

Table S1. List of abbreviations for endocannabinoid system, gliosis and inflammation-related genes, their protein products, and corresponding functions.

Gene	Protein	Full Name / Function
<i>Cnr1</i>	CB1	Cannabinoid receptor type 1 – Mainly found in the central nervous system, involved in modulating neurotransmitter release.
<i>Cnr2</i>	CB2	Cannabinoid receptor type 2 – Primarily expressed in immune cells, involved in immune regulation and inflammation.
<i>Ppara</i>	PPAR α	Peroxisome proliferator-activated receptor alpha – Regulates lipid metabolism and inflammation.
<i>Nape-pld</i>	NAPE-PLD	N-acyl phosphatidylethanolamine phospholipase D – Key enzyme in the biosynthesis of N-acylethanolamines, including anandamide (AEA).
<i>Dagla</i>	DAGL α	Diacylglycerol lipase alpha – Enzyme responsible for the biosynthesis of 2-arachidonoylglycerol (2-AG), an endocannabinoid.
<i>Daglb</i>	DAGL β	Diacylglycerol lipase beta – Another enzyme involved in 2-AG production, with a role in immune system regulation.
<i>Faah</i>	FAAH	Fatty acid amide hydrolase – Enzyme that degrades anandamide (AEA), terminating its signaling activity.
<i>Mgll</i>	MAGL	Monoacylglycerol lipase – Enzyme that breaks down 2-AG, regulating endocannabinoid signaling.

Gene	Protein	Full Name / Function
<i>Iba1</i>	IBA1	Ionized calcium-binding adapter molecule 1 – Microglial activation marker, involved in neuroinflammation.
<i>Gfap</i>	GFAP	Glial fibrillary acidic protein – Astrocyte marker, key for gliosis and astrocyte response to injury.
<i>Mrc1</i>	MRC1	Mannose receptor C-type 1 – Involved in microglial/macrophage function and endocytosis.
<i>Fcgr2b</i>	Fc γ RIIb	Fc gamma receptor IIb – Regulates immune responses, inhibits excessive inflammation.
<i>Vimentin</i>	VIM	Vimentin – Intermediate filament protein, involved in astrocyte cytoskeleton organization and gliosis.

Gene	Protein	Full Name / Function
<i>Il1b</i>	IL-1 β	Interleukin-1 beta – Key pro-inflammatory cytokine, mediates immune and inflammatory responses.
<i>Ikbkb</i>	IKK β	Inhibitor of nuclear factor kappa-B kinase subunit beta – Regulates NF- κ B signaling, critical for inflammation.
<i>Nos2</i>	iNOS	Inducible nitric oxide synthase – Produces nitric oxide (NO), involved in immune defense and inflammation.
<i>Ptgs2</i>	COX-2	Prostaglandin-endoperoxide synthase 2 (Cyclooxygenase-2) – Enzyme involved in prostaglandin synthesis and inflammation.
<i>Nfkb1</i>	NF- κ B1 (p50)	NF-kappa B p50 subunit – The main activator of the classical NF- κ B pathway, regulates inflammatory gene expression.
<i>Rela</i>	RelA (p65)	NF- κ B p65 subunit – Key transcription factor regulating immune and inflammatory responses.

Table S2. Primer references for TaqMan® Gene Expression Assays

Genes	Accession no	Assay ID	Amplicon length
<i>Cnr1</i>	NM_012784.4	Rn02758689_s1	92
<i>Cnr2</i>	NM_020543.4	Rn01637601_s1	68
<i>Ppara</i>	NM_013196.1	Rn00566193_m1	98
<i>Dagla</i>	NM_001005886.1	Rn01454303_m1	61
<i>Daglβ</i>	NM_001107120.1	Rn01453770_m1	57
<i>Mgll</i>	NM_138502.2	Rn00593297_m1	78
<i>Nape-pld</i>	NM_199381.1	Rn01786262_m1	71
<i>Faah</i>	NM_024132.3	Rn00577086_m1	63
<i>Iba1 (Aif1)</i>	NM_017196.3	Rn00574125_g1	126
<i>Gfap</i>	NM_017009.2	Rn01253033_m1	75
<i>Mrc1</i>	NM_001106123.2	Rn01487342_m1	62
<i>Fcgr2b</i>	NM_175756.1	Rn01490232_m1	60
<i>Il1b</i>	NM_031512.2	Rn00580432_m1	74
<i>Ikkkb (IKKβ)</i>	NM_053355.2	Rn00584379_m1	84
<i>Nos2</i>	NM_012611.3	Rn00561646_m1	77
<i>Ptgs2 (COX2)</i>	NM_017232.3	Rn01483828_m1	112
<i>Rela (NF-κB)</i>	NM_199267.2	Rn01502266_m1	67
<i>Actb</i>	NM_031144.2	Rn00667869_m1	91

Abbreviations: *Actb*, actin beta; *Cnr1*, cannabinoid receptor 1 (brain); *Cnr2*, cannabinoid receptor 2 (macrophage); *Dagla*, diacylglycerol lipase, alpha; *Daglβ*, diacylglycerol lipase, beta; *Faah*, fatty acid amide hydrolase, *Fcgr2b*, Fc fragment of IgG, low affinity IIb, receptor; *Gfap*, glial fibrillary acidic protein; *Iba1*, ionized calcim-binding adapter molecule 1 (allograft inflammatory factor 1); *Ikkkb*, inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta; *Il1b*, interleukin 1 beta; *Mgll*, monoglyceride lipase; *Mrc1*, mannose receptor, C type 1; *Nape-pld*, N-acyl phosphatidylethanolamine phospholipase D; *Nos2*, nitric oxide synthase 2, inducible; *Ppara*, peroxisome proliferator activated receptor alpha; *Ptgs2*, prostaglandin-endoperoxide synthase 2 (cyclooxygenase-2); *Rela*, v-rel avian reticuloendotheliosis viral oncogene homolog A (nuclear factor kappa B).

Table S3. Primary antibodies used

Antigen	Immunogen	Manufacturing details	Dilution	Predicted molecular weight (kDa)
CB1	Synthetic peptide: MSVSTDTSAEAL, corresponding to C terminal amino acid 461-472 of Human Cannabinoid Receptor I.	Abcam Polyclonal IgG antibody Produced in rabbit Code No.: ab23703 RRID:AB_447623	1:200	53
CB2	Fusion proteinm corresponding to amino acids 1-32 of Rat Cannabinoid Receptor II.	Abcam Polyclonal IgG antibody Produced in rabbit Code No.: ab3561	1:200	40
PPAR α	Synthetic peptide corresponding to residues M(1)VDTESPICPLSPLEADD(18)C of mouse PPAR alpha	Fitzgerald Polyclonal IgG antibody Produced in rabbit Code No.: 20R-PR021 Lot. No.: P15092226	1:200	52
DAGL α	KLH conjugated synthetic peptide derived from human DAGLA	BioNova Polyclonal IgG antibody Produced in rabbit Code No.: orb156533	1:100	115
DAGL β	KLH conjugated synthetic peptide derived from human DAGLB	BioNova Polyclonal IgG antibody Produced in rabbit Code No.: orb182976	1:100	74
MAGL	Human monoacylglycerol lipase amino acids 1-14: MPEESSPRRTPQSI	Cayman Chemical Polyclonal IgG antibody Produced in rabbit Code No.: 100035 Lot. No.: 163084	1:200	35
NAPE-PLD	Human NAPE-PLD amino acids 6-20: SNQSLMTSSQYPKEA	Cayman Chemical Polyclonal IgG antibody Produced in rabbit Code No.: 10306	1:100	46
FAAH	Synthetic peptide from rat fatty acid amid hydrolase amino acids 561-579 (CLRFMREVEQLMTPQKQPS) conjugated to KLK	Cayman Chemical Polyclonal IgG antibody Produced in rabbit Code No.: 101600 Lot. No.: 157878	1:200	63
IBA1	Linear peptide corresponding to human Iba1/AIF1	Millipore Monoclonal IgG antibody Produced in mouse Code No.: MABN92 Lot. No.: 2383608	1:500	17
GFAP	Purified GFAP from pig spinal cord	Sigma Monoclonal IgG antibody Produced in mouse Code No.: G3893	1:500	48

VIM	Human thymic nuclear extract	Sigma Monoclonal IgG antibody Produced in mouse Code No.: V6630	1:200	58
IKK β	Synthetic peptide corresponding to residues near the carboxy terminus of human IKK β protein	CellSignaling Monoclonal IgG antibody Produced in rabbit Code No.: 8943	1:1000	87
COX2	Synthetic peptide corresponding to residues surrounding His108 of human Cox2 protein	CellSignaling Monoclonal IgG antibody Produced in rabbit Code No.: 122821	1:500	74
NF- κ B	Synthetic peptide corresponding to residues surrounding Glu498 of human NF- κ B p65/RelA protein	CellSignaling Monoclonal IgG antibody Produced in rabbit Code No.: 8242	1:1000	65
γ -Adaptin	Mouse adaptin γ amino acids 642-821	BD Biosciences Monoclonal IgG Produced in mouse Code No.: 610385	1:2000	104

Abbreviations: VIM, vimentin

Table S4. Two-way ANOVA showing interaction and main effects of dependence and drug on the mRNA expression of main components of the endocannabinoid system in the prefrontal cortex.

	Source of Variation	F (DFn, DFd)	P value
<i>Cnr1</i>	Interaction	F (2, 42) = 0.8843	ns
	Dependence	F (1, 42) = 4.239	0.0457
	Drug	F (2, 42) = 1.352	ns
<i>Cnr2</i>	Interaction	F (2, 42) = 6.722	0.0029
	Dependence	F (1, 42) = 12.95	0.0008
	Drug	F (2, 42) = 2.284	ns
<i>Ppara</i>	Interaction	F (2, 42) = 0.5126	ns
	Dependence	F (1, 42) = 30.59	<0.0001
	Drug	F (2, 42) = 3.923	0.0274
<i>Dagla</i>	Interaction	F (2, 42) = 2.842	0.0695
	Dependence	F (1, 42) = 0.4525	ns
	Drug	F (2, 42) = 0.6112	ns
<i>Daglb</i>	Interaction	F (2, 42) = 4.076	0.0241
	Dependence	F (1, 42) = 9.870	0.0031
	Drug	F (2, 42) = 0.4598	ns
<i>Mgll</i>	Interaction	F (2, 42) = 2.896	0.0663
	Dependence	F (1, 42) = 0.9844	ns
	Drug	F (2, 42) = 0.5993	ns
<i>Napepld</i>	Interaction	F (2, 42) = 1.811	ns
	Dependence	F (1, 42) = 0.8492	ns
	Drug	F (2, 42) = 0.1386	ns
<i>Faah</i>	Interaction	F (2, 42) = 4.234	0.0211
	Dependence	F (1, 42) = 8.965	0.0046
	Drug	F (2, 42) = 1.121	ns

ns, not significant

Table S5. Two-way ANOVA showing interaction and main effects of dependence and drug on the protein levels of main components of the endocannabinoid system in the prefrontal cortex.

	Source of Variation	F (DFn, DFd)	P value
CB1	Interaction	F (2, 19) = 0.331	ns
	Dependence	F (1, 19) = 7.750	0.0118
	Drug	F (2, 19) = 11.45	0.0005
CB2	Interaction	F (2, 19) = 1.812	ns
	Dependence	F (1, 19) = 6.828	0.0171
	Drug	F (2, 19) = 6.496	0.0071
PPAR α	Interaction	F (2, 19) = 12.15	0.0004
	Dependence	F (1, 19) = 0.038	ns
	Drug	F (2, 19) = 4.183	0.0312
DAGL α	Interaction	F (2, 19) = 2.829	ns
	Dependence	F (1, 19) = 27.19	<0.0001
	Drug	F (2, 19) = 3.681	0.0445
DAGL β	Interaction	F (2, 19) = 7.568	0.0038
	Dependence	F (1, 19) = 1.653	ns
	Drug	F (2, 19) = 12.44	0.0004
MAGL	Interaction	F (2, 19) = 5.977	0.0097
	Dependence	F (1, 19) = 88.41	<0.0001
	Drug	F (2, 19) = 29.48	<0.0001
NAPE-PLD	Interaction	F (2, 19) = 12.37	0.0004
	Dependence	F (1, 19) = 0.807	ns
	Drug	F (2, 19) = 2.955	ns
FAAH	Interaction	F (2, 19) = 44.71	<0.0001
	Dependence	F (1, 19) = 38.53	<0.0001
	Drug	F (2, 19) = 3.940	0.037

ns, not significant

Table S6. Two-way ANOVA showing interaction and main effects of dependence and drug on the mRNA expression of main components of gliosis and inflammation in the prefrontal cortex.

	Source of Variation	F (DFn, DFd)	P value
<i>Iba1</i>	Interaction	F (2, 42) = 0.591	ns
	Dependence	F (1, 42) = 1.427	ns
	Drug	F (2, 42) = 0.056	ns
<i>Gfap</i>	Interaction	F (2, 42) = 3.014	0.0598
	Dependence	F (1, 42) = 0.295	ns
	Drug	F (2, 42) = 1.284	ns
<i>Mrc1</i>	Interaction	F (2, 42) = 0.647	ns
	Dependence	F (1, 42) = 12.58	0.001
	Drug	F (2, 42) = 0.766	ns
<i>Fcgr2b</i>	Interaction	F (2, 42) = 0.944	ns
	Dependence	F (1, 42) = 0.937	ns
	Drug	F (2, 42) = 4.159	0.0225
<i>Il1b</i>	Interaction	F (2, 42) = 0.738	ns
	Dependence	F (1, 42) = 6.953	0.0117
	Drug	F (2, 42) = 1.341	ns
<i>Ikbkb</i>	Interaction	F (2, 42) = 3.520	0.0386
	Dependence	F (1, 42) = 8.359	0.0061
	Drug	F (2, 42) = 0.012	ns
<i>Nos2</i>	Interaction	F (2, 42) = 2.319	ns
	Dependence	F (1, 42) = 9.709	0.0033
	Drug	F (2, 42) = 0.320	ns
<i>Ptgs2</i>	Interaction	F (2, 42) = 2.800	ns
	Dependence	F (1, 42) = 13.83	0.0006
	Drug	F (2, 42) = 3.653	0.0344
<i>Rela</i>	Interaction	F (2, 42) = 3.501	0.0392
	Dependence	F (1, 42) = 5.645	0.0221
	Drug	F (2, 42) = 5.187	0.0097

ns, not significant

Table S7. Two-way ANOVA showing interaction and main effects of dependence and drug on the protein levels of main components of gliosis and inflammation in the prefrontal cortex.

	Source of Variation	F (DFn, DFd)	P value
IBA1	Interaction	F (2, 19) = 13.32	0.0002
	Dependence	F (1, 19) = 34.40	<0.0001
	Drug	F (2, 19) = 0.883	ns
GFAP	Interaction	F (2, 19) = 6.839	0.0058
	Dependence	F (1, 19) = 2.779	ns
	Drug	F (2, 19) = 3.212	0.0628
Vimentin	Interaction	F (2, 19) = 2.544	ns
	Dependence	F (1, 19) = 0.042	ns
	Drug	F (2, 19) = 20.78	<0.0001
COX2	Interaction	F (2, 19) = 0.625	ns
	Dependence	F (1, 19) = 0.0003	ns
	Drug	F (2, 19) = 2.431	ns
NF-κB	Interaction	F (2, 19) = 6.111	0.0089
	Dependence	F (1, 19) = 4.425	0.049
	Drug	F (2, 19) = 8.371	0.0025
IKKβ	Interaction	F (2, 19) = 17.87	<0.0001
	Dependence	F (1, 19) = 48.89	<0.0001
	Drug	F (2, 19) = 39.09	<0.0001

ns, not significant

Table S8. Two-way ANOVA showing interaction and main effects of dependence and drug on the mRNA expression of main components of the endocannabinoid system in the hippocampus.

	Source of Variation	F (DFn, DFd)	P value
<i>Cnr1</i>	Interaction	F (2, 42) = 0.148	ns
	Dependence	F (1, 42) = 1.739	ns
	Drug	F (2, 42) = 2.338	ns
<i>Cnr2</i>	Interaction	F (2, 42) = 12.25	<0.0001
	Dependence	F (1, 42) = 0.648	ns
	Drug	F (2, 42) = 3.481	0.0399
<i>Ppara</i>	Interaction	F (2, 42) = 2.449	ns
	Dependence	F (1, 42) = 12.20	0.0011
	Drug	F (2, 42) = 3.701	0.0331
<i>Dagla</i>	Interaction	F (2, 42) = 2.161	ns
	Dependence	F (1, 42) = 17.49	0.0001
	Drug	F (2, 42) = 2.620	ns
<i>Daglb</i>	Interaction	F (2, 42) = 4.609	0.0155
	Dependence	F (1, 42) = 2.889	ns
	Drug	F (2, 42) = 0.153	ns
<i>Mgll</i>	Interaction	F (2, 42) = 6.569	0.0033
	Dependence	F (1, 42) = 103.2	<0.0001
	Drug	F (2, 42) = 0.147	ns
<i>Napepld</i>	Interaction	F (2, 42) = 0.906	ns
	Dependence	F (1, 42) = 0.674	ns
	Drug	F (2, 42) = 1.688	ns
<i>Faah</i>	Interaction	F (2, 42) = 12.85	<0.0001
	Dependence	F (1, 42) = 1.203	ns
	Drug	F (2, 42) = 0.475	ns

ns, not significant

Table S9. Two-way ANOVA showing interaction and main effects of dependence and drug on the protein levels of main components of the endocannabinoid system in the hippocampus.

	Source of Variation	F (DFn, DFd)	P value
CB1	Interaction	F (2, 19) = 10.70	0.0008
	Dependence	F (1, 19) = 0.372	ns
	Drug	F (2, 19) = 2.667	ns
CB2	Interaction	F (2, 19) = 0.545	ns
	Dependence	F (1, 19) = 10.51	0.0043
	Drug	F (2, 19) = 0.030	ns
PPAR α	Interaction	F (2, 19) = 1.926	ns
	Dependence	F (1, 19) = 8.540	0.0087
	Drug	F (2, 19) = 0.662	ns
DAGL α	Interaction	F (2, 19) = 2.860	ns
	Dependence	F (1, 19) = 2.388	ns
	Drug	F (2, 19) = 18.32	<0.0001
DAGL β	Interaction	F (2, 19) = 3.168	0.065
	Dependence	F (1, 19) = 1.020	ns
	Drug	F (2, 19) = 4.578	0.0238
MAGL	Interaction	F (2, 19) = 1.040	ns
	Dependence	F (1, 19) = 4.128	0.0564
	Drug	F (2, 19) = 1.005	ns
NAPE-PLD	Interaction	F (2, 19) = 1.250	ns
	Dependence	F (1, 19) = 3.070	ns
	Drug	F (2, 19) = 1.818	ns
FAAH	Interaction	F (2, 19) = 1.809	ns
	Dependence	F (1, 19) = 0.167	ns
	Drug	F (2, 19) = 2.164	ns

ns, not significant

Table S10. Two-way ANOVA showing interaction and main effects of dependence and drug on the mRNA expression of main components of gliosis and inflammation in the hippocampus.

	Source of Variation	F (DFn, DFd)	P value
<i>Iba1</i>	Interaction	F (2, 42) = 1.358	ns
	Dependence	F (1, 42) = 17.72	0.0001
	Drug	F (2, 42) = 1.721	ns
<i>Gfap</i>	Interaction	F (2, 42) = 4.172	0.0222
	Dependence	F (1, 42) = 20.28	<0.0001
	Drug	F (2, 42) = 1.886	ns
<i>Mrc1</i>	Interaction	F (2, 42) = 0.842	ns
	Dependence	F (1, 42) = 12.41	0.001
	Drug	F (2, 42) = 5.032	0.011
<i>Fcgr2b</i>	Interaction	F (2, 42) = 5.496	0.0076
	Dependence	F (1, 42) = 0.453	ns
	Drug	F (2, 42) = 3.621	0.0354
<i>Il1b</i>	Interaction	F (2, 42) = 0.360	ns
	Dependence	F (1, 42) = 17.10	0.0002
	Drug	F (2, 42) = 1.891	ns
<i>Ikbkb</i>	Interaction	F (2, 42) = 3.770	0.0312
	Dependence	F (1, 42) = 148.6	<0.0001
	Drug	F (2, 42) = 0.473	ns
<i>Nos2</i>	Interaction	F (2, 42) = 8.321	0.0009
	Dependence	F (1, 42) = 9.949	0.003
	Drug	F (2, 42) = 3.769	0.0312
<i>Ptgs2</i>	Interaction	F (2, 42) = 0.836	ns
	Dependence	F (1, 42) = 25.65	<0.0001
	Drug	F (2, 42) = 0.063	ns
<i>Rela</i>	Interaction	F (2, 42) = 3.150	0.0531
	Dependence	F (1, 42) = 20.46	<0.0001
	Drug	F (2, 42) = 19.88	<0.0001

ns, not significant

Table S11. Two-way ANOVA showing interaction and main effects of dependence and drug on the protein levels of main components of gliosis and inflammation in the hippocampus.

	Source of Variation	F (DFn, DFd)	P value
IBA1	Interaction	F (2, 19) = 2.639	ns
	Dependence	F (1, 19) = 22.31	0.0001
	Drug	F (2, 19) = 6.472	0.0072
GFAP	Interaction	F (2, 19) = 1.211	ns
	Dependence	F (1, 19) = 6.005	0.0241
	Drug	F (2, 19) = 2.031	ns
Vimentin	Interaction	F (2, 19) = 2.544	ns
	Dependence	F (1, 19) = 0.042	ns
	Drug	F (2, 19) = 20.78	<0.0001
COX2	Interaction	F (2, 19) = 1.131	ns
	Dependence	F (1, 19) = 5.926	0.0249
	Drug	F (2, 19) = 7.690	0.0036
NF-κB	Interaction	F (2, 19) = 3.595	0.0474
	Dependence	F (1, 19) = 0.164	ns
	Drug	F (2, 19) = 0.603	ns
IKKβ	Interaction	F (2, 19) = 1.064	ns
	Dependence	F (1, 19) = 6.136	0.0228
	Drug	F (2, 19) = 4.498	0.0252

ns, not significant

Table S12. Corresponding p values for Spearman correlation of genes corresponding to the endocannabinoid system, gliosis and inflammation during repeated administration of WIN 55,212-2 and HU-210 in the prefrontal cortex.

	<i>Cnr1</i>	<i>Cnr2</i>	<i>Ppara</i>	<i>Dagla</i>	<i>Daglb</i>	<i>Mgll</i>	<i>Napepld</i>	<i>Faah</i>	<i>Iba1</i>	<i>Gfap</i>	<i>Mrc1</i>	<i>Fcgr2b</i>	<i>Il1b</i>	<i>Ikbkb</i>	<i>Nos2</i>	<i>Ptgs2</i>	<i>Rela</i>
<i>Cnr1</i>		0.496	0.125	0.031	0.029	0.033	0.002	0.011	0.237	0.011	0.525	0.953	0.360	0.035	0.048	0.412	0.060
<i>Cnr2</i>	0.496		0.548	0.498	0.134	0.942	0.673	0.351	0.304	0.820	0.304	0.809	0.402	0.851	0.787	0.204	0.074
<i>Ppara</i>	0.125	0.548		0.475	0.347	0.174	0.070	0.360	0.239	0.000	0.037	0.581	0.090	0.014	0.375	0.450	0.576
<i>Dagla</i>	0.031	0.498	0.475		0.013	0.000	0.185	0.000	0.082	0.465	0.974	0.682	0.974	0.000	0.000	0.004	0.048
<i>Daglb</i>	0.029	0.134	0.347	0.013		0.044	0.262	0.043	0.527	0.146	0.713	0.605	0.965	0.008	0.015	0.560	0.000
<i>Mgll</i>	0.033	0.942	0.174	0.000	0.044		0.281	0.000	0.131	0.240	0.310	0.689	0.453	0.000	0.001	0.019	0.043
<i>Napepld</i>	0.002	0.673	0.070	0.185	0.262	0.281		0.197	0.539	0.004	0.106	0.709	0.657	0.041	0.007	0.872	0.904
<i>Faah</i>	0.011	0.351	0.360	0.000	0.043	0.000	0.197		0.063	0.424	0.815	0.369	0.793	0.003	0.000	0.001	0.092
<i>Iba1</i>	0.237	0.304	0.239	0.082	0.527	0.131	0.539	0.063		0.275	0.549	0.173	0.370	0.200	0.280	0.225	0.815
<i>Gfap</i>	0.011	0.820	0.000	0.465	0.146	0.240	0.004	0.424	0.275		0.026	0.910	0.557	0.027	0.204	0.668	0.379
<i>Mrc1</i>	0.525	0.304	0.037	0.974	0.713	0.310	0.106	0.815	0.549	0.026		0.971	0.018	0.787	0.878	0.768	0.265
<i>Fcgr2b</i>	0.953	0.809	0.581	0.682	0.605	0.689	0.709	0.369	0.173	0.910	0.971		0.916	0.788	0.192	0.835	0.868
<i>Il1b</i>	0.360	0.402	0.090	0.974	0.965	0.453	0.657	0.793	0.370	0.557	0.018	0.916		0.974	0.686	0.268	0.971
<i>Ikbkb</i>	0.035	0.851	0.014	0.000	0.008	0.000	0.041	0.003	0.200	0.027	0.787	0.788	0.974		0.000	0.187	0.026
<i>Nos2</i>	0.048	0.787	0.375	0.000	0.015	0.001	0.007	0.000	0.280	0.204	0.878	0.192	0.686	0.000		0.062	0.049
<i>Ptgs2</i>	0.412	0.204	0.450	0.004	0.560	0.019	0.872	0.001	0.225	0.668	0.768	0.835	0.268	0.187	0.062		0.722
<i>Rela</i>	0.060	0.074	0.576	0.048	0.000	0.043	0.904	0.092	0.815	0.379	0.265	0.868	0.971	0.026	0.049	0.722	

Table S13. Corresponding p values for Spearman correlation of genes corresponding to the endocannabinoid system, gliosis and inflammation during withdrawal of WIN 55,212-2 and HU-210 in the prefrontal cortex.

	<i>Cnr1</i>	<i>Cnr2</i>	<i>Ppara</i>	<i>Dagla</i>	<i>Daglb</i>	<i>Mgll</i>	<i>Napepld</i>	<i>Faah</i>	<i>Iba1</i>	<i>Gfap</i>	<i>Mrc1</i>	<i>Fcgr2b</i>	<i>Il1b</i>	<i>Ikbkb</i>	<i>Nos2</i>	<i>Ptgs2</i>	<i>Rela</i>
<i>Cnr1</i>		0.952	0.862	0.572	0.064	0.509	0.277	0.342	0.448	0.683	0.728	0.939	0.300	0.252	0.501	0.027	0.043
<i>Cnr2</i>	0.952		0.832	0.795	0.126	0.353	0.492	0.254	0.024	0.245	0.569	0.003	0.576	0.709	0.543	0.410	0.161
<i>Ppara</i>	0.862	0.832		0.354	0.395	0.493	0.276	0.405	0.306	0.306	0.105	0.284	0.549	0.762	0.692	0.625	0.248
<i>Dagla</i>	0.572	0.795	0.354		0.006	0.000	0.002	0.002	0.864	0.017	0.931	0.609	0.091	0.065	0.712	0.001	0.835
<i>Daglb</i>	0.064	0.126	0.395	0.006		0.001	0.019	0.033	0.246	0.182	0.421	0.259	0.028	0.173	0.036	0.005	0.107
<i>Mgll</i>	0.509	0.353	0.493	0.000	0.001		0.006	0.000	0.965	0.063	0.747	0.093	0.064	0.013	0.113	0.000	0.778
<i>Napepld</i>	0.277	0.492	0.276	0.002	0.019	0.006		0.221	0.554	0.001	0.630	0.742	0.211	0.973	0.629	0.115	0.380
<i>Faah</i>	0.342	0.254	0.405	0.002	0.033	0.000	0.221		0.853	0.990	0.336	0.203	0.001	0.008	0.142	0.002	0.083
<i>Iba1</i>	0.448	0.024	0.306	0.864	0.246	0.965	0.554	0.853		0.334	0.010	0.017	0.007	0.220	0.113	0.802	0.051
<i>Gfap</i>	0.683	0.245	0.306	0.017	0.182	0.063	0.001	0.990	0.334		0.071	0.045	0.316	0.288	0.286	0.171	0.046
<i>Mrc1</i>	0.728	0.569	0.105	0.931	0.421	0.747	0.630	0.336	0.010	0.071		0.046	0.001	0.022	0.028	0.923	0.015
<i>Fcgr2b</i>	0.939	0.003	0.284	0.609	0.259	0.093	0.742	0.203	0.017	0.045	0.046		0.139	0.223	0.125	0.223	0.117
<i>Il1b</i>	0.300	0.576	0.549	0.091	0.028	0.064	0.211	0.001	0.007	0.316	0.001	0.139		0.001	0.001	0.076	0.016
<i>Ikbkb</i>	0.252	0.709	0.762	0.065	0.173	0.013	0.973	0.008	0.220	0.288	0.022	0.223	0.001		0.001	0.007	0.096
<i>Nos2</i>	0.501	0.543	0.692	0.712	0.036	0.113	0.629	0.142	0.113	0.286	0.028	0.125	0.001	0.001		0.353	0.038
<i>Ptgs2</i>	0.027	0.410	0.625	0.001	0.005	0.000	0.115	0.002	0.802	0.171	0.923	0.223	0.076	0.007	0.353		0.571
<i>Rela</i>	0.043	0.161	0.248	0.835	0.107	0.778	0.380	0.083	0.051	0.046	0.015	0.117	0.016	0.096	0.038	0.571	

Table S14. Corresponding p values for Spearman correlation of genes corresponding to the endocannabinoid system, gliosis and inflammation during repeated administration of WIN 55,212-2 and HU-210 in the hippocampus.

	<i>Cnr1</i>	<i>Cnr2</i>	<i>Ppara</i>	<i>Dagla</i>	<i>Daglb</i>	<i>Mgll</i>	<i>Napepld</i>	<i>Faah</i>	<i>Iba1</i>	<i>Gfap</i>	<i>Mrc1</i>	<i>Fcgr2b</i>	<i>Il1b</i>	<i>Ikbkb</i>	<i>Nos2</i>	<i>Ptgs2</i>	<i>Rela</i>
<i>Cnr1</i>		0.179	0.001	0.004	0.012	0.756	0.005	0.005	0.003	0.012	0.000	0.000	0.660	0.009	0.491	0.001	0.668
<i>Cnr2</i>	0.179		0.961	0.639	0.961	0.367	0.971	0.971	0.658	0.945	0.010	0.725	0.366	0.880	0.000	0.929	0.020
<i>Ppara</i>	0.001	0.961		0.049	0.105	0.501	0.028	0.028	0.158	0.159	0.210	0.000	0.379	0.023	0.511	0.011	0.778
<i>Dagla</i>	0.004	0.639	0.049		0.005	0.271	0.001	0.001	0.027	0.001	0.035	0.045	0.098	0.001	0.853	0.007	0.660
<i>Daglb</i>	0.012	0.961	0.105	0.005		0.106	0.000	0.000	0.001	0.000	0.023	0.021	0.913	0.007	0.409	0.001	0.622
<i>Mgll</i>	0.756	0.367	0.501	0.271	0.106		0.916	0.916	0.731	0.206	0.968	0.349	0.197	0.382	0.088	0.767	0.277
<i>Napepld</i>	0.005	0.971	0.028	0.001	0.000	0.916		0.000	0.000	0.000	0.004	0.009	0.784	0.014	0.428	0.000	0.384
<i>Faah</i>	0.005	0.971	0.028	0.001	0.000	0.916	0.000		0.000	0.000	0.004	0.009	0.784	0.014	0.428	0.000	0.384
<i>Iba1</i>	0.003	0.658	0.158	0.027	0.001	0.731	0.000	0.000		0.000	0.012	0.000	0.308	0.011	0.878	0.000	0.409
<i>Gfap</i>	0.012	0.945	0.159	0.001	0.000	0.206	0.000	0.000	0.000		0.029	0.035	0.579	0.013	0.424	0.001	0.438
<i>Mrc1</i>	0.000	0.010	0.210	0.035	0.023	0.968	0.004	0.004	0.012	0.029		0.013	0.599	0.184	0.087	0.022	0.734
<i>Fcgr2b</i>	0.000	0.725	0.000	0.045	0.021	0.349	0.009	0.009	0.000	0.035	0.013		0.657	0.010	0.662	0.002	0.443
<i>Il1b</i>	0.660	0.366	0.379	0.098	0.913	0.197	0.784	0.784	0.308	0.579	0.599	0.657		0.175	0.177	0.875	0.961
<i>Ikbkb</i>	0.009	0.880	0.023	0.001	0.007	0.382	0.014	0.014	0.011	0.013	0.184	0.010	0.175		0.519	0.013	0.636
<i>Nos2</i>	0.491	0.000	0.511	0.853	0.409	0.088	0.428	0.428	0.878	0.424	0.087	0.662	0.177	0.519		0.554	0.004
<i>Ptgs2</i>	0.001	0.929	0.011	0.007	0.001	0.767	0.000	0.000	0.000	0.001	0.022	0.002	0.875	0.013	0.554		0.369
<i>Rela</i>	0.668	0.020	0.778	0.660	0.622	0.277	0.384	0.384	0.409	0.438	0.734	0.443	0.961	0.636	0.004	0.369	

Table S15. Corresponding p values for Spearman correlation of genes corresponding to the endocannabinoid system, gliosis and inflammation during withdrawal of WIN 55,212-2 and HU-210 in the hippocampus.

	<i>Cnr1</i>	<i>Cnr2</i>	<i>Ppara</i>	<i>Dagla</i>	<i>Daglb</i>	<i>Mgll</i>	<i>Napepld</i>	<i>Faah</i>	<i>Iba1</i>	<i>Gfap</i>	<i>Mrc1</i>	<i>Fcgr2b</i>	<i>Il1b</i>	<i>Ikbkb</i>	<i>Nos2</i>	<i>Ptgs2</i>	<i>Rela</i>
<i>Cnr1</i>		0.001	0.821	0.088	0.538	0.409	0.867	0.867	0.886	0.174	0.229	0.764	0.718	0.595	0.000	0.501	0.724
<i>Cnr2</i>	0.001		0.020	0.853	0.857	0.633	0.543	0.543	0.192	0.249	0.334	0.609	0.904	0.670	0.000	0.363	0.068
<i>Ppara</i>	0.821	0.020		0.583	0.458	0.400	0.746	0.746	0.718	0.093	0.716	0.719	0.340	0.062	0.078	0.965	0.840
<i>Dagla</i>	0.088	0.853	0.583		0.114	0.025	0.066	0.066	0.695	0.111	0.182	0.266	0.113	0.933	0.241	0.375	0.068
<i>Daglb</i>	0.538	0.857	0.458	0.114		0.072	0.300	0.300	0.095	0.212	0.024	0.084	0.132	0.067	0.628	0.625	0.394
<i>Mgll</i>	0.409	0.633	0.400	0.025	0.072		0.182	0.182	1.000	0.033	0.236	0.248	0.042	0.045	0.192	0.557	0.104
<i>Napepld</i>	0.867	0.543	0.746	0.066	0.300	0.182		0.000	0.148	0.136	0.040	0.010	0.002	0.459	0.969	0.212	0.010
<i>Faah</i>	0.867	0.543	0.746	0.066	0.300	0.182	0.000		0.148	0.136	0.040	0.010	0.002	0.459	0.969	0.212	0.010
<i>Iba1</i>	0.886	0.192	0.718	0.695	0.095	1.000	0.148	0.148		0.025	0.120	0.001	0.648	0.660	0.501	0.159	0.932
<i>Gfap</i>	0.174	0.249	0.093	0.111	0.212	0.033	0.136	0.136	0.025		0.010	0.001	0.062	0.271	0.103	0.045	0.030
<i>Mrc1</i>	0.229	0.334	0.716	0.182	0.024	0.236	0.040	0.040	0.120	0.010		0.000	0.094	0.707	0.850	0.480	0.065
<i>Fcgr2b</i>	0.764	0.609	0.719	0.266	0.084	0.248	0.010	0.010	0.001	0.001	0.000		0.243	0.336	0.395	0.063	0.061
<i>Il1b</i>	0.718	0.904	0.340	0.113	0.132	0.042	0.002	0.002	0.648	0.062	0.094	0.243		0.038	0.465	0.450	0.010
<i>Ikbkb</i>	0.595	0.670	0.062	0.933	0.067	0.045	0.459	0.459	0.660	0.271	0.707	0.336	0.038		0.799	0.579	0.034
<i>Nos2</i>	0.000	0.000	0.078	0.241	0.628	0.192	0.969	0.969	0.501	0.103	0.850	0.395	0.465	0.799		0.316	0.367
<i>Ptgs2</i>	0.501	0.363	0.965	0.375	0.625	0.557	0.212	0.212	0.159	0.045	0.480	0.063	0.450	0.579	0.316		0.642
<i>Rela</i>	0.724	0.068	0.840	0.068	0.394	0.104	0.010	0.010	0.932	0.030	0.065	0.061	0.010	0.034	0.367	0.642	

Supplementary Figure S1

Western Blots Gels and immunoblots Prefrontal Cortex

...involving the prefrontal cortex of Wistar rats treated with WIN 55,212-2, HU-210, and a vehicle under conditions of repeated administration and withdrawal.

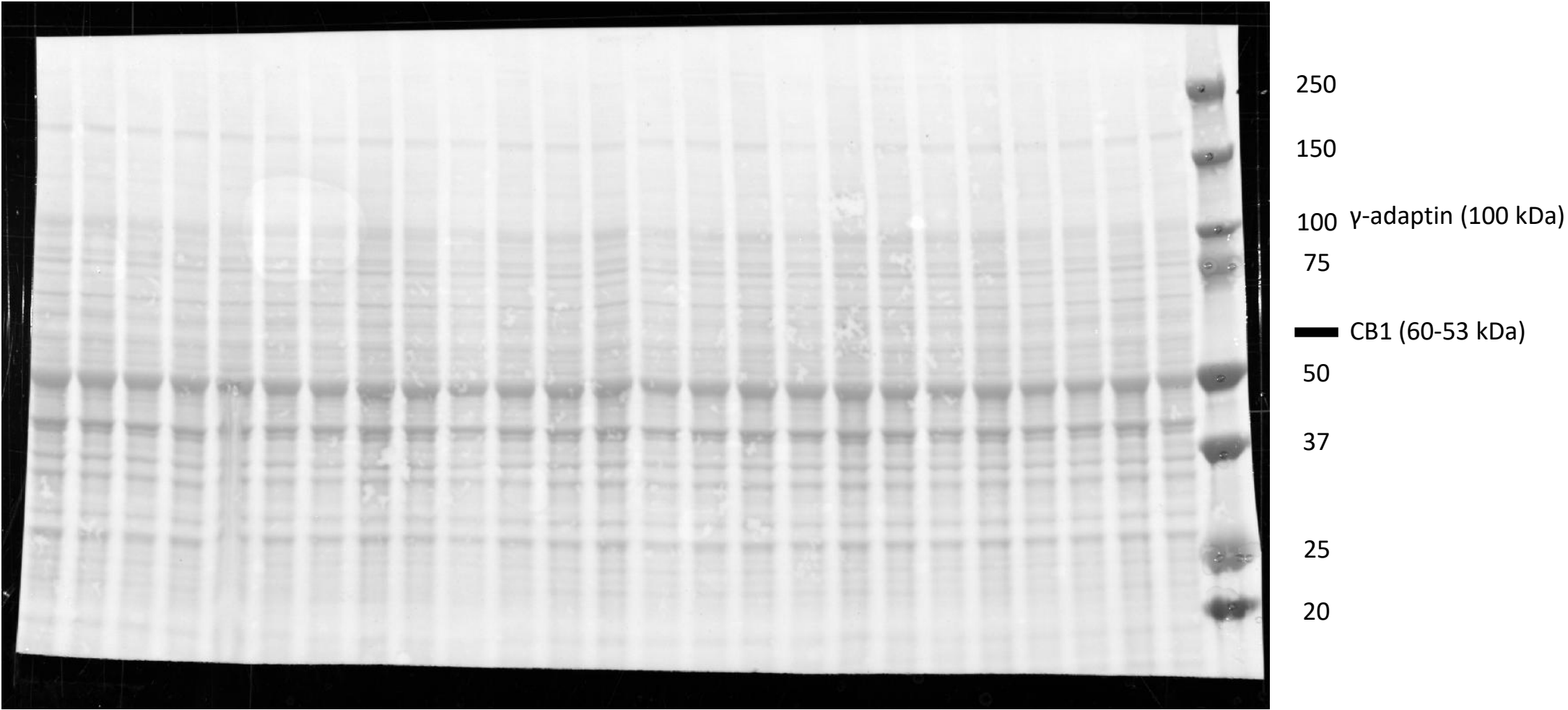
Each lane represents a sample from one rat, with the following groups:

- **WIN 55,212-2 Repeated administration:** n = 4
- **HU-210 Repeated administration:** n = 4
- **Vehicle Repeated administration:** n = 5
- **WIN 55,212-2 Withdrawal:** n = 4
- **HU-210 Withdrawal:** n = 4
- **Vehicle Withdrawal:** n = 4

Gel 1: Ponceau S Red Staining

Prefrontal cortex
Main components (receptors and enzymes) of the endocannabinoid system: CB1

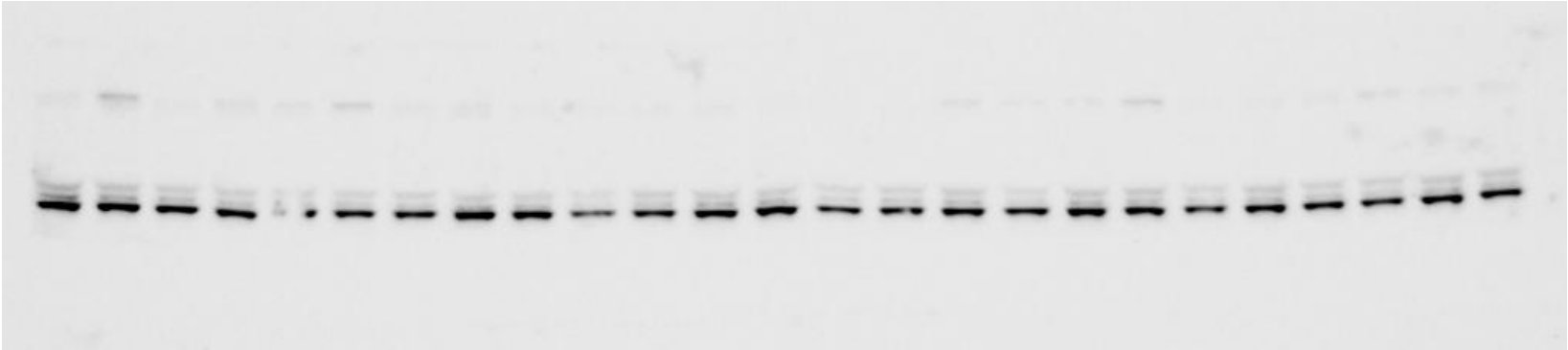
Group	WIN-REP				HU-REP				VEH-REP				WIN-WD				HU-WD				VEH-WD				MW (kDa)
	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 1: Immunoblot

Prefrontal cortex
CB1 (≈ 53-60 kDa)

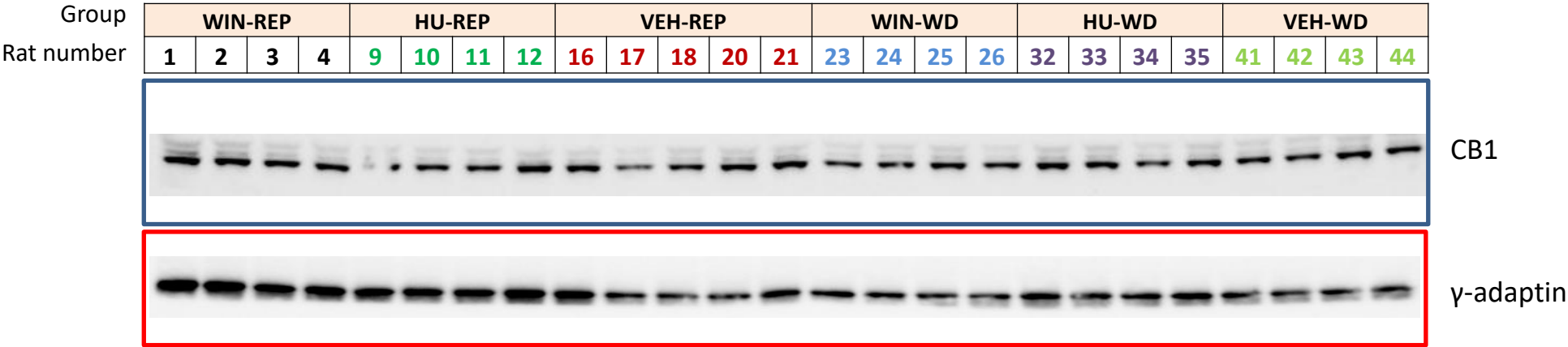
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



CB1

Membrane 1: Immunoblot

Seeman Prefrontal cortex
CB1 (≈ 53-60 kDa)

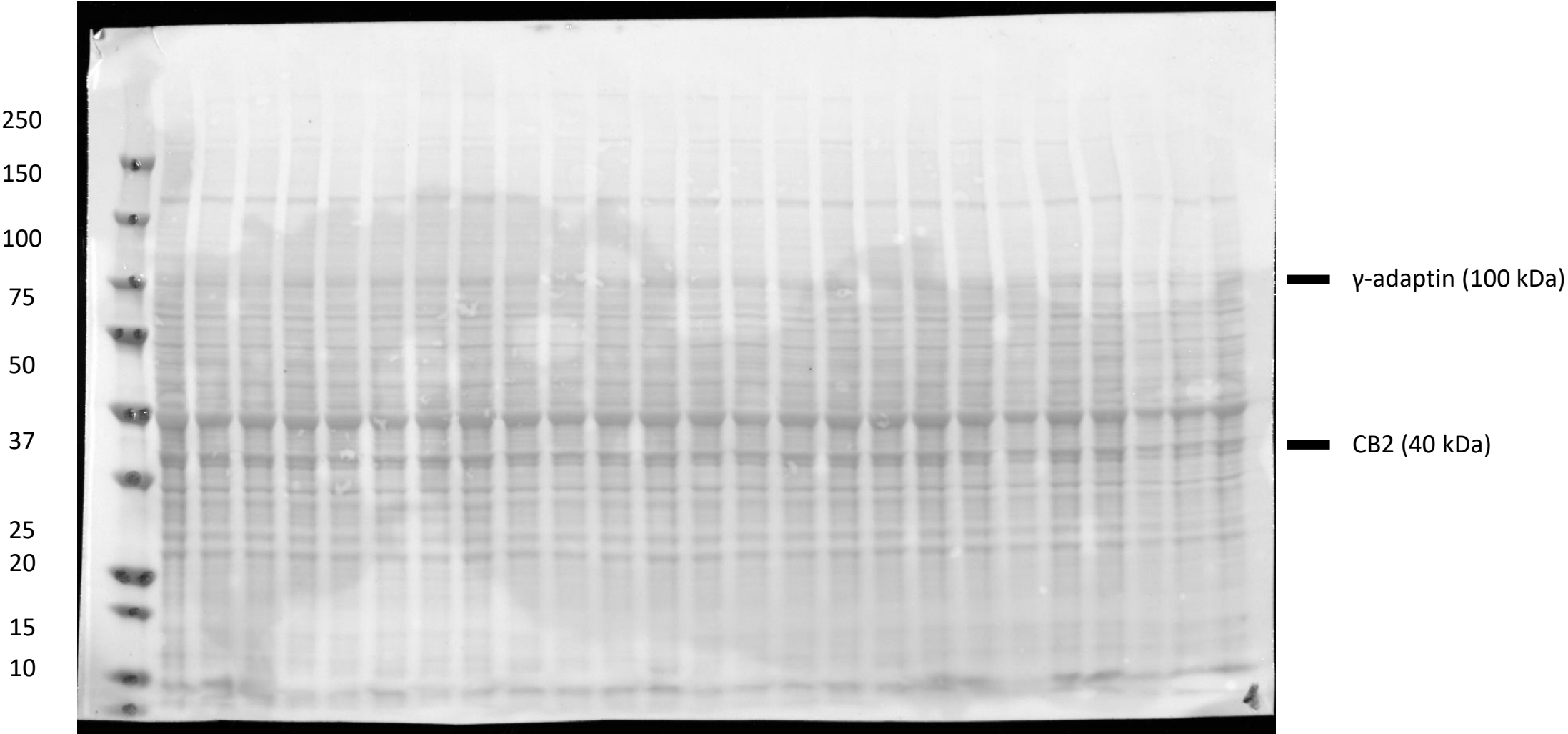


Gel 2: Ponceau S Red Staining

Prefrontal cortex

Main components (receptors and enzymes) of the endocannabinoid system: CB2

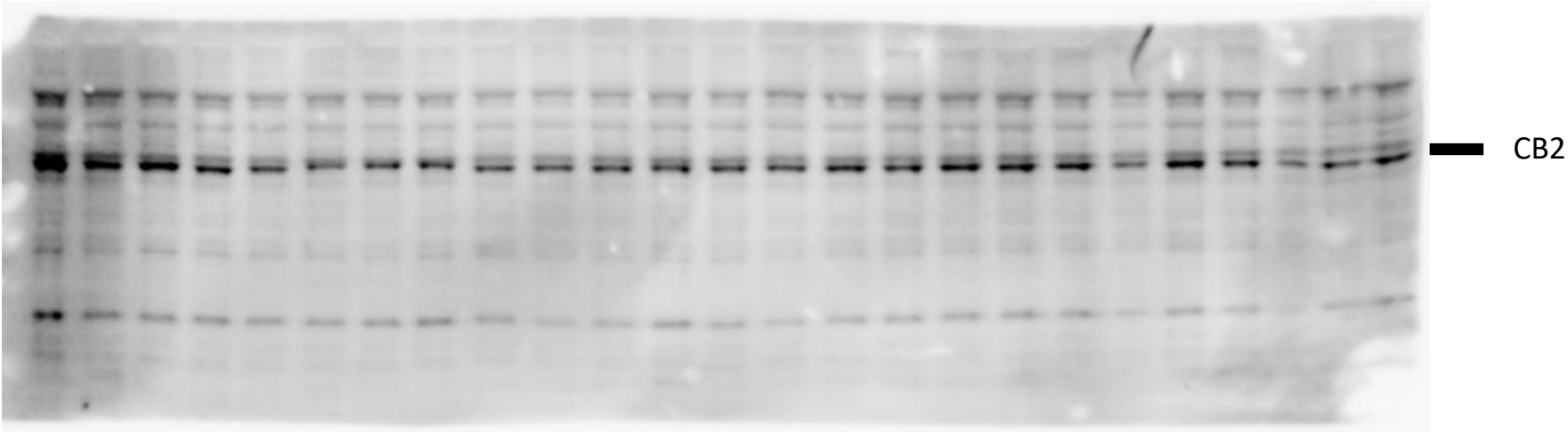
Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 2: Immunoblot

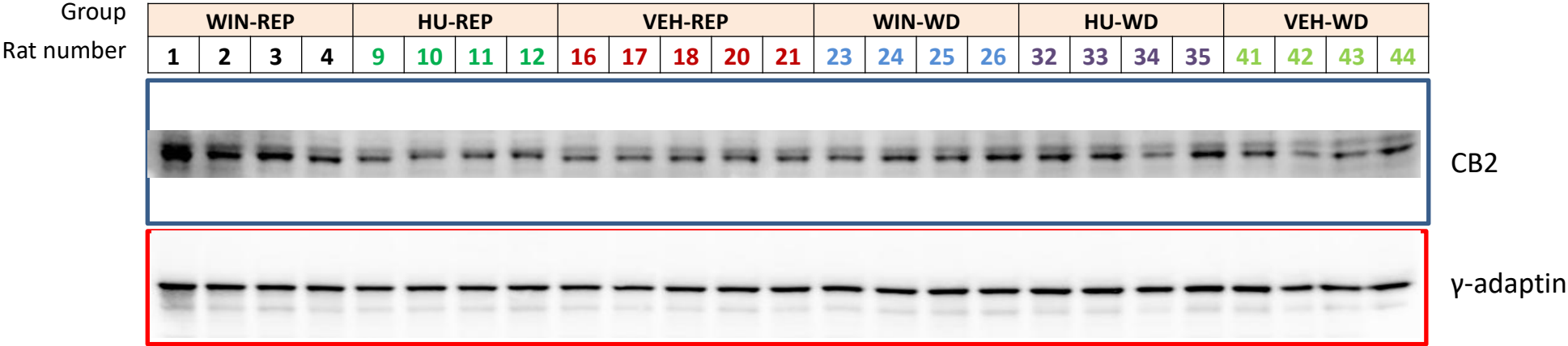
Prefrontal cortex
CB2 (≈ 40 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 2: Immunoblot

Prefrontal cortex
CB2 (≈ 40 kDa)

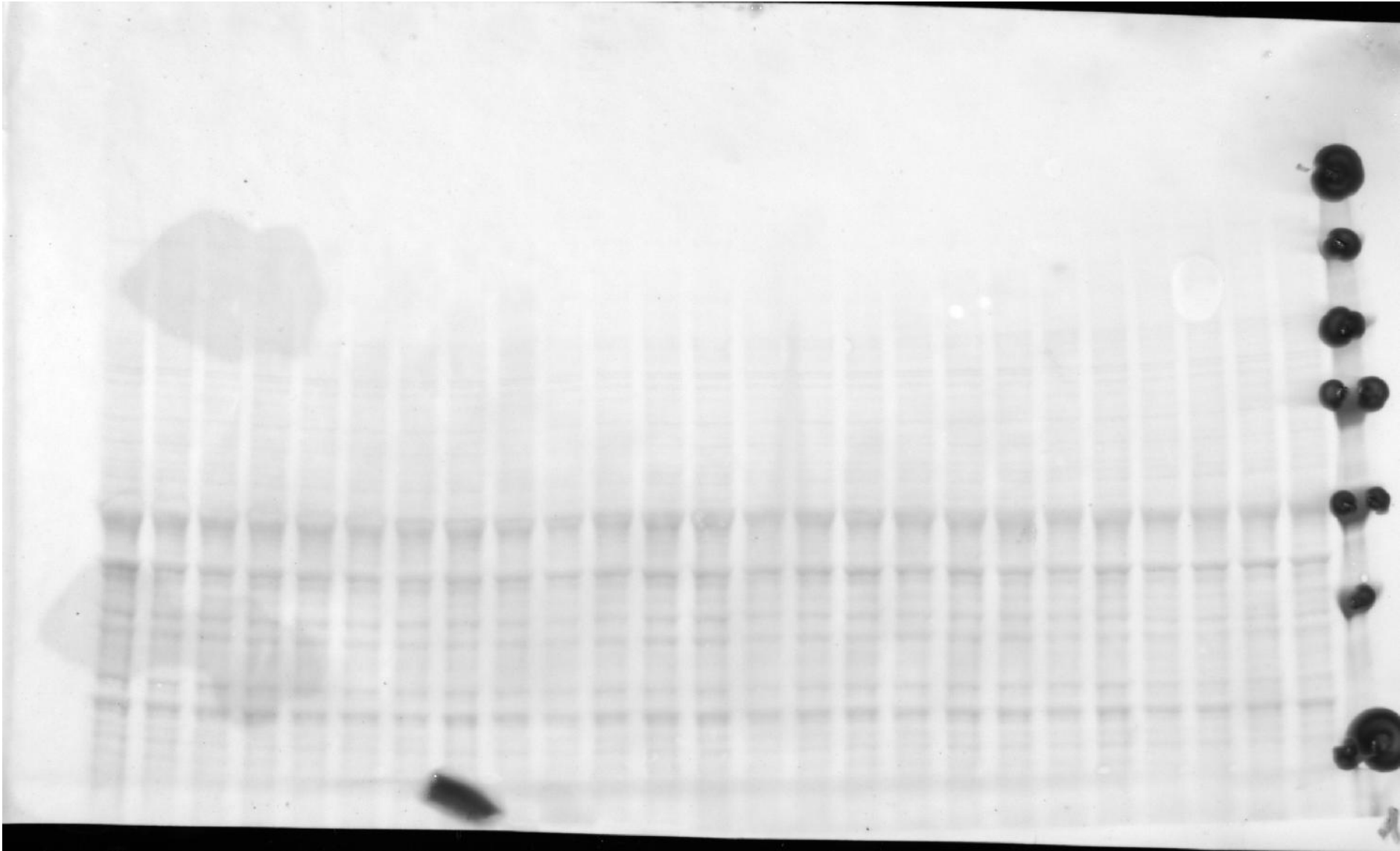


Gel 3: Ponceau S Red Staining

Prefrontal cortex

Main components (receptors and enzymes) of the endocannabinoid system: DAGLα, PPARα, FAAH

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD				MW (kDa)
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44	

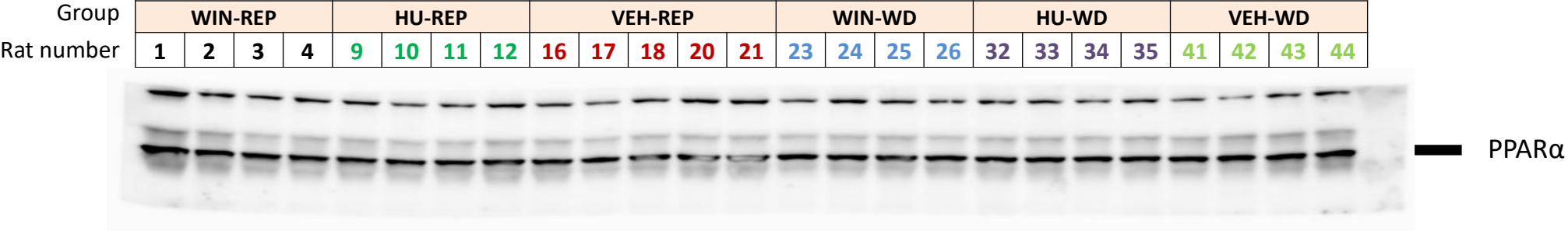


250
150
100
75
50
37
25

— DAGLα (115 kDa)
— γ-adaptin (100 kDa)
— FAAH (63 kDa)
— PPARα (52 kDa)

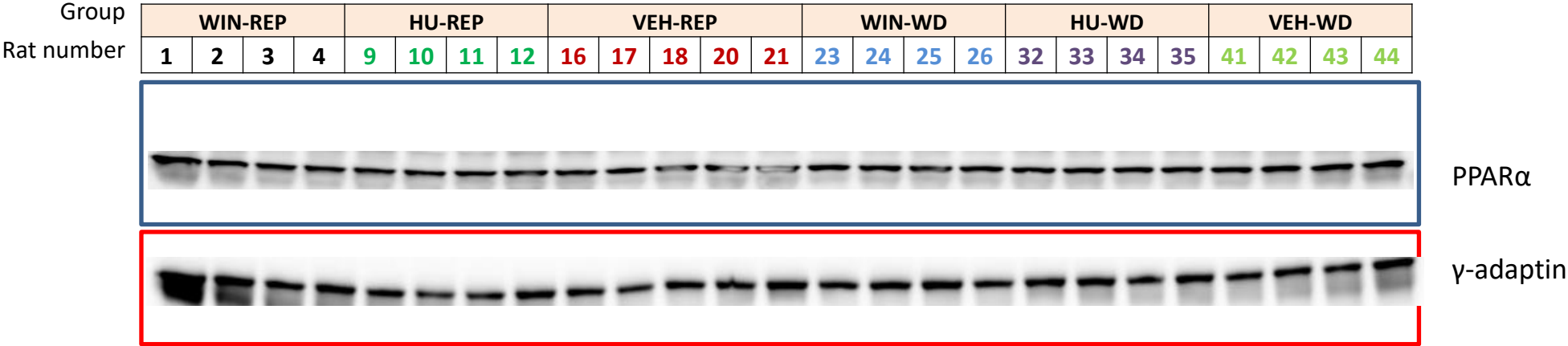
Membrane 3: Immunoblot

Prefrontal cortex
PPARα (≈ 52 kDa)



Membrane 3: Immunoblot

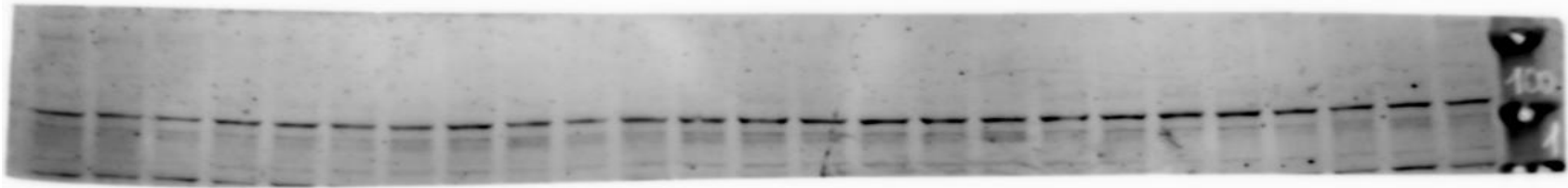
Prefrontal cortex
PPARα (≈ 52 kDa)



Membrane 3: Immunoblot

Prefrontal cortex
DAGLα (≈ 115 kDa)

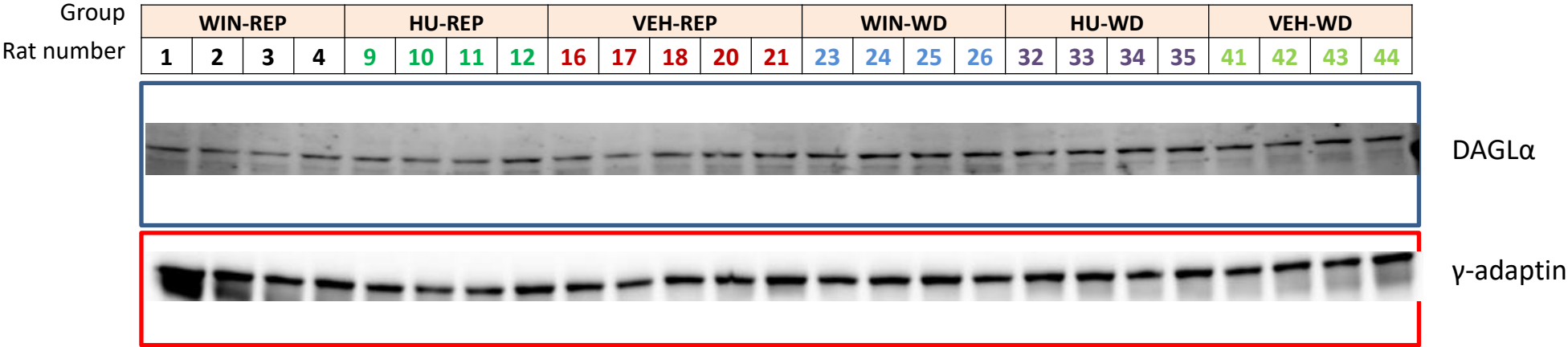
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



— DAGLα

Membrane 3: Immunoblot

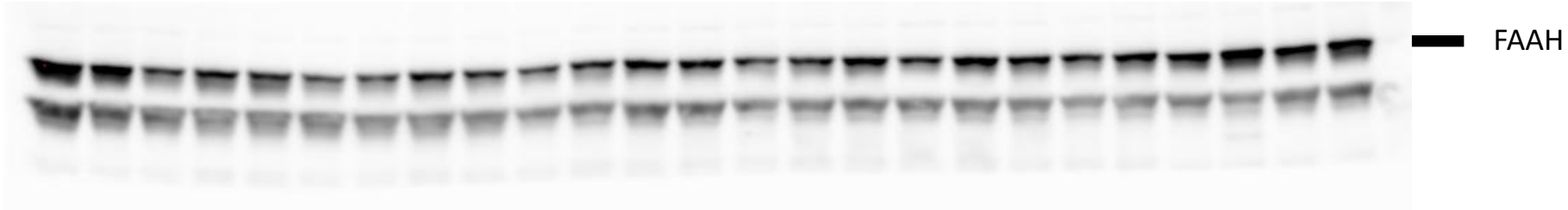
Prefrontal cortex
DAGLα (≈ 115 kDa)



Membrane 3: Immunoblot

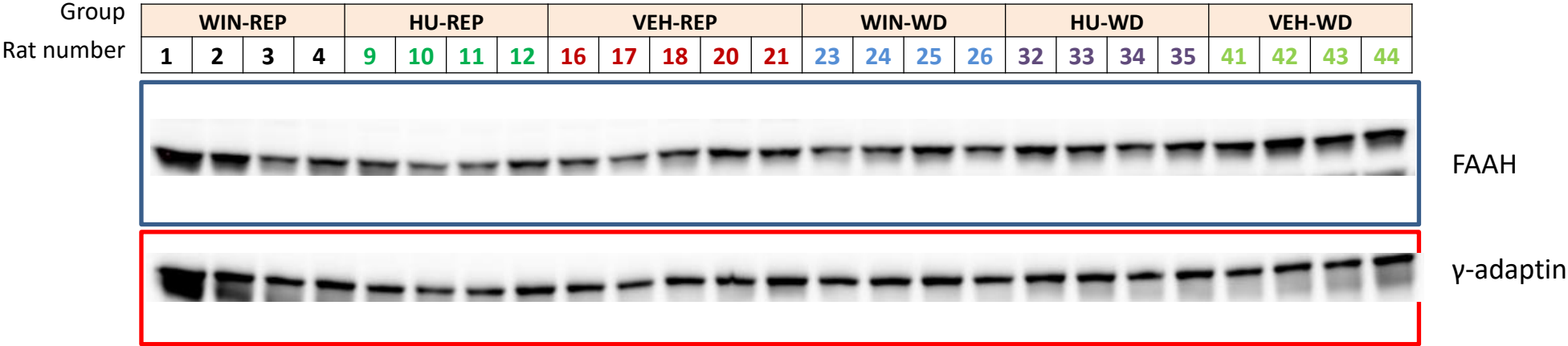
Prefrontal cortex
FAAH (≈ 63 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 3: Immunoblot

Prefrontal cortex
FAAH (≈ 63 kDa)

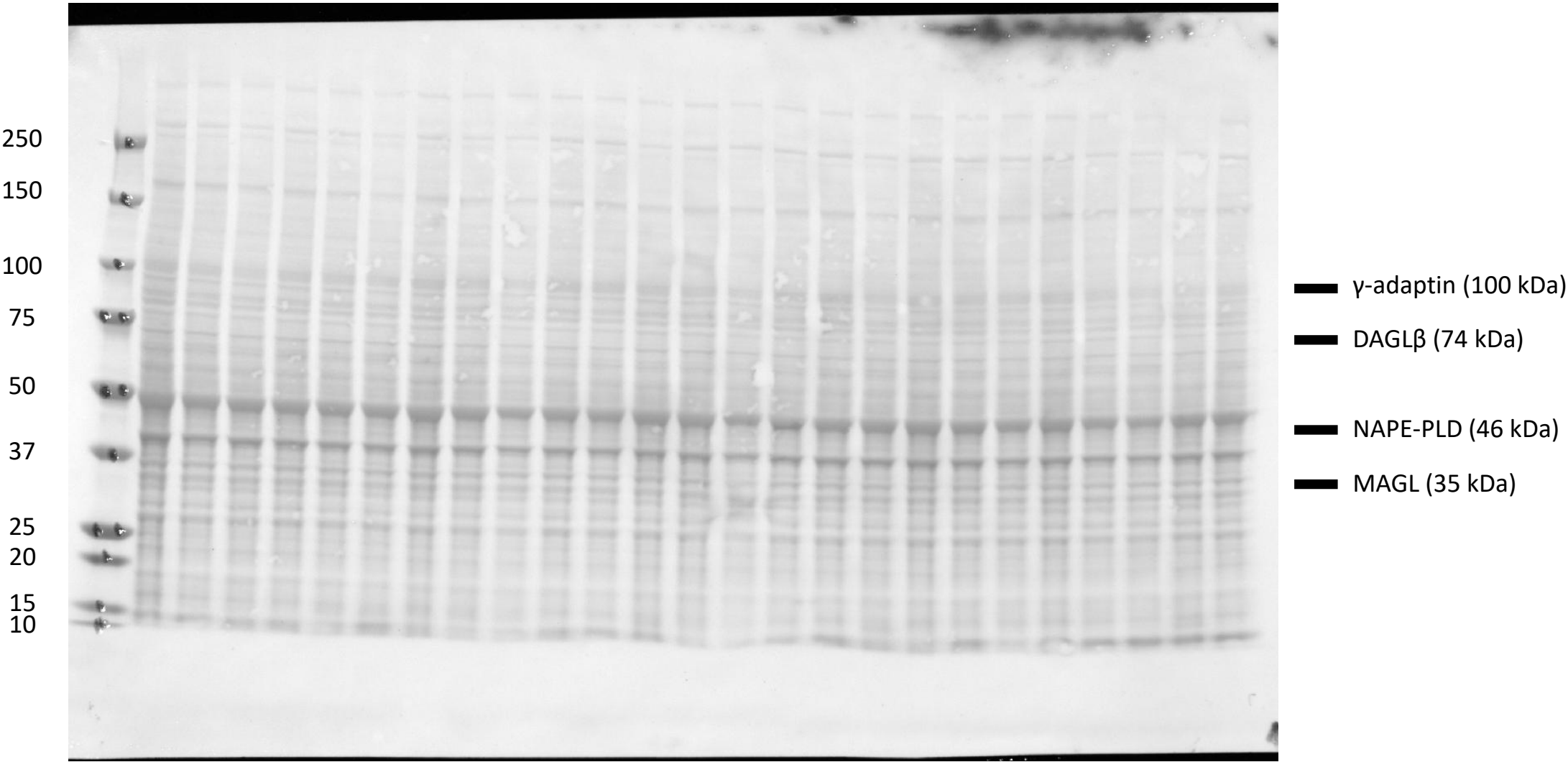


Gel 4: Ponceau S Red Staining

Prefrontal cortex

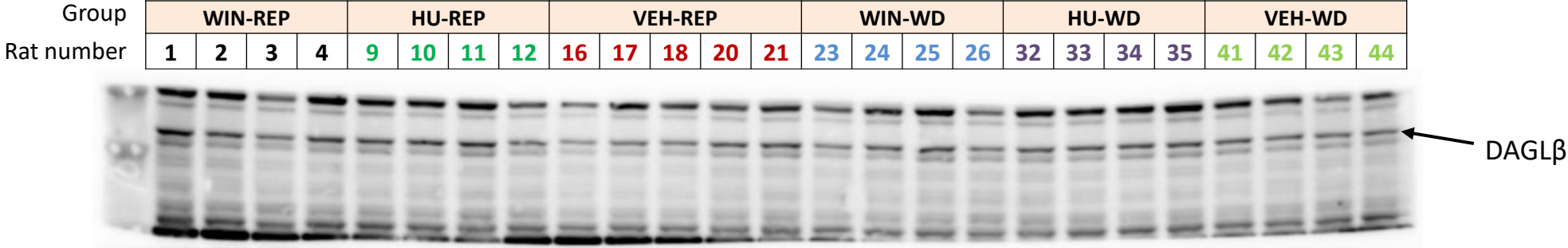
Main components (receptors and enzymes) of the endocannabinoid system: DAGLβ, NAPE-PLD, MAGL

Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



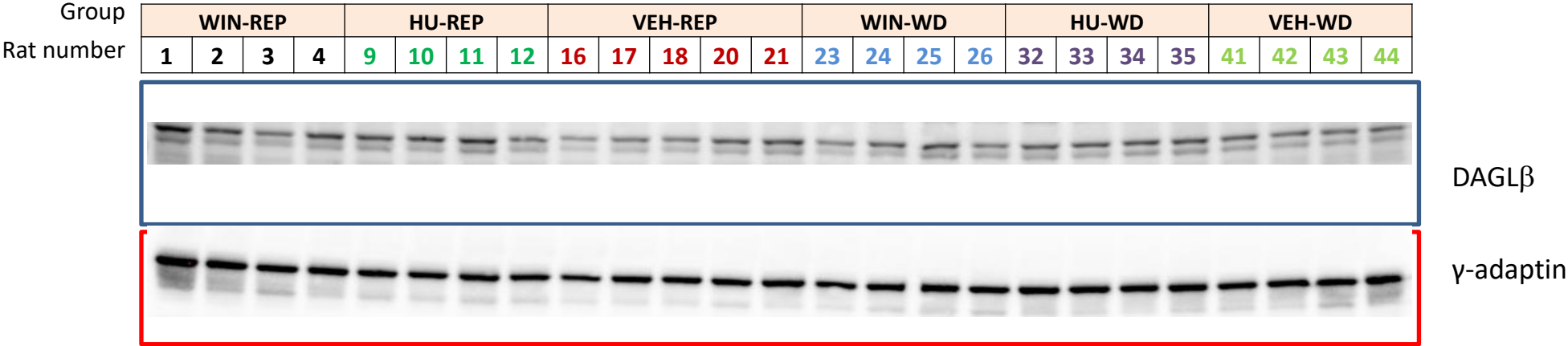
Membrane 4: Immunoblot

Prefrontal cortex
DAGLβ (≈ 74 kDa)



Membrane 4: Immunoblot

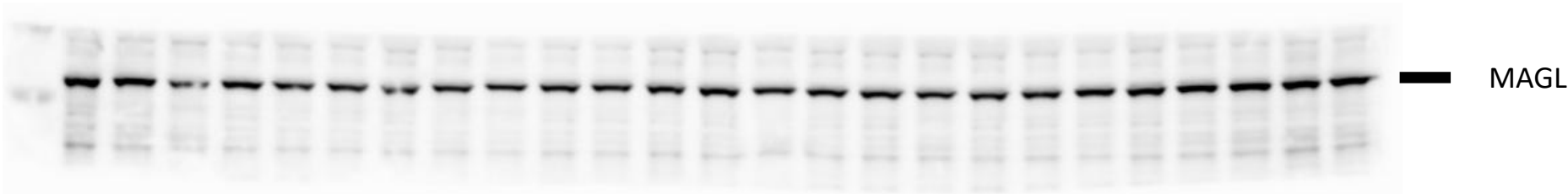
Prefrontal cortex
DAGLβ (≈ 74 kDa)



Membrane 4: Immunoblot

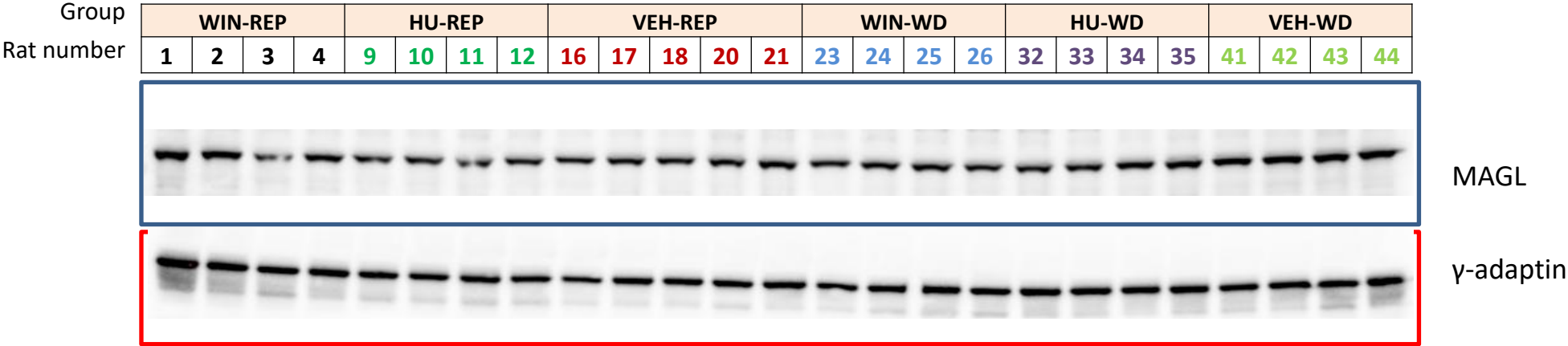
Prefrontal cortex
MAGL (≈ 35 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 4: Immunoblot

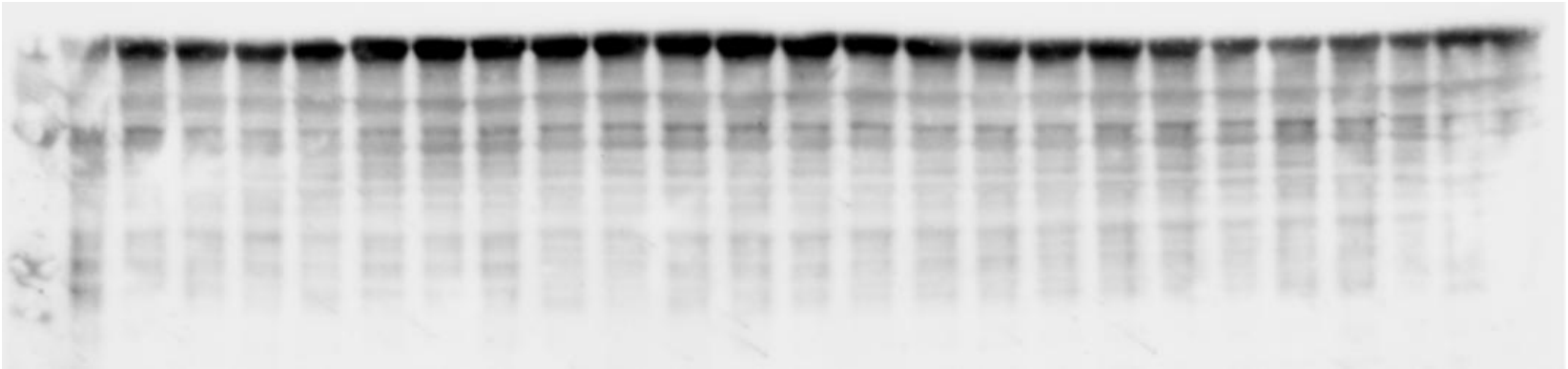
Prefrontal cortex
MAGL (≈ 35 kDa)



Membrane 4: Immunoblot

Prefrontal cortex
NAPE-PLD (≈ 46 kDa)

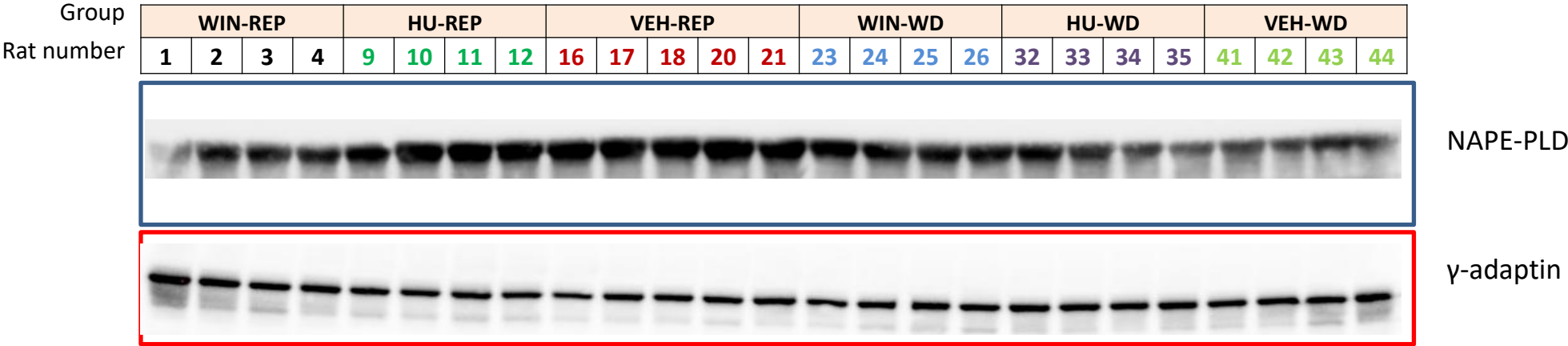
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



NAPE-PLD

Membrane 4: Immunoblot

Prefrontal cortex
NAPE-PLD (≈ 46 kDa)



Gel 5: Ponceau S Red Staining

Prefrontal cortex
Biomarkers of glial cells: GFAP, IBA1, vimentin

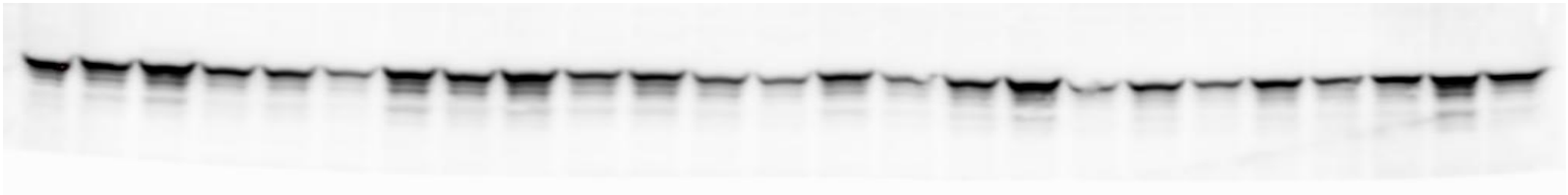
Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44

missing

Membrane 5: Immunoblot

Prefrontal cortex
GFAP (≈ 48 kDa)

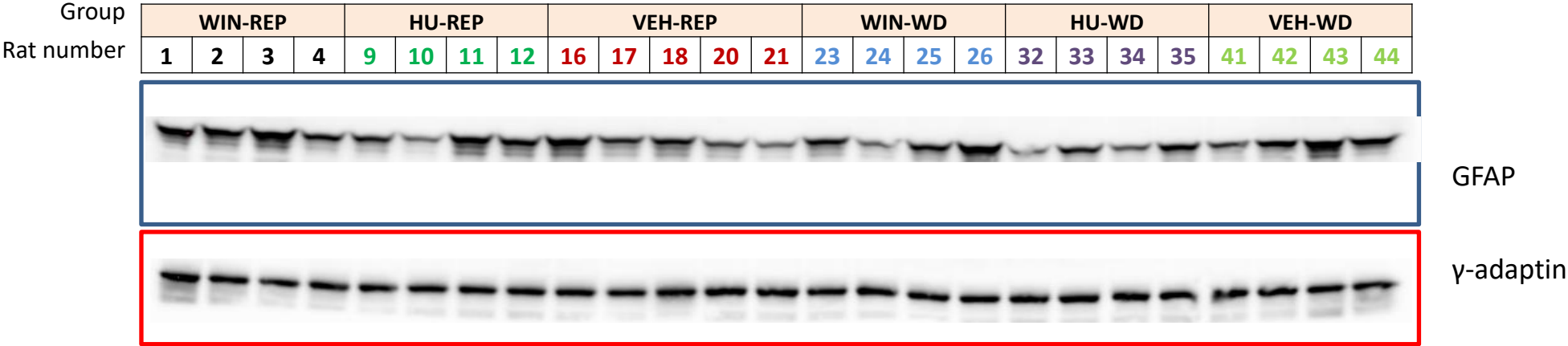
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



— GFAP

Membrane 5: Immunoblot

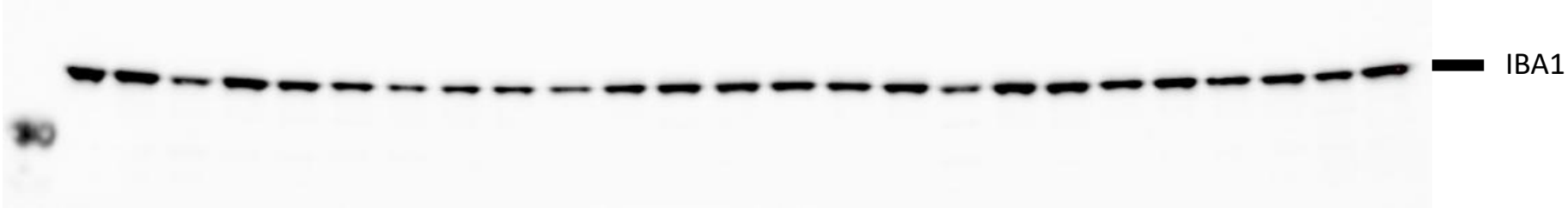
Prefrontal cortex
GFAP (≈ 48 kDa)



Membrane 5: Immunoblot

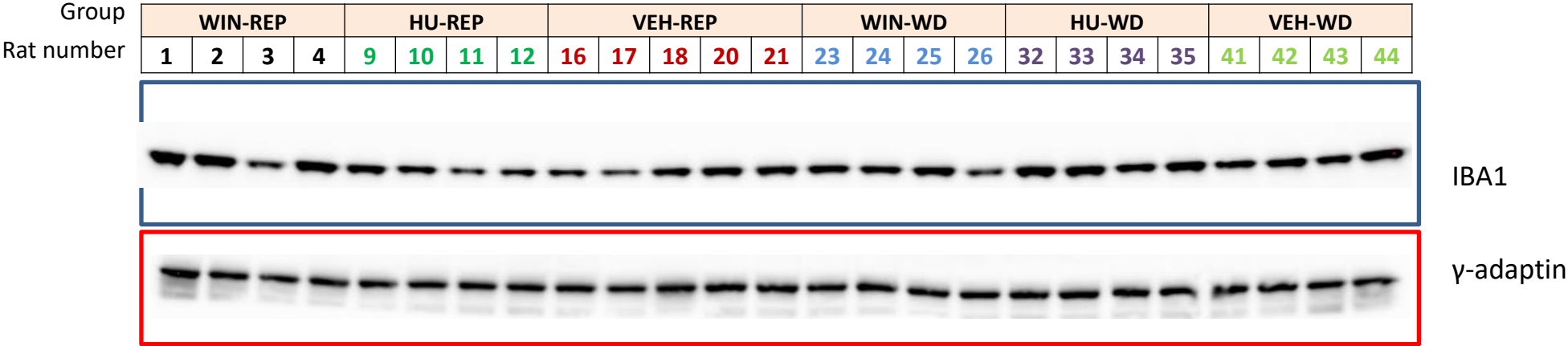
Prefrontal cortex
IBA1 (≈ 17 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 5: Immunoblot

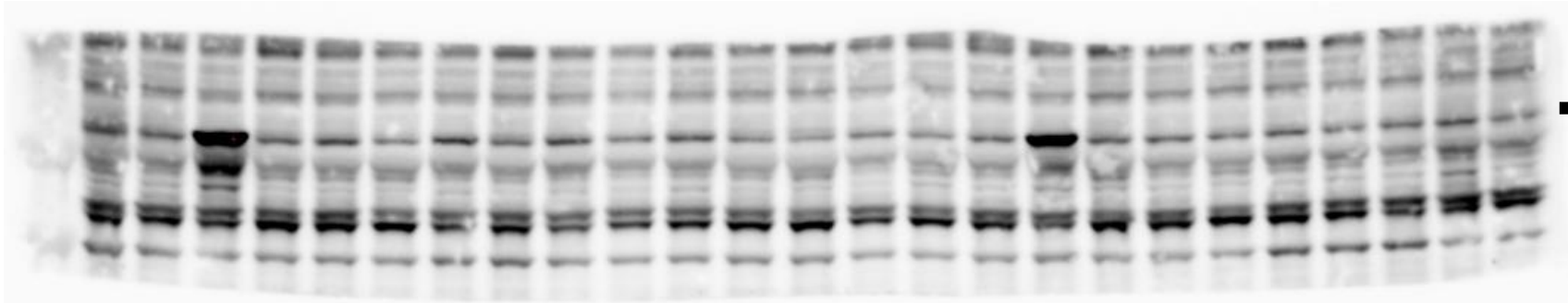
Prefrontal cortex
IBA1 (≈ 17 kDa)



Membrane 5: Immunoblot

Prefrontal cortex
Vimentin (≈ 54 kDa)

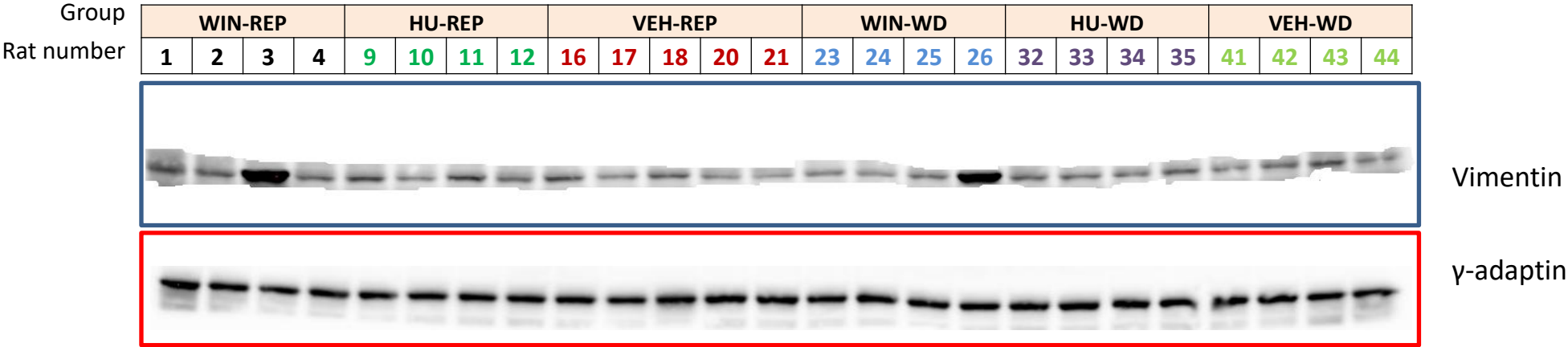
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



— Vimentin

Membrane 5: Immunoblot

Prefrontal cortex
Vimentin (≈ 54 kDa)

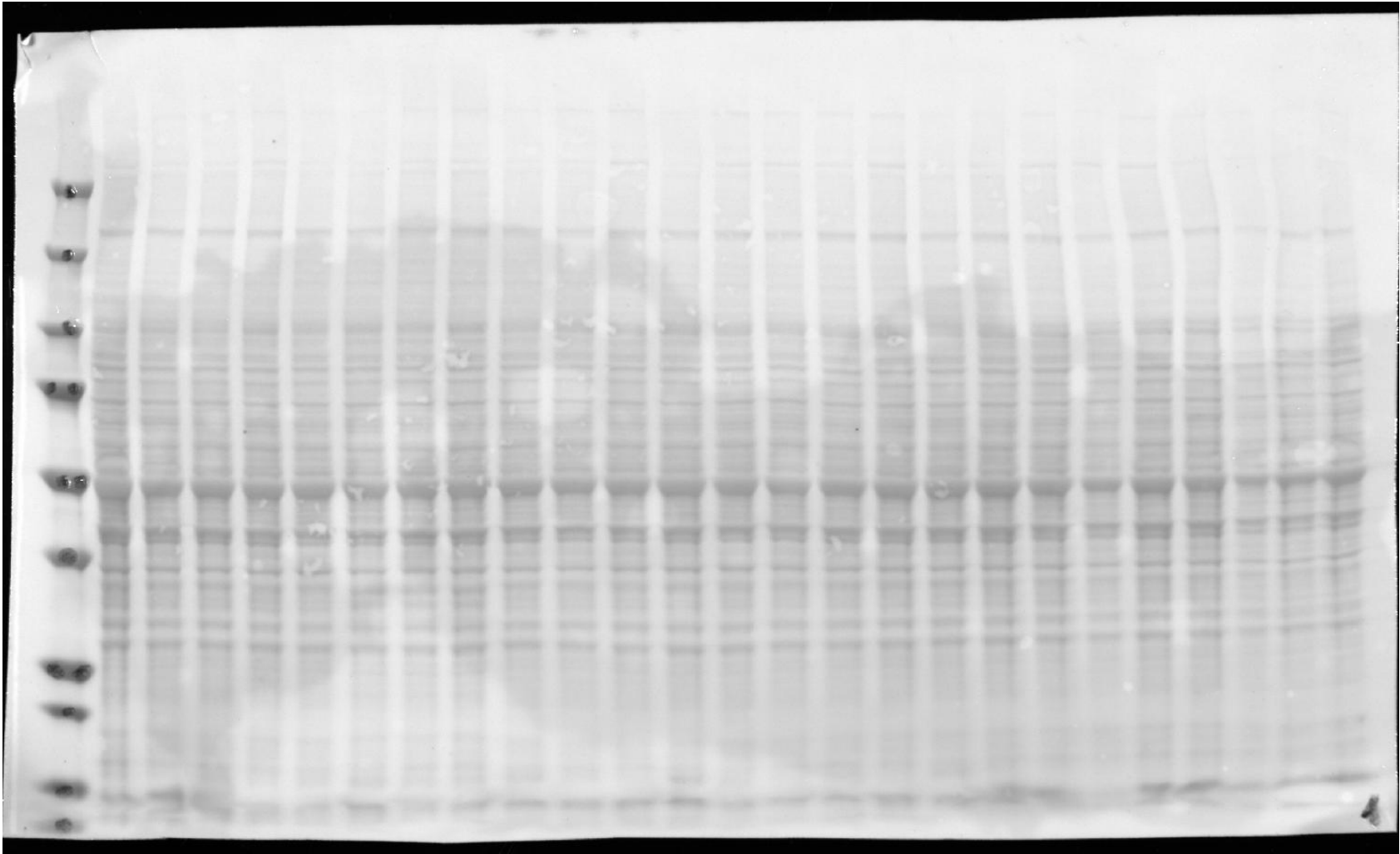


Gel 6: Ponceau S Red Staining

Prefrontal cortex
Factors involved in neuroinflammation: COX2

Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44

250
150
100
75
50
37
25
20
15
10

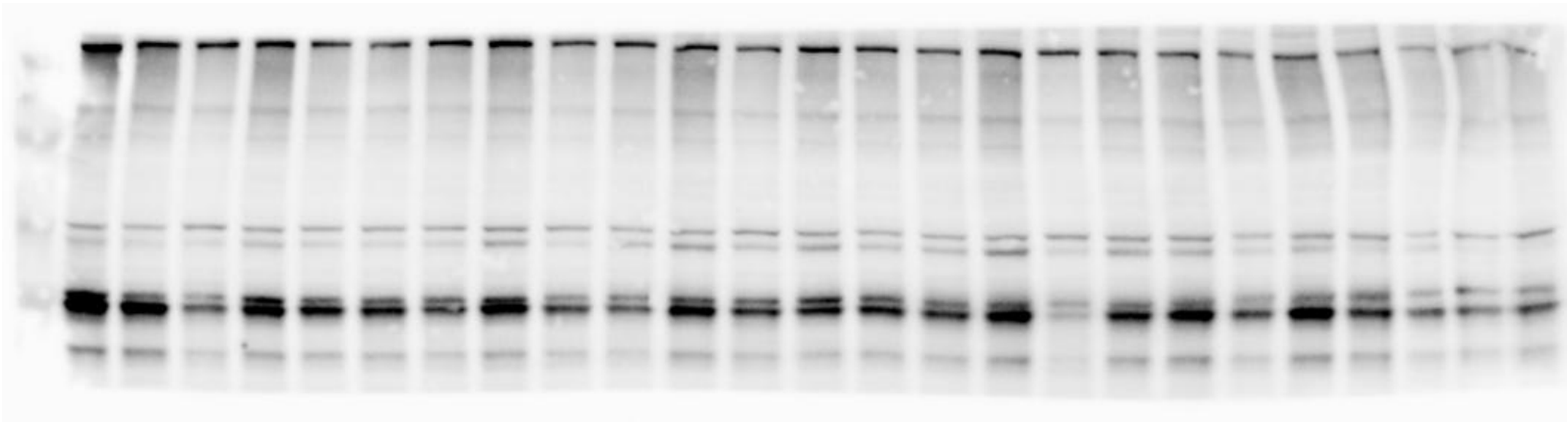


γ-adaptin (100 kDa)
COX2 (74 kDa)

Membrane 6: Immunoblot

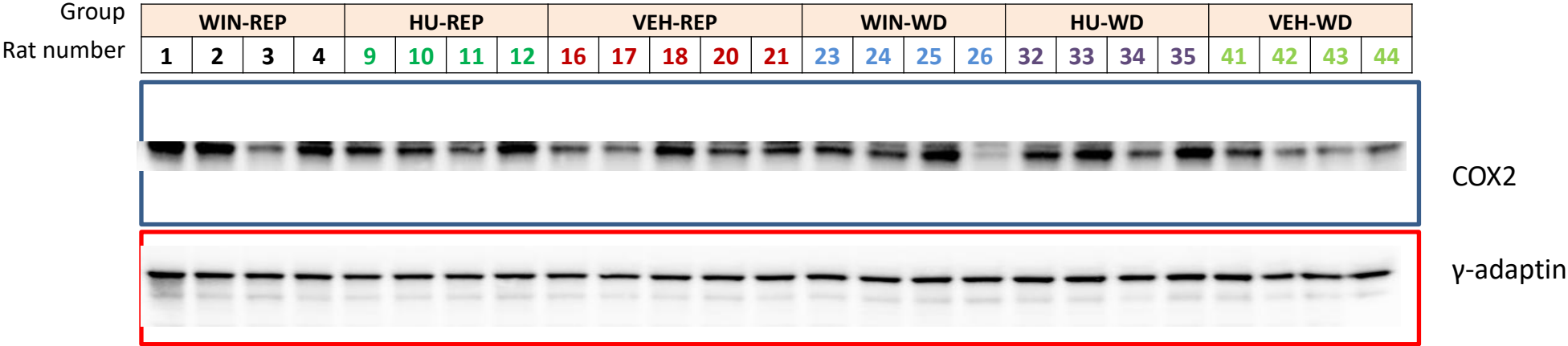
Prefrontal cortex
COX2 (≈ 74 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 6: Immunoblot

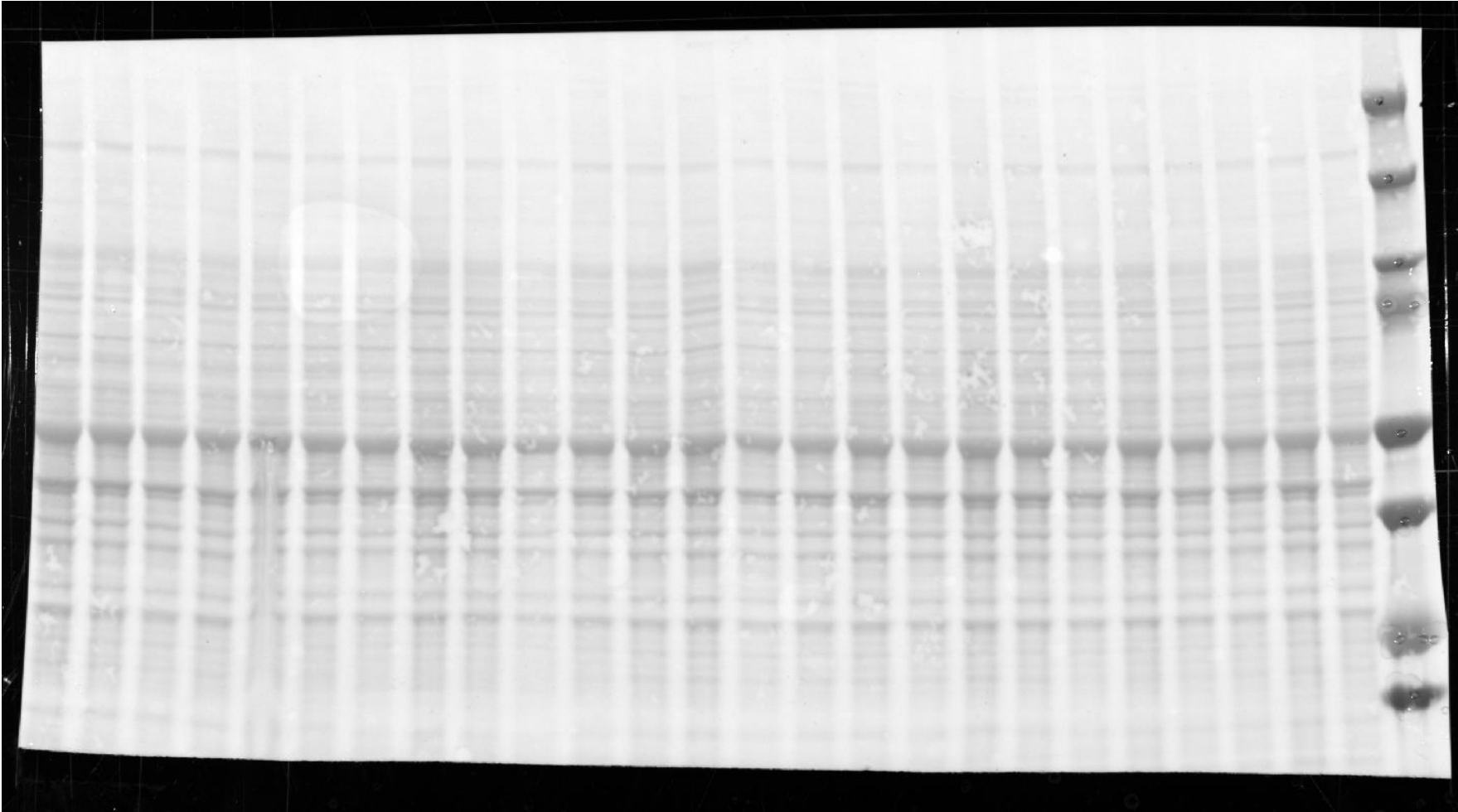
Prefrontal cortex
COX2 (≈ 74 kDa)



Gel 7: Ponceau S Red Staining

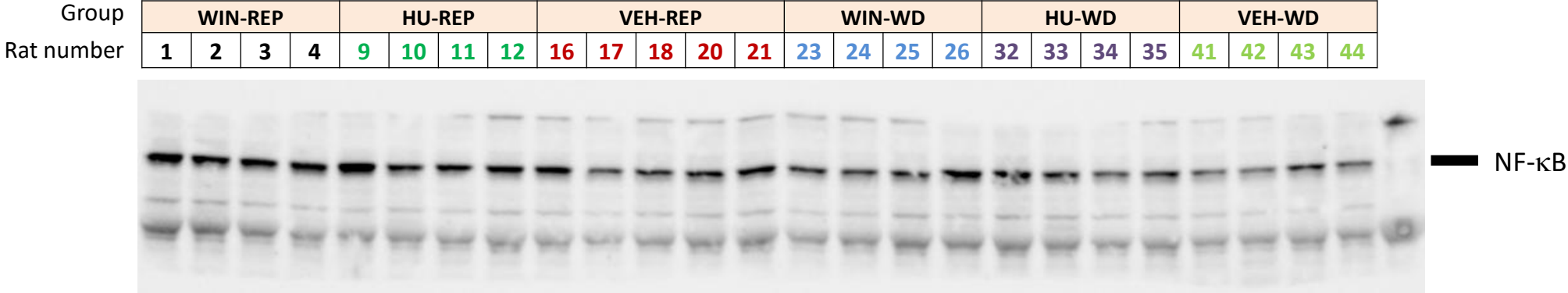
Prefrontal cortex
Factors involved in neuroinflammation: IKKβ, NF-κB

Group	WIN-REP				HU-REP				VEH-REP				WIN-WD				HU-WD				VEH-WD				MW (kDa)
	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



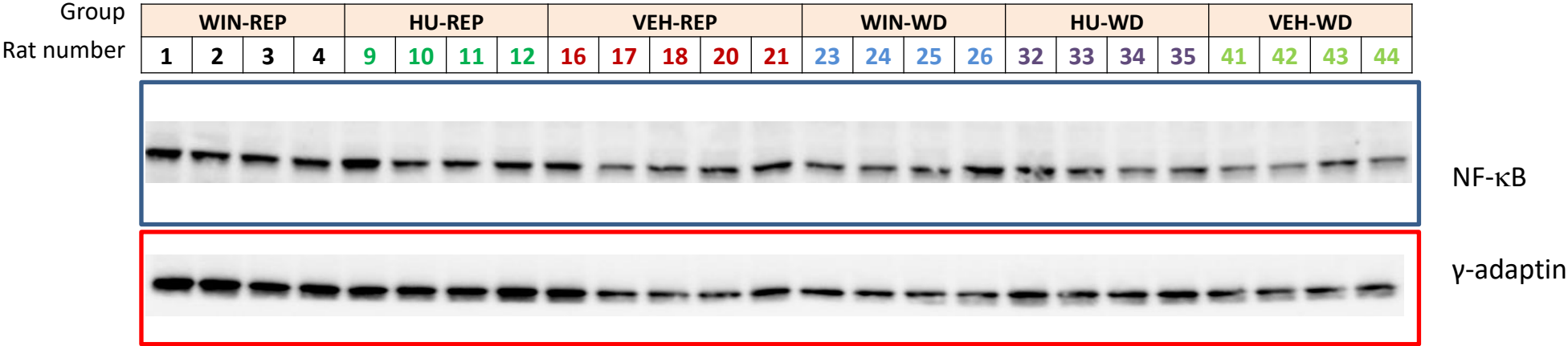
Membrane 7: Immunoblot

Prefrontal cortex
NF-κB (≈ 65 kDa)



Membrane 7: Immunoblot

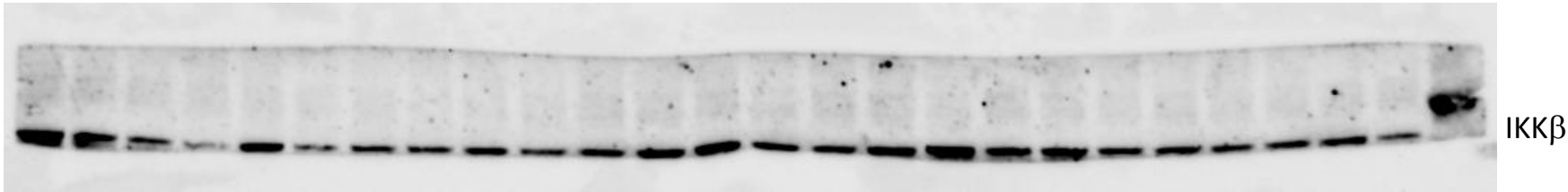
Prefrontal cortex
NF-κB (≈ 65 kDa)



Membrane 7: Immunoblot

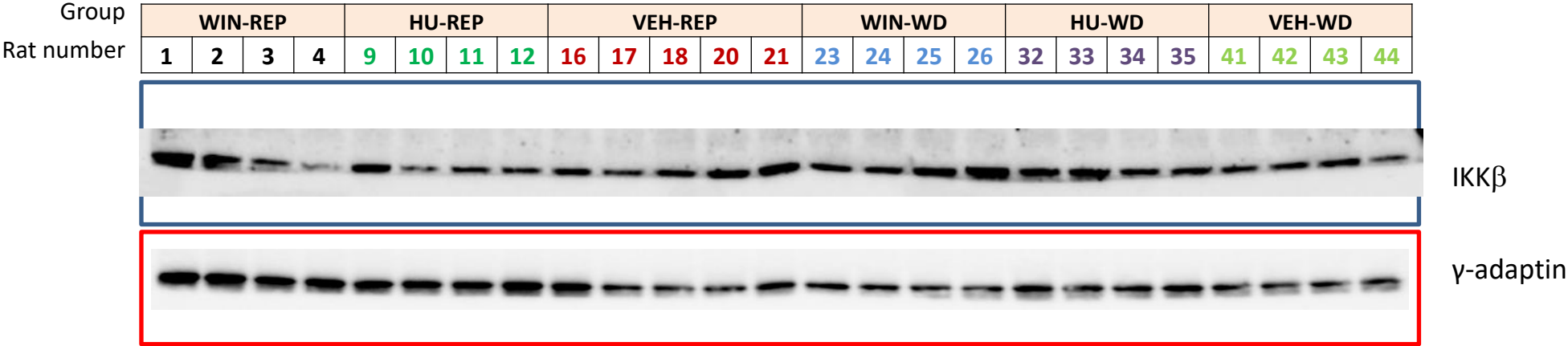
Prefrontal cortex
IKKβ (≈ 87 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44

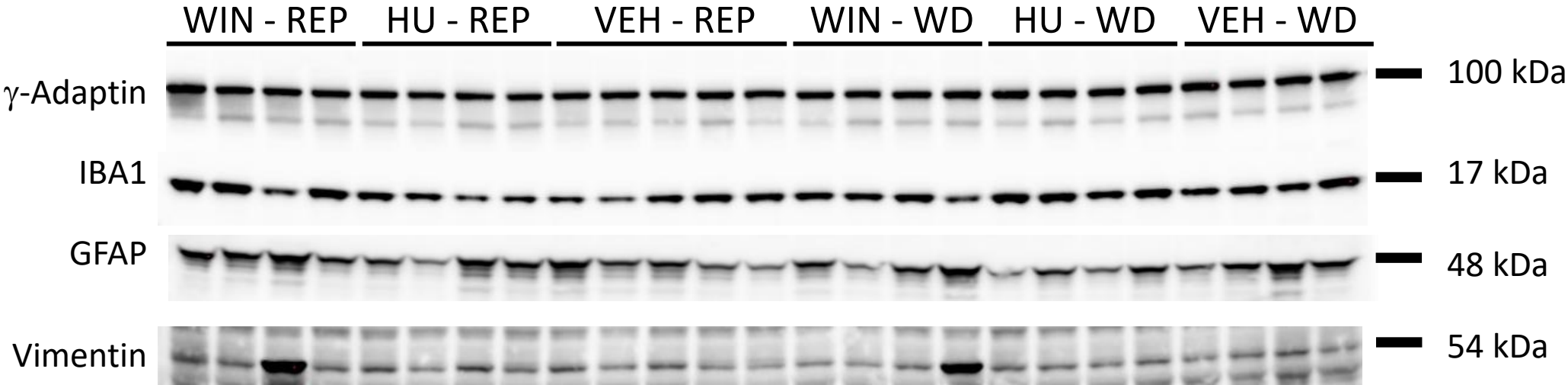


Membrane 7: Immunoblot

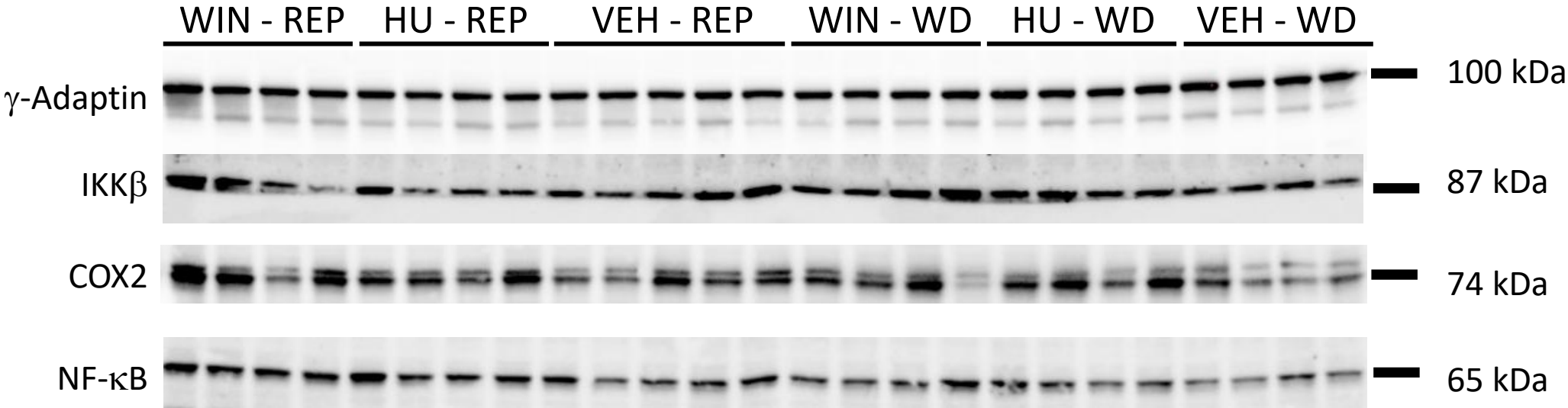
Prefrontal cortex
IKKβ (≈ 87 kDa)



Summary of immunoblots (see Figure 3)



Summary of immunoblots (see Figure 3)



Western Blots Gels and immunoblots Hippocampus

...involving the hippocampus of Wistar rats treated with WIN 55,212-2, HU-210, and a vehicle under conditions of repeated administration and withdrawal.

Each lane represents a sample from one rat, with the following groups:

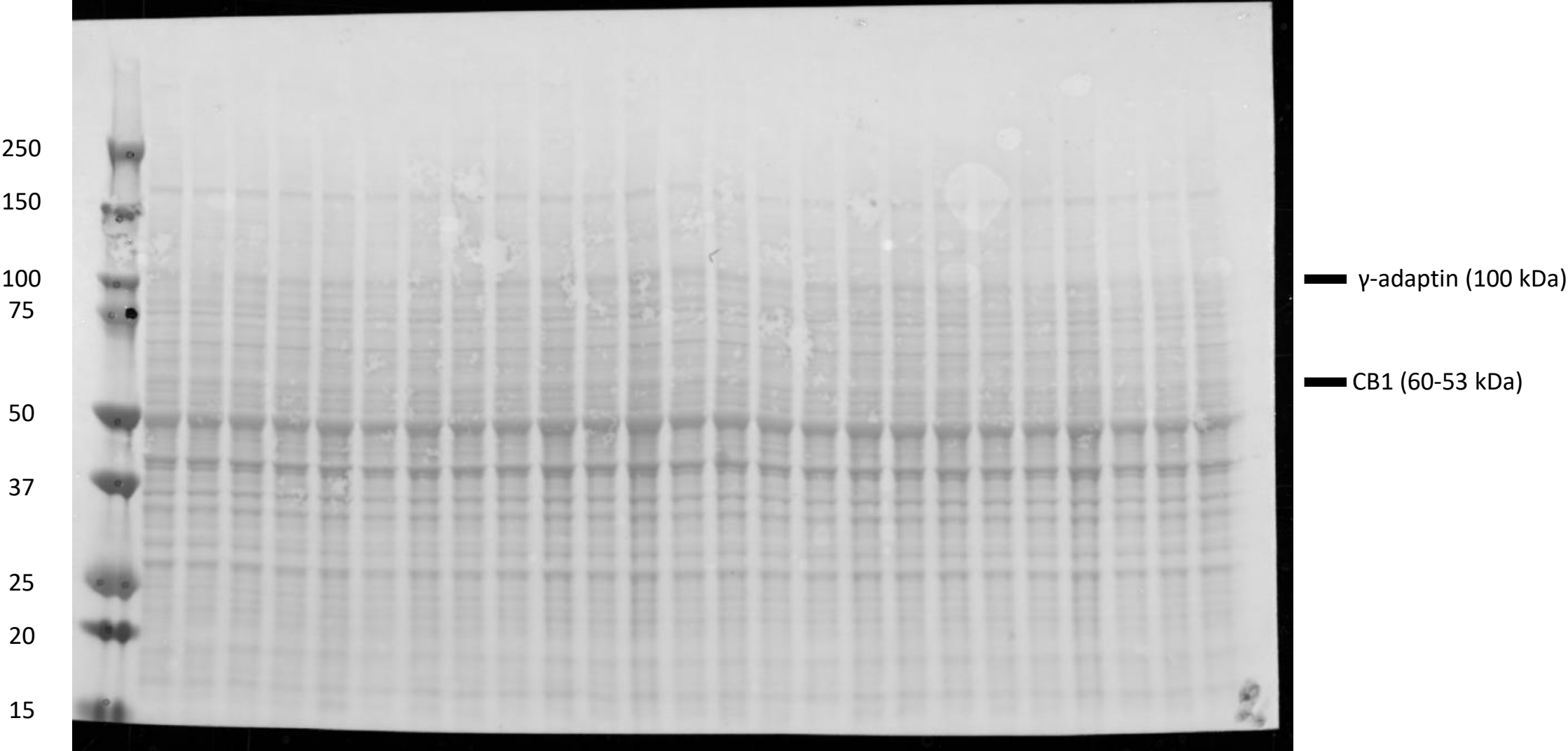
- **WIN 55,212-2 Repeated administration:** n = 4
- **HU-210 Repeated administration:** n = 4
- **Vehicle Repeated administration:** n = 5
- **WIN 55,212-2 Withdrawal:** n = 4
- **HU-210 Withdrawal:** n = 4
- **Vehicle Withdrawal:** n = 4

Gel 1: Ponceau S Red Staining

Hippocampus

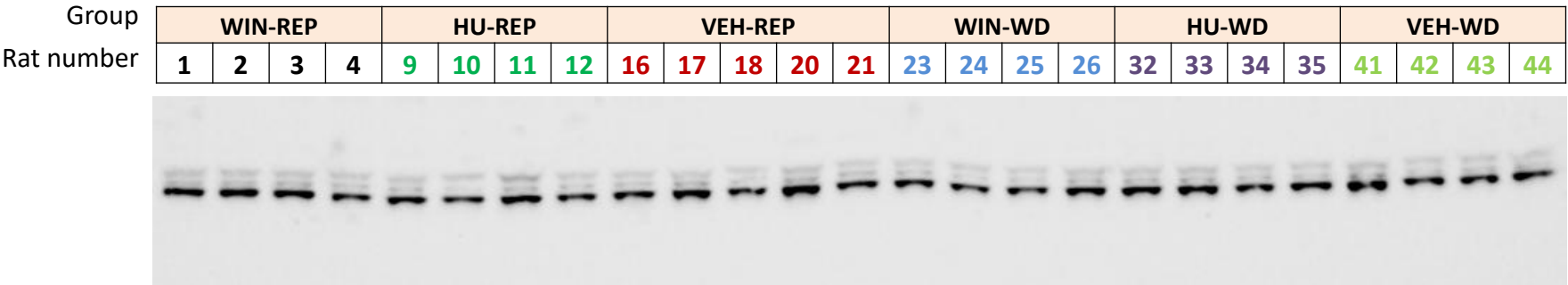
Main components (receptors and enzymes) of the endocannabinoid system: CB1

Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 1: Immunoblot

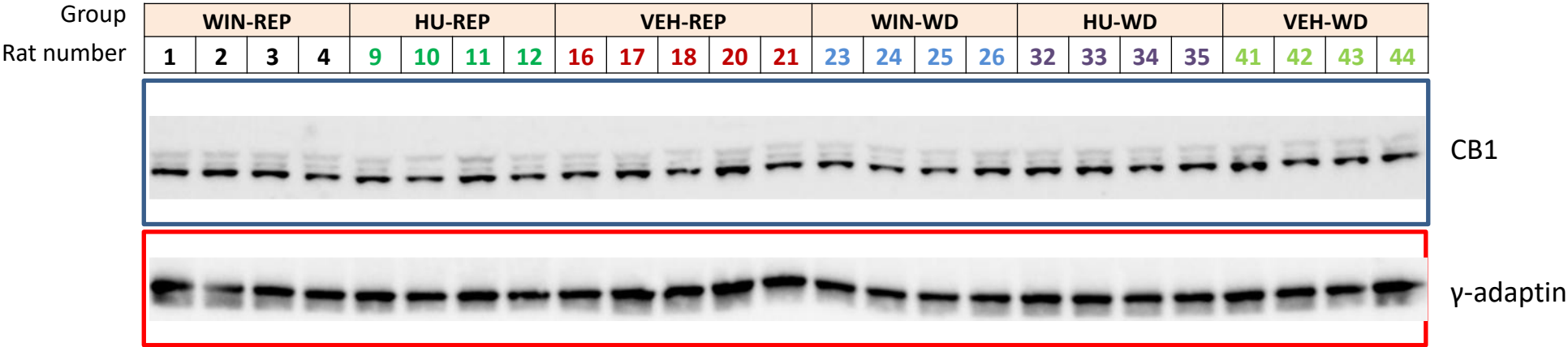
Hippocampus
CB1 (≈ 53-60 kDa)



CB1

Membrane 1: Immunoblot

Seeman Hippocampus
CB1 (≈ 53-60 kDa)

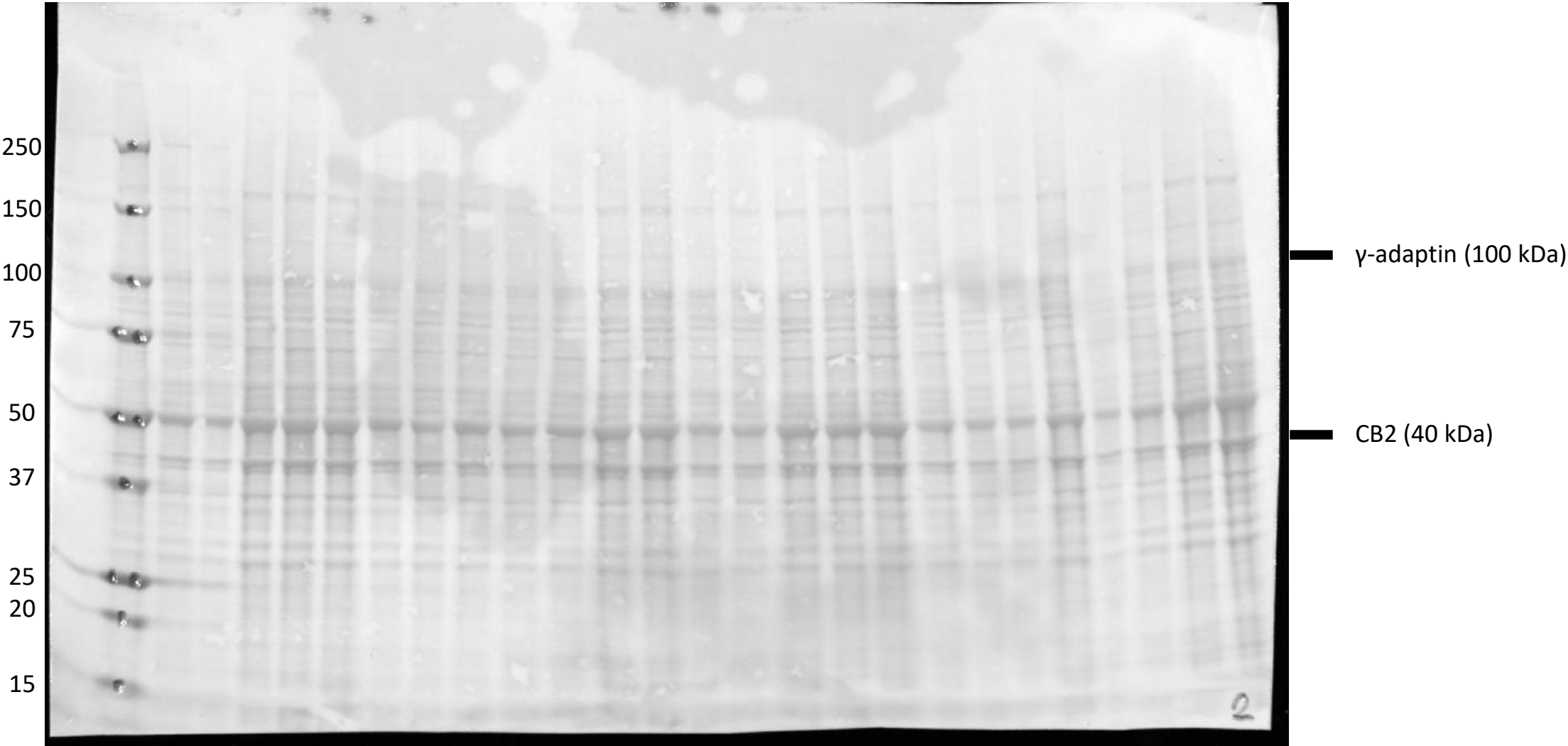


Gel 2: Ponceau S Red Staining

Hippocampus

Main components (receptors and enzymes) of the endocannabinoid system: CB2

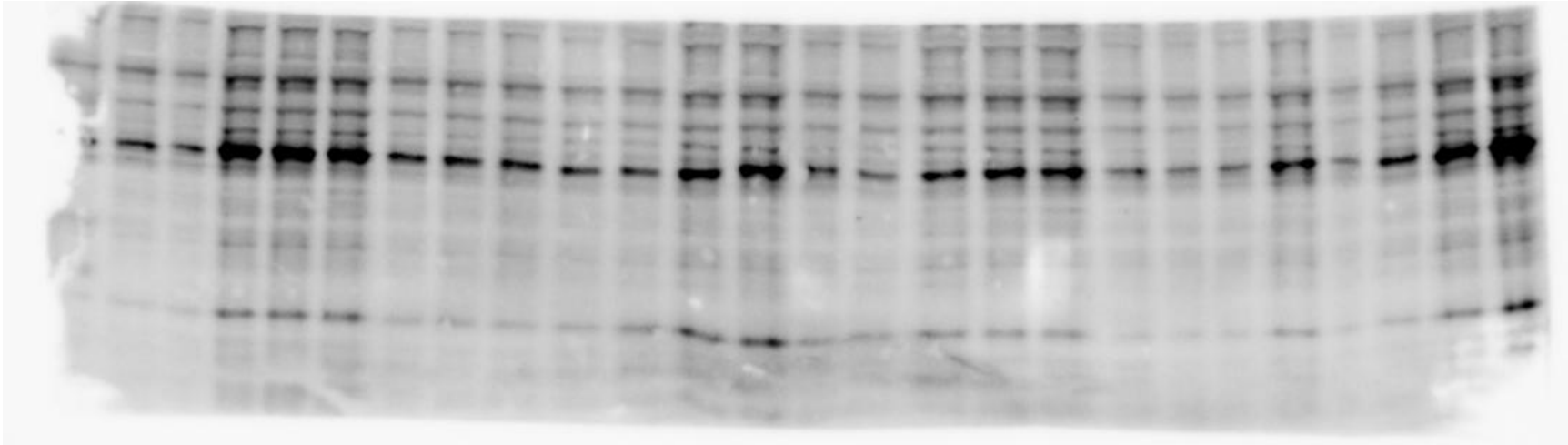
Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 2: Immunoblot

Hippocampus
CB2 (≈ 40 kDa)

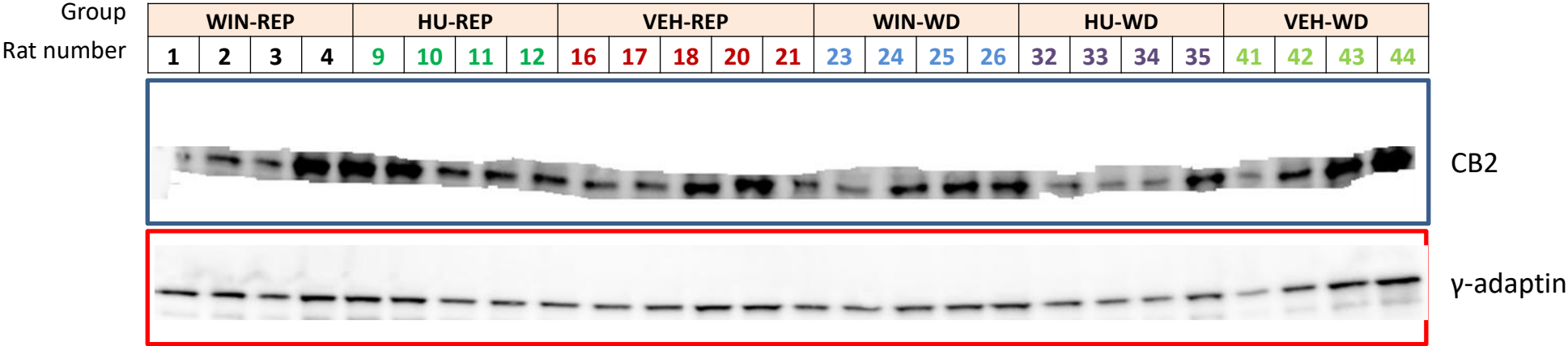
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



— CB2

Membrane 2: Immunoblot

Hippocampus
CB2 (≈ 40 kDa)

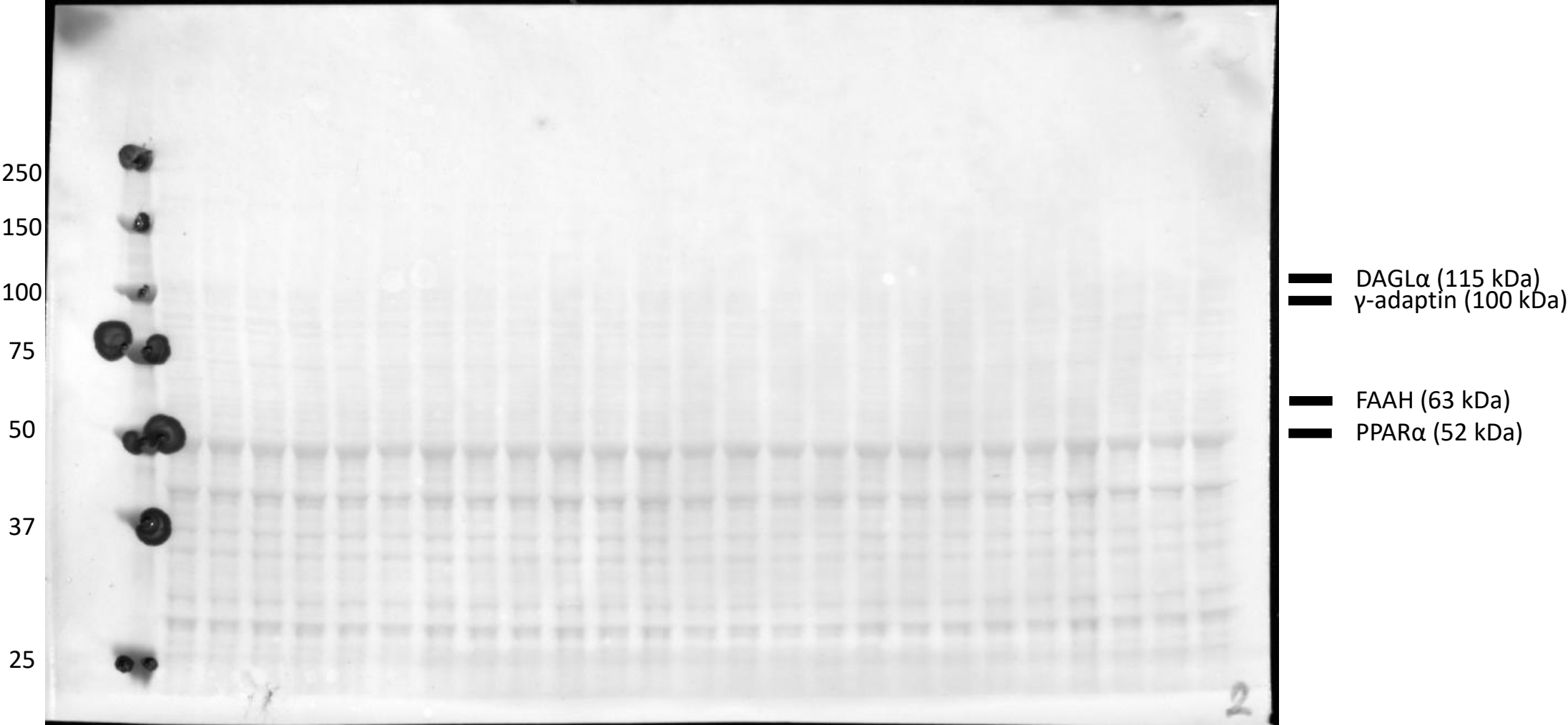


Gel 3: Ponceau S Red Staining

Hippocampus

Main components (receptors and enzymes) of the endocannabinoid system: DAGLα, PPARα, FAAH

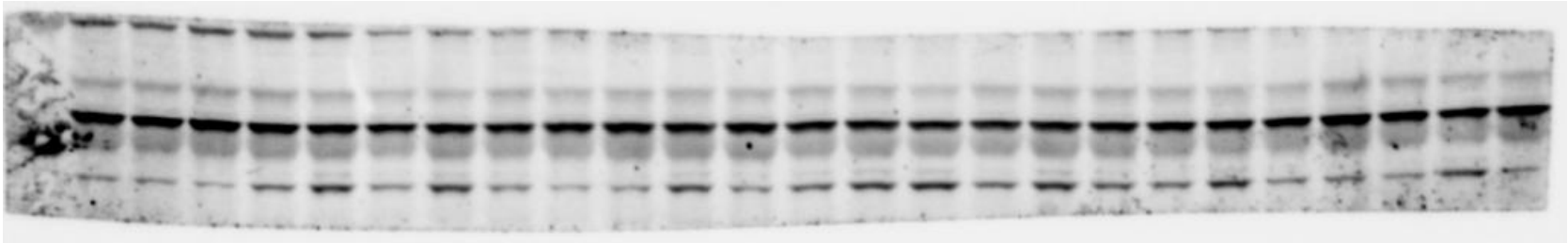
Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 3: Immunoblot

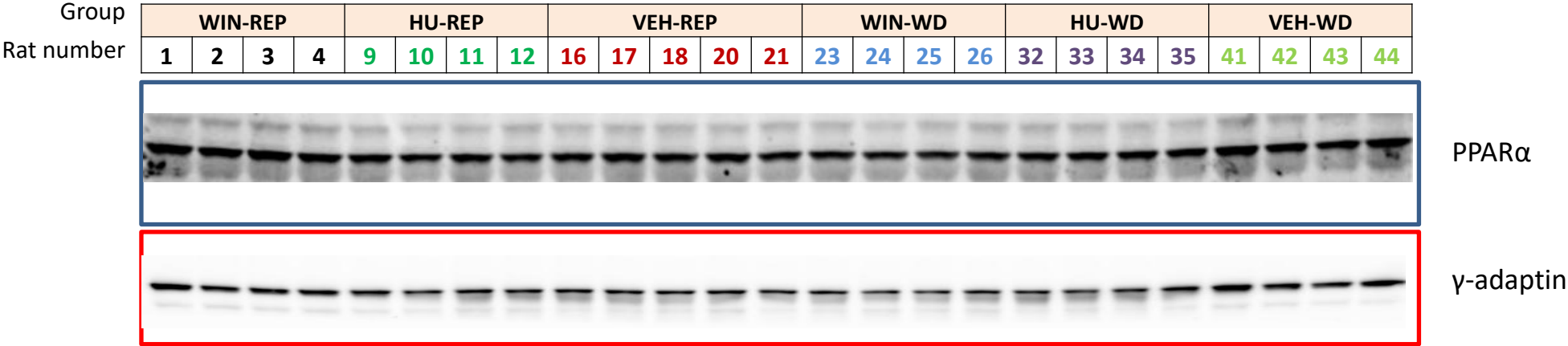
Hippocampus
PPARα (≈ 52 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 3: Immunoblot

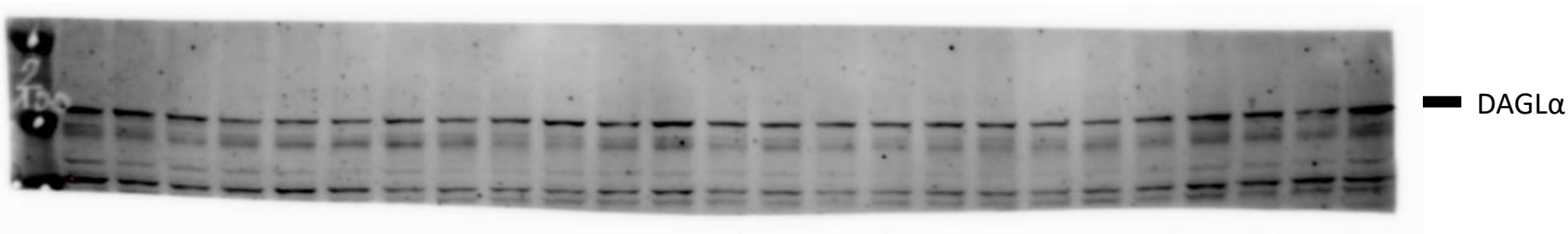
Hippocampus
PPARα (≈ 52 kDa)



Membrane 3: Immunoblot

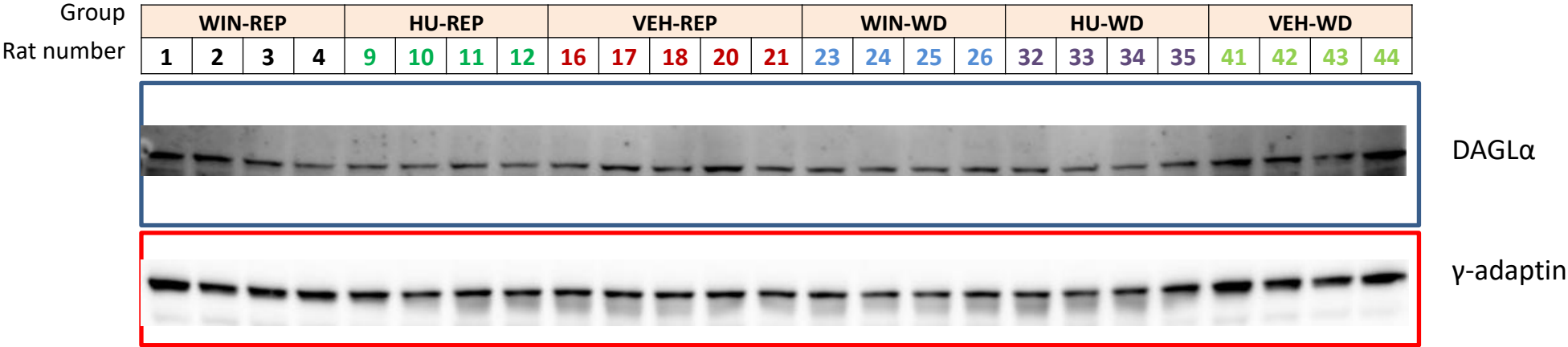
Hippocampus
DAGLα (≈ 115 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 3: Immunoblot

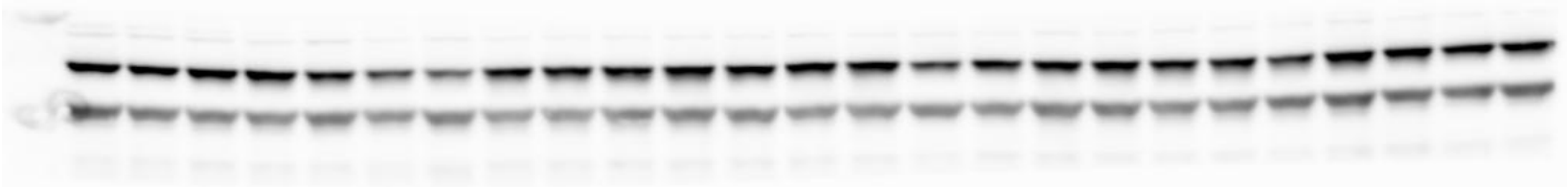
Hippocampus
DAGLα (≈ 115 kDa)



Membrane 3: Immunoblot

Hippocampus
FAAH (≈ 63 kDa)

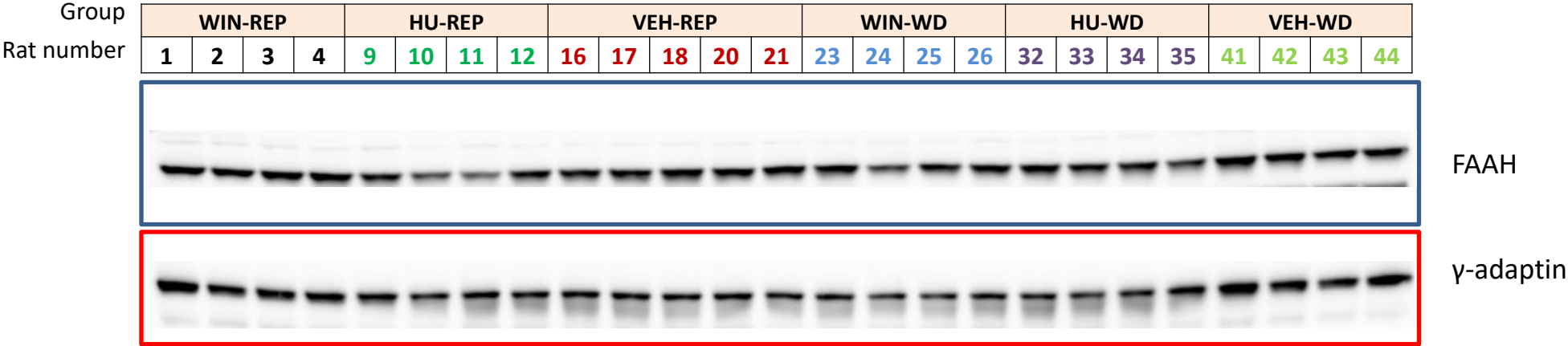
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



FAAH

Membrane 3: Immunoblot

Hippocampus
FAAH (≈ 63 kDa)

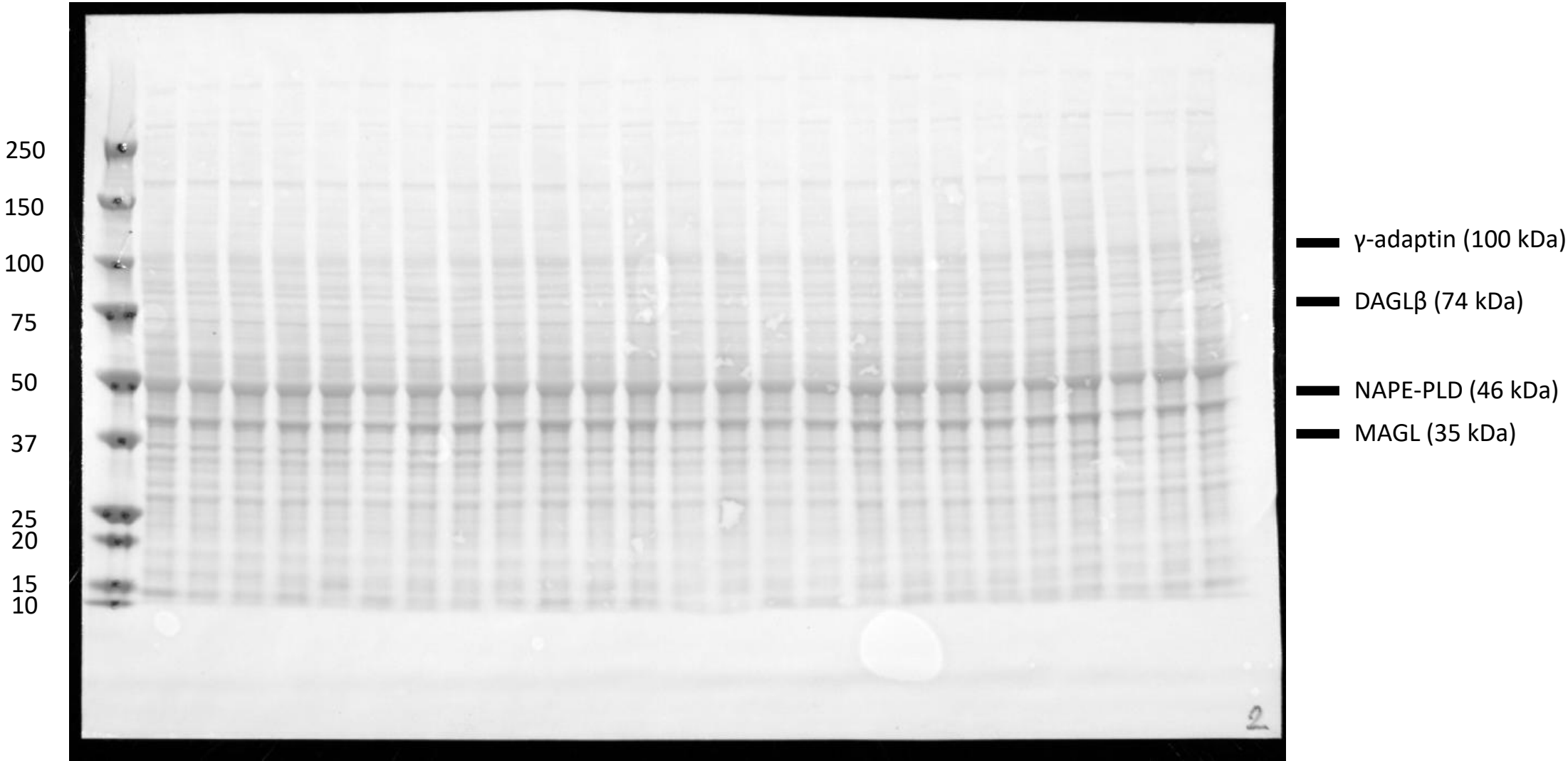


Gel 4: Ponceau S Red Staining

Hippocampus

Main components (receptors and enzymes) of the endocannabinoid system: DAGLβ, NAPE-PLD, MAGL

Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 4: Immunoblot

Hippocampus
DAGLβ (≈ 74 kDa)

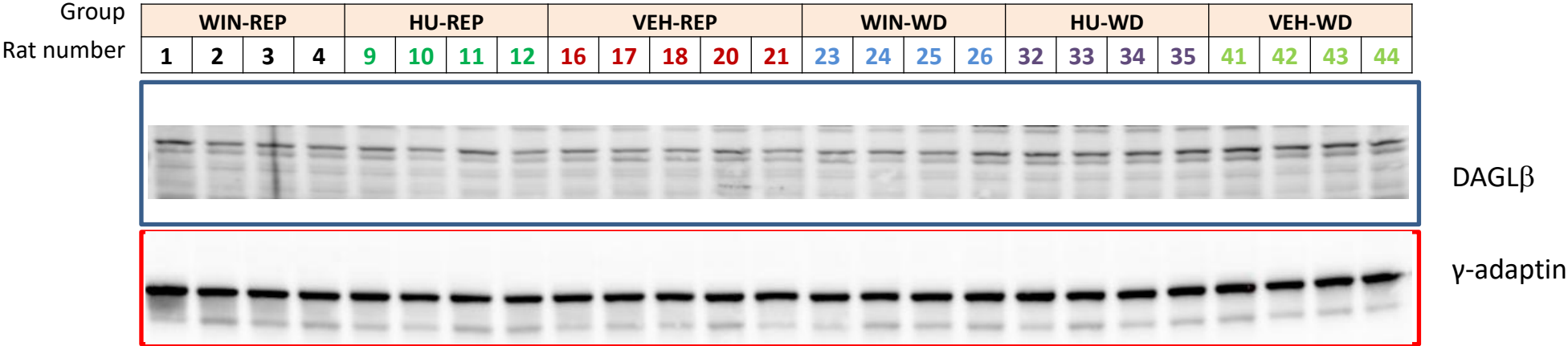
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



DAGLβ

Membrane 4: Immunoblot

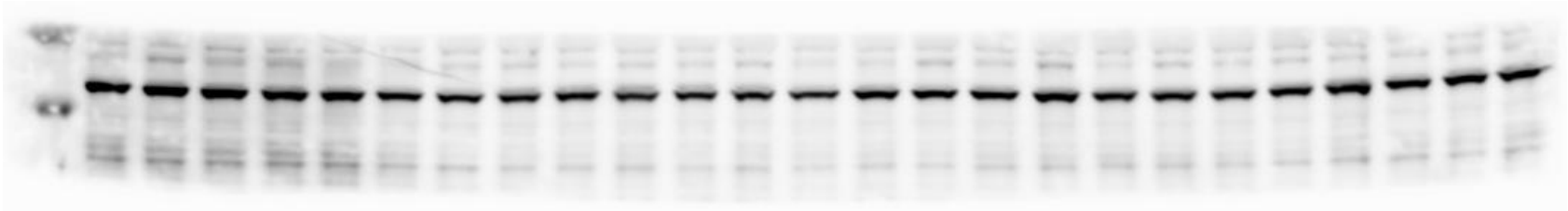
Hippocampus
DAGLβ (≈ 74 kDa)



Membrane 4: Immunoblot

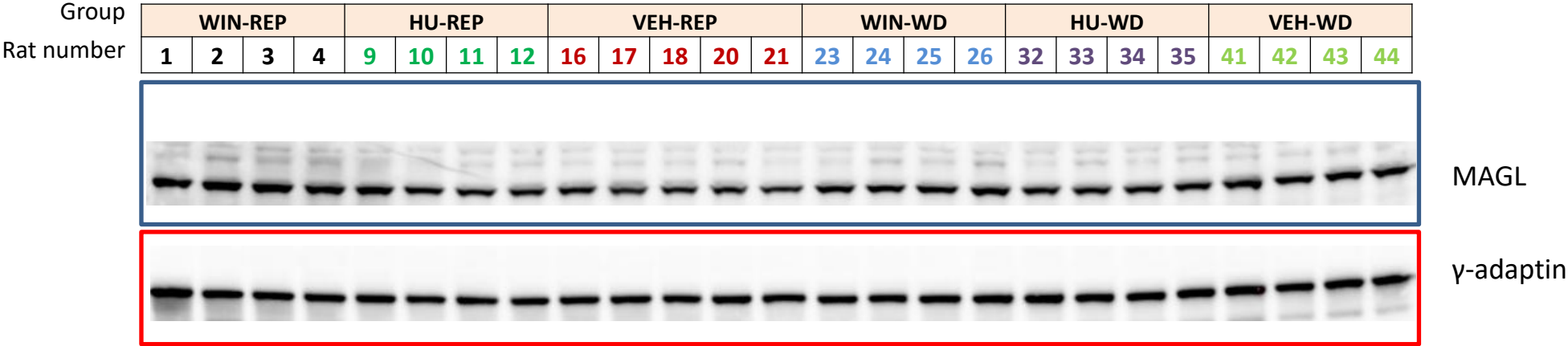
Hippocampus
MAGL (≈ 35 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 4: Immunoblot

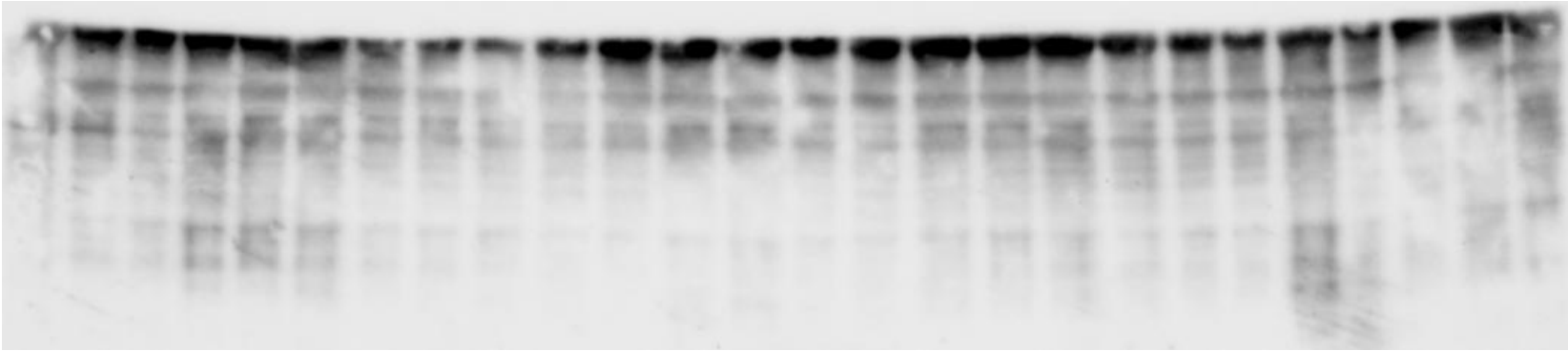
Hippocampus
MAGL (≈ 35 kDa)



Membrane 4: Immunoblot

Hippocampus
NAPE-PLD (≈ 46 kDa)

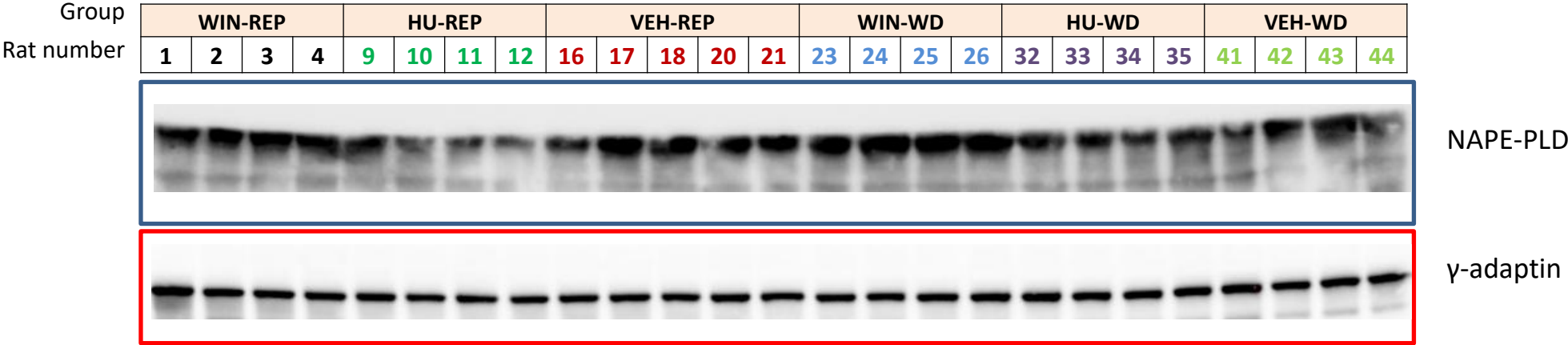
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



— NAPE-PLD

Membrane 4: Immunoblot

Hippocampus
NAPE-PLD (≈ 46 kDa)



Gel 5: Ponceau S Red Staining

Hippocampus
Biomarkers of glial cells: GFAP, IBA1, vimentin

Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44

missing

Membrane 5: Immunoblot

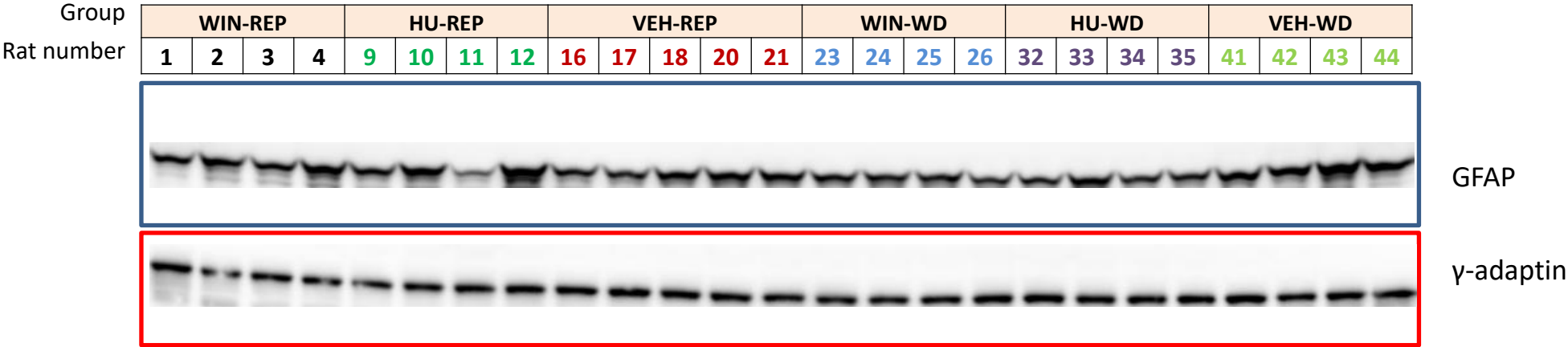
Hippocampus
GFAP (≈ 48 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 5: Immunoblot

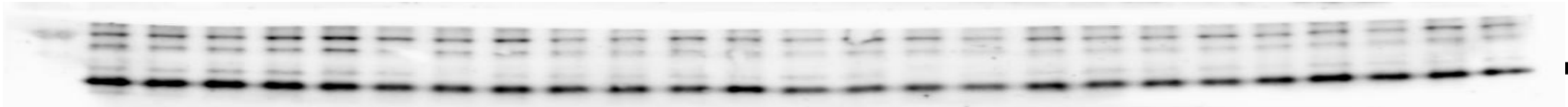
Hippocampus
GFAP (≈ 48 kDa)



Membrane 5: Immunoblot

Hippocampus
IBA1 (≈ 17 kDa)

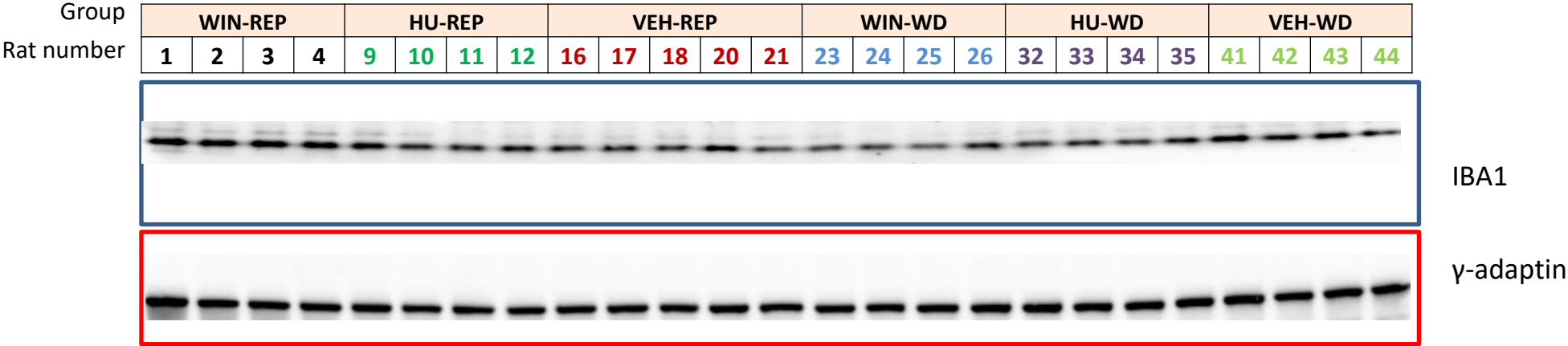
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



■ IBA1

Membrane 5: Immunoblot

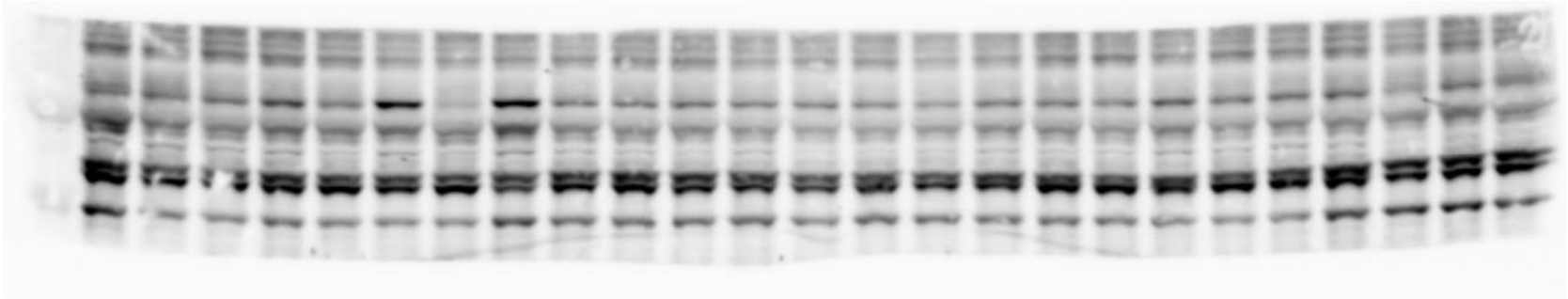
Hippocampus
IBA1 (≈ 17 kDa)



Membrane 5: Immunoblot

Hippocampus
Vimentin (≈ 54 kDa)

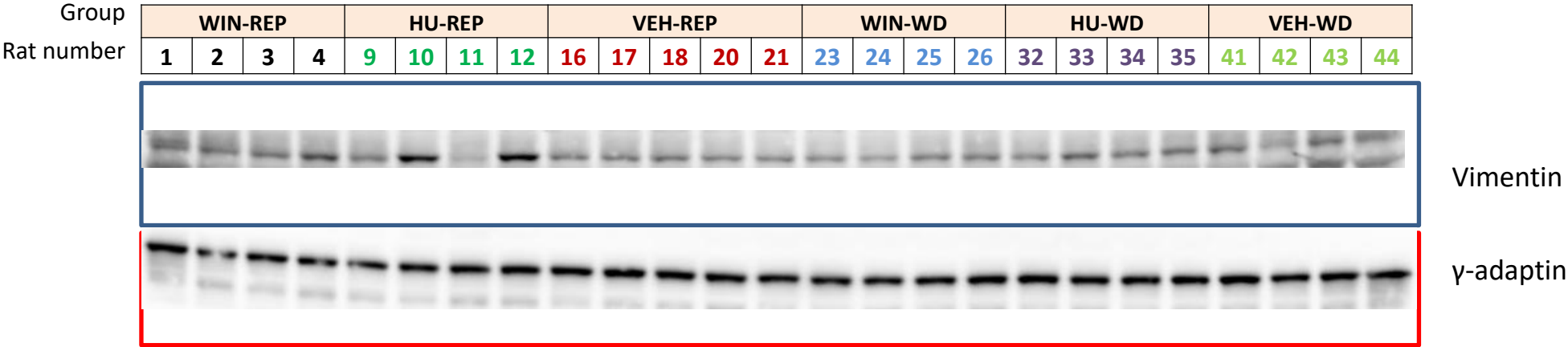
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



— Vimentin

Membrane 5: Immunoblot

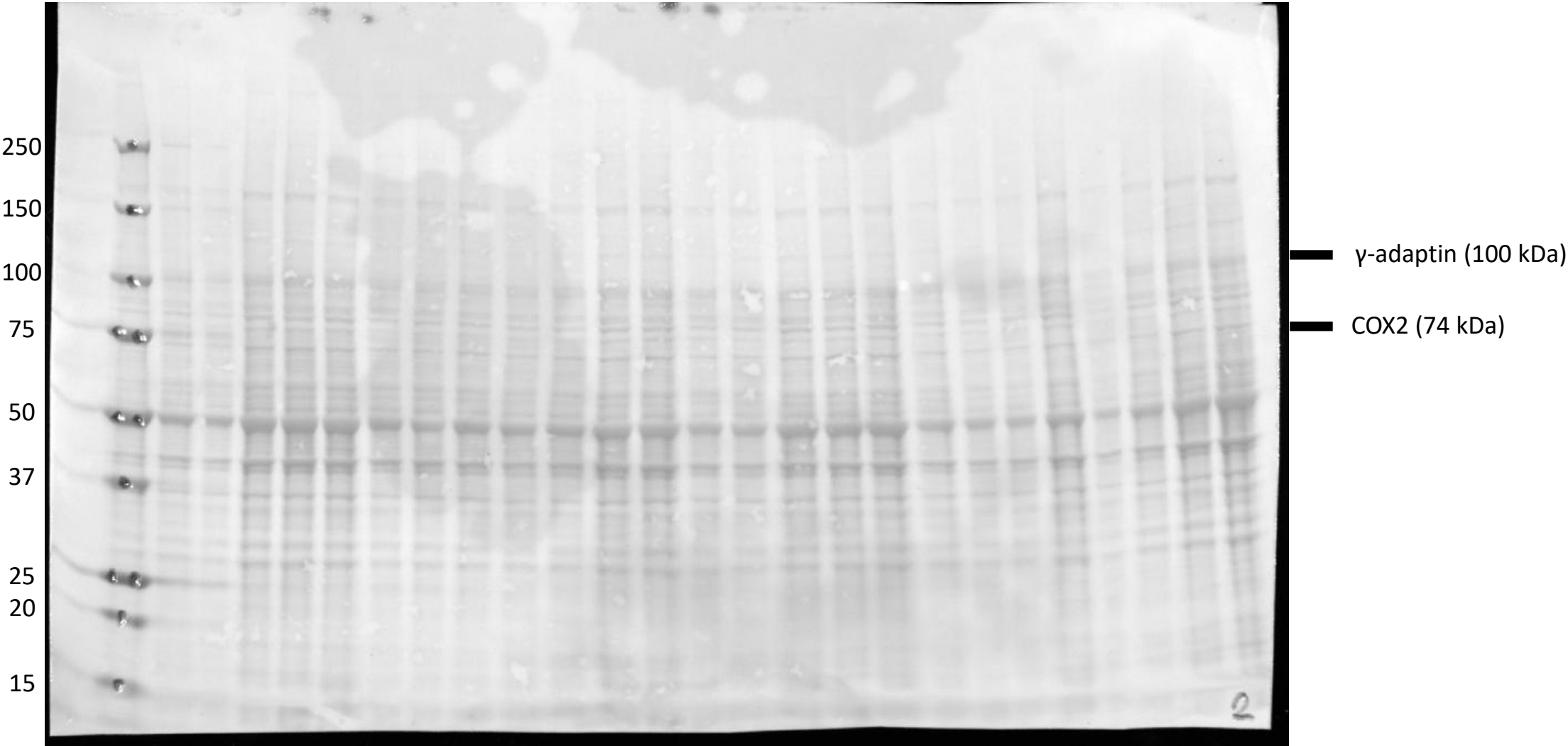
Hippocampus
Vimentin (≈ 54 kDa)



Gel 6: Ponceau S Red Staining

Hippocampus
Factors involved in neuroinflammation: COX2

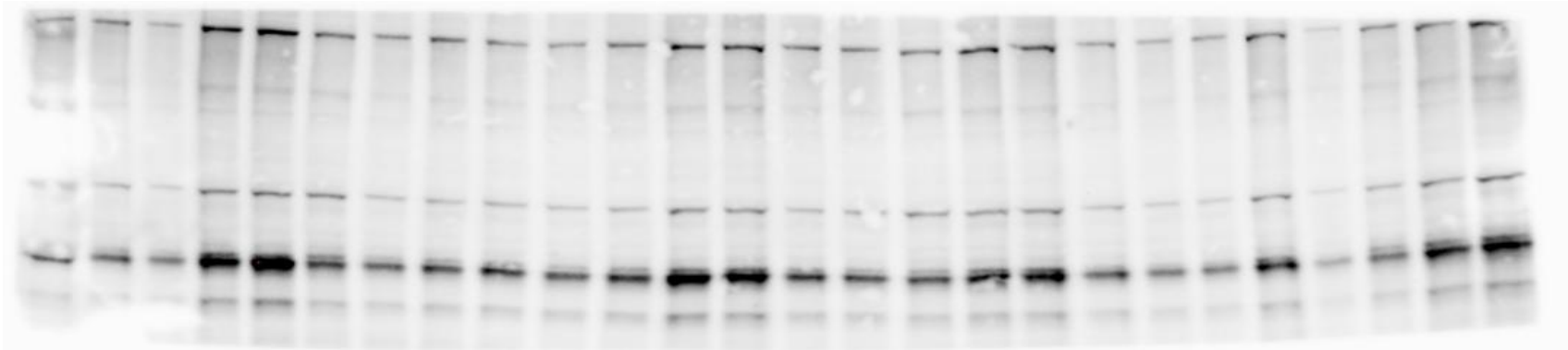
Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 6: Immunoblot

Hippocampus
COX2 (≈ 74 kDa)

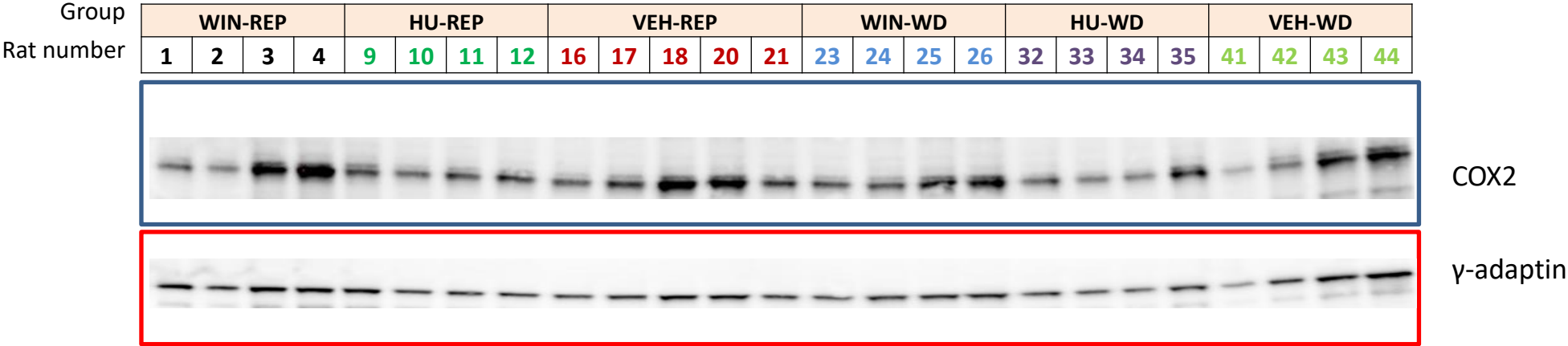
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



— COX2

Membrane 6: Immunoblot

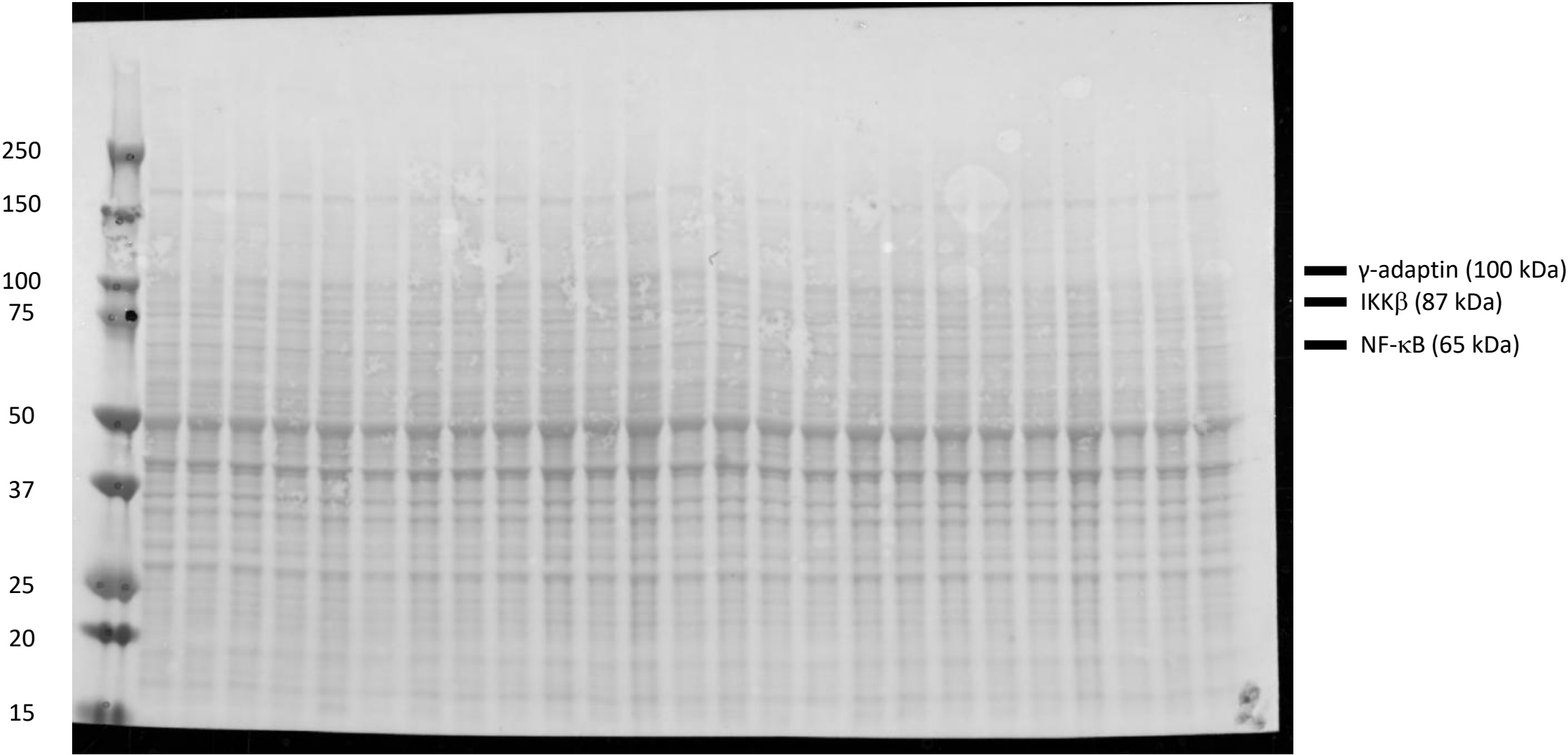
Hippocampus
COX2 (≈ 74 kDa)



Gel 7: Ponceau S Red Staining

Hippocampus
Factors involved in neuroinflammation: IKKβ, NF-κB

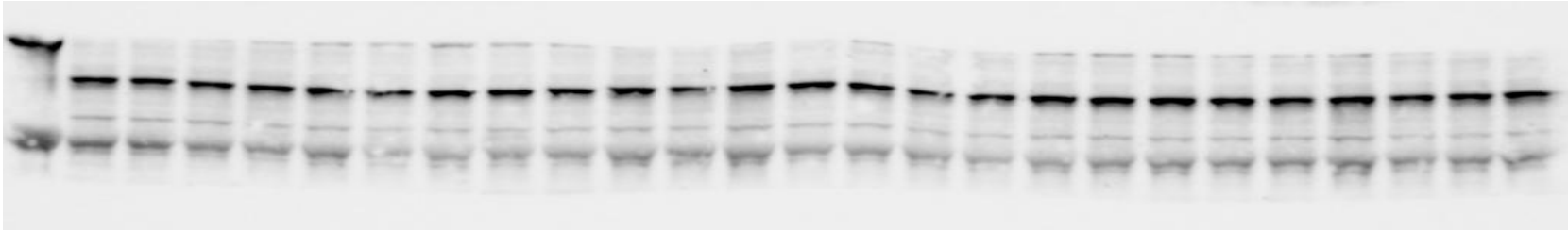
Group	MW (kDa)	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number		1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 7: Immunoblot

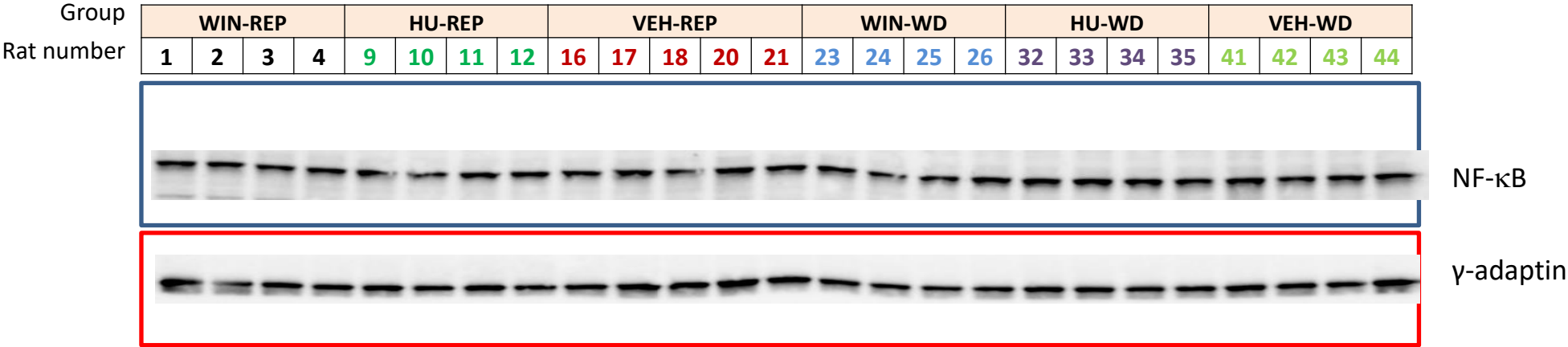
Hippocampus
NF-κB (≈ 65 kDa)

Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



Membrane 7: Immunoblot

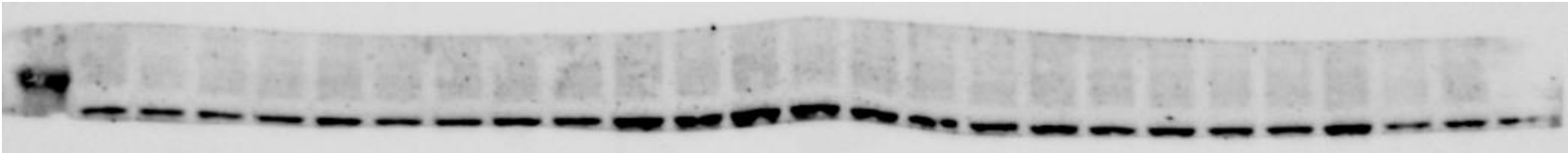
Hippocampus
NF-κB (≈ 65 kDa)



Membrane 7: Immunoblot

Hippocampus
IKKβ (≈ 87 kDa)

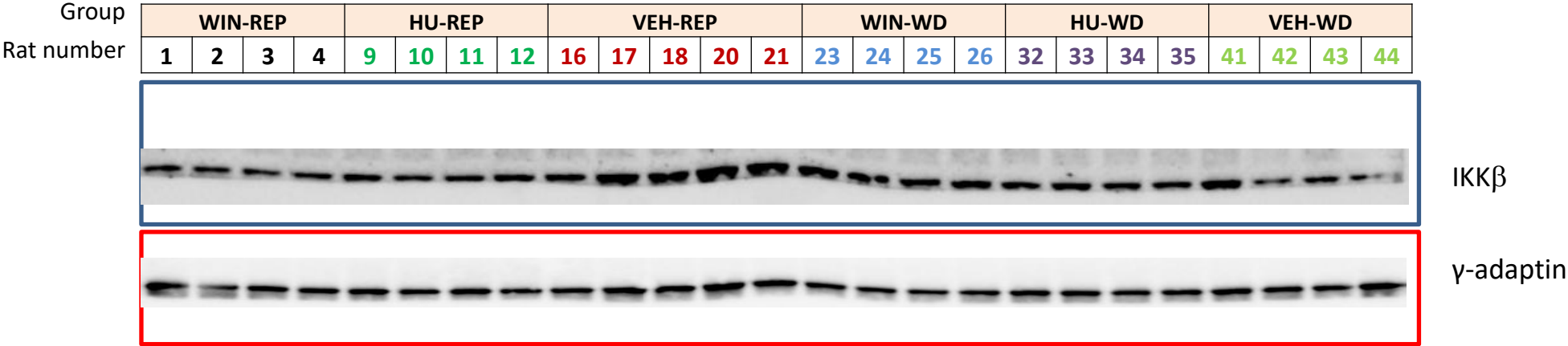
Group	WIN-REP				HU-REP				VEH-REP					WIN-WD				HU-WD				VEH-WD			
Rat number	1	2	3	4	9	10	11	12	16	17	18	20	21	23	24	25	26	32	33	34	35	41	42	43	44



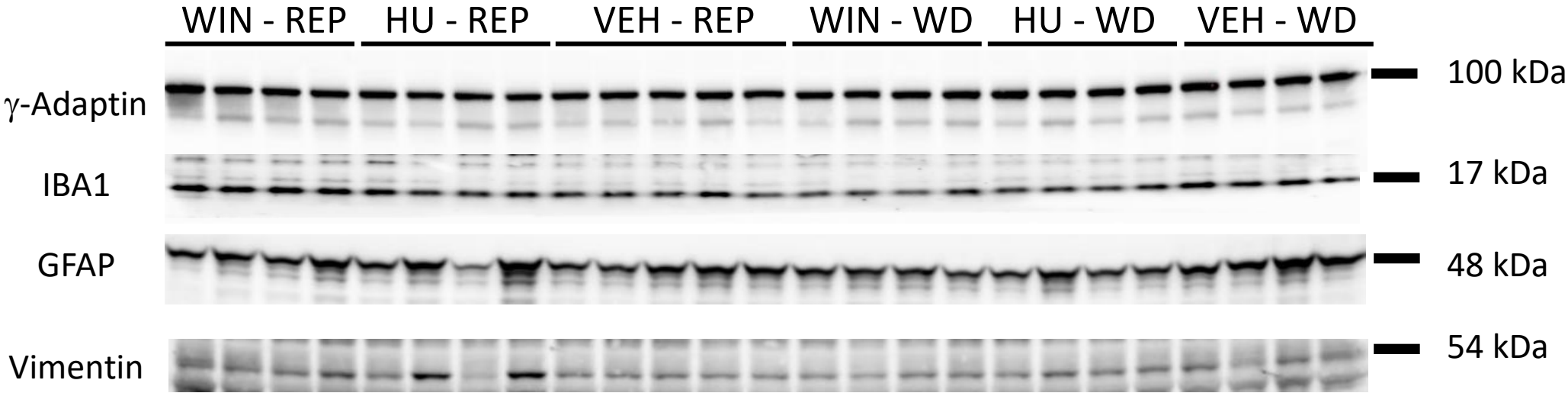
IKKβ

Membrane 7: Immunoblot

Hippocampus
IKKβ (≈ 87 kDa)



Summary of immunoblots (see Figure 5)



Summary of immunoblots (see Figure 5)

