptor, subfamily B, member 4; D630002G06Rik, RIKEN cDNA D630002G06 gene
2,2849452	up	Csf3r, colony stimulating factor 3 receptor (granulocyte)
2,2655497	up	Gm11428, predicted gene 11428
2,2569838	up	Irf8, interferon regulatory factor 8
2,231863	up	H2-K1, histocompatibility 2, K1K region; Gm7035, predicted gene 7035; H2-Q2, histocompatibility 2, Q region locus 2; LOC100044874, similar to H-2K(d) antigen
2,2273088	up	Cybrd1, cytochrome b reductase 1
2,1967485	up	Tlr13, toll-like receptor 13
2,1918335	up	4632428N05Rik, RIKEN cDNA 4632428N05 gene
2,191425	up	Cx3cr1, chemokine (C-X3-C) receptor 1
2,182198	up	H2-D1, histocompatibility 2, D region locus 1; H2-Q2, histocompatibility 2, Q region locus 2; H2-L, histocompatibility 2, L region; H2-K1, histocompatibility 2, K1, K region
2,1029935	up	Hpgds, hematopoietic prostaglandin D synthase
2,0661345	up	Nckap11, NCK associated protein 1 like
2,040309	up	Csflr, colony stimulating factor 1 receptor
2,0336578	up	Havcr2, hepatitis A virus cellular receptor 2
2,0043225	up	Man2b1, mannosidase 2, alpha B1
2,001403	up	Trf, transferrin