Supplementary information

Supplement S1. Detailed overview of the genes that were selected for examination of methylxanthines-caused transcriptional changes and their classification in pathways.

gene	gene name	reference
oxidative stress		
CAT	Catalase	- depletion of cellular hydrogen peroxide - deficiency or malfunction of catalase can be linked to degenerative diseases [1] - there is a broad agreement in the role of oxidative stress in the development of cardiovascular injuries [2] - oxidative stress is reported as important pathophysiological change in COPD [3]
GPX1	Glutathione peroxidase 1	- detoxification of H_2O_2 - GPX shows an age related reduced activity and are decreased in plasma samples of AD patients [4,5] - modulation of GPx-3 activity is associated with altered risk of cardio-renal disease [6] - a study reported a reduced activity of GPx in COPD cases compared to healthy controls [7]
GPX3	Glutathione peroxidase 3	
GPX7	Glutathione peroxidase 7	
NQO1	NAD(P)H dehydrogenase, quinone 1	- polymorphism in NQO1 as a risk factor for sporadic AD [8,9] - gender-dependent (women) association with coronary artery disease and NQO1 polymorphism was found [10]
NUDT15	Nudix type motif 15	- Methylation levels of NUDT15 were altered in mild cognitive impairment (MCI) patients [11]
PARK7	Parkinsonism associated deglycase	- up-regulated DJ-1 expression related to oxidative stress and AD [12] - PARK7 protein found to be regulating vascular contractility and blood pressure, thus being a risk factor for cardiovascular diseases [13] - Protein levels of PARK7 were decreased in the lungs of COPD patients [14]
PPP1R15B	protein phosphatase 1, regulatory subunit 15B	- altered expression of PPP1R15B in murine cardiac tissue after intestinal ischemia-reperfusion [15] - inhibitors of PPP1R15B were shown to be beneficial in a model of neurodegenerative disease [16]
PRDX1	Peroxiredoxin 1	- a correlation of peroxiredoxin isoforms has been shown for traditional cardiovascular risk factors [17] - significant up-regulation of PRDX1 gene could be seen in COPD patients versus healthy smokers [18]
PRDX2	Peroxiredoxin 2	
PRDX6	Peroxiredoxin 6	
SOD1	Superoxide dismutase 1	- SOD1 deficiency drives Aβ loss [19] - a prospective study with 2799 subjects showed an association with CV deaths in the general population with a variation in the SOD1 gene [20] - SOD1 and SOD3 show associations between polymorphisms and increased risk for COPD [21]
TXNIP	Thioredoxin interacting Protein	- overexpression of TXNIP in hippocampus of AD mice model [22] - TXNIP binds to thioredoxin (TRX) causing inhibition of its antioxidant activity [22] - TXNIP function as a TRX inhibitor leads to pathological effects in diabetes and cardiovascular disease [23] - a lower expression of TXNIP was revealed in COPD subjects than in smokers, the gene could distinguish smokers from COPD subjects [24]
TXNRD2	Thioredoxin reductase 2	- KO of heart specific mt TXNRD2 in mice showed an abnormal heart development which is lethal to mice embryos; inactivation led to dilated cardiomyopathy [25] - study showed a negative correlation between mRNA levels of TXNRD2-3 and age in lung [26]
UCP3	uncoupling	- 1057 European adolescents from the HELENA study have shown UCP3 polymorphisms

	protein 3	which are associated with CVD risk factors/risk score [27] - impairs myocardial fatty acid oxidation (mice model) [28] - UCP3 protein levels were decreased in COPD patients compared to a healthy age matched control, the study could show a significant correlation between UCP3 content and FEV1 [29]
UQCRC1	ubiquinol-cytochrome c reductase core protein I	- overexpression of UQCRC1 has shown a protective effect in H9c2 cardiac cells against simulated ischemia/reperfusion via zinc binding [30] - was found to be significantly differently expressed in GO enrichment analysis in patients during AECOPD [31]
UQCRC2	ubiquinol-cytochrome c reductase core protein II	- significantly increased UQCRC2 protein levels were found in patients with CAD compared to non-CAD patients [32] - known interaction between NLRX1 via binding at UQCRC2 in respiratory chain complex III regulating ROS production in mitochondria - NLRX1 expression is decreased in patients with COPD [33]
CDK5	Cyclin-dependent kinase 5	- substrates of Cdk5 are APP and tau; deregulation of Cdk5 leads to an array of pathological events in AD [34] - activity and expression of Cdk5 is stimulated by oxidative stress [35] - in the context of cardiovascular diseases targeted inhibition of Cdk5 is discussed as potential therapeutic target [36]
DUOX1	Dual oxidase 1	- DUOX1 is an H_2O_2 producing oxidative stress related gene [37] - NADPH oxidases play a role in neurodegenerative diseases [38] - DUOX-mediated H_2O_2 is linked to different features of allergic asthma and oxidative stress, that is an important pathogenesis of cardiovascular diseases [39]
IDH1	Isocitrate dehydrogenase 1 (NADP+)	- even the oxidative stress but also the nitrosative stress are dependent on the deletion of IDP1 [40] - it was observed, that IDH1 could be linked to alterations in the energy metabolism that is a late pathomechanism for Alzheimer's Disease [41]
ERCC2	ERCC excision repair 2 TFIIH core complex helicase subunit	- higher expression of excision repair-cross-complementing (ERCC) proteins in brains of patients with AD [42] - a role for DNA repair proteins is described in atherosclerosis and cardiovascular diseases [43] - ERCC proteins participates in the repair of oxidative stress induced lesions [44]
ERCC6	ERCC excision repair 6, chromatin remodeling factor	
XPA	xeroderma pigmentosum, complemen-tation group A	- molecular misreading in AD [45] - a strong correlation between XPA expression and fibrous plaques was observed in NSTEMI patients [46] - genes which demonstrated a high module membership and gene significance for clinical indices of COPD severity included XPA (& ERCC5) [47]

lipid & energy metabolism		
ABCA1	ATP-binding cassette, subfamily A, member 1	- ABCA1 has a regulatory role in brain amyloidogenesis and amyloid clearance [48] - an ABCA1 gene variation was reported to be associated with the risk of a heart disease during pravastatin treatment [49] - ABCA1 is discussed as therapeutic target for therapy of cardiovascular diseases (cholesterol is major cardiovascular disease risk factor) [50] - as reviewed in [51] ATP-binding cassette transporters appear to have a crucial and protective role in respiratory diseases
ACAT1	Acetyl-CoA acetyltransferase 1	- cholesteryl ester levels were correlated with Aβ generation and blocking ACAT activity diminished Aβ generation [52,53] - polymorphism in the ACAT1-gene is linked with a higher risk of coronary artery disease (CAD) [54] - expression of ACAT1 seems to be induced by oxidative stress [55]
APOA1	Apolipoprotein A-I	- the HDL-cholesterol transporter ApoA1 inhibits amyloid-beta aggregation [56] - Abeta production is influenced by cholesterol levels [57] - The ratio of ApoB and ApoA1 is suggested as marker for atherosclerotic risk in prevention of coronary artery disease [58] - ApoA1 is suggested to be beneficial in the prevention and the treatment of lung diseases [59] - overexpression of ApoA1 suppressed the generation of ROS in lungs of cigarette smoke exposed mice [60]
HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase	- AD risk is associated with HMGCR gene [61] - variants of HMGCR and PCSK9 have similar effects on the risk of cardiovascular events and diabetes in correlation to the LDL cholesterol level [62]
APOE	Apolipoprotein E	- ApoE is co-deposited in senile plaques in AD brains [63] - a primarily protective role in lung biology and respiratory disease is observed for ApoE in different studies [64] - ApoE and its isoforms play a role in the pathomechanism of cardiovascular diseases [65] - deficiency of ApoE promotes increased oxidative stress [66]
HADH2	3-hydroxyacyl-CoA dehydrogenase type II	- Hadh2 is interacting with the amyloid-beta peptide [67]
LRP6	Low density lipoprotein receptor-related protein 6	- Alzheimer´s Disease is associated with a single-nucleotide polymorphism in exon 18 of LRP6 [68] - association between a mutation in LRP6 (R611C) and early coronary artery disease was observed [68]
LPL	Lipoprotein lipase	- LPL accumulation in Abeta plaques; polymorphisms of lipoprotein lipase associated with AD risk [69-71] - LPL stimulation could probably lead to lower plasma lipids that could have a positive impact of cardiovascular outcomes [72]
INSR	Insulin receptor	- significant upregulation of INSR expression in the hippocampus and the entorhinal cortex in AD [73] - defective INSR leads to an acceleration of atherosclerosis which is a cause of cardiovascular diseases [74] - INSR is down-regulated in diseases like Asthma and COPD [75]
PRKAA1	Protein kinase, AMP-activated, alpha 1 catalytic subunit	- AMPK can phosphorylate and directly activate PGC-1alpha and can also phosphorylate substrates including Tau protein, leading to tau hyperphosphorylation [76] - PRKAA1 deletion accelerated atherosclerotic lesions in hyperlipidemic mice [77] - encodes AMPKa1 which is involved in pathological changes in vessels of pulmonary hypertension patients [78]

PRKAA2	Protein kinase, AMP-activated, alpha 2 catalytic subunit	- altered expression of *PRKAA2* in APP/PS1 mice [79]
ERN1	Endoplasmatic reticulum to nucleus signaling 1	- polymorphism in the *ERN1* promoter are discussed as risk factor for the development of AD [80] - Evidence arise that ERN1 plays an important role in cardiovascular disease [81]
CLU	Clusterin	- CLU is a cellular biosensor of oxidative load alterations and is linked to different pathological conditions like atherosclerosis [82] - in regard to AD clusterin was identified as Aβ toxicity mediator [83]
AASS	Aminoadipate-semialdehyde synthase	- AD is associated with protein carbonylation [84] - hyperexpression of this gene in cardiac tissue is discussed as protection against the harmful action of ROS [15]

| signal transduction & gene expression		
PRKCA	Protein kinase C, alpha	- direct activation of the alpha secretase mediated cleavage of APP; gain-of-function-mutations in PKCalpha may promote synaptic defects [85,86] - Protein kinase C activation has shown a link to cardiovascular disease states as reviewed in [87]
PRKCD	Protein kinase C, delta	- PKCd-/- mice showed an attenuation of pulmonary fibrosis via inhibition of the NF-KB [88]
PRKCE	Protein kinase C, epsilon	- direct activation of the alpha secretase mediated cleavage of APP [85] - PRKCE showed a strong association with forced one second expiratory volume and the FEV1/FVC ratio [89]
PRKCG	Protein kinase C, gamma	- decreased PKCG level in AD fibroblasts [90]
PRKCQ	Protein kinase C, theta	- PRKCQ was reported to influence the permeability of the blood-brain barrier via tight junction protein disruption [91] - PRKCQ is an important intermediate in signaling pathways for a robust lung inflammatory response [92]
PRKCZ	Protein kinase C, zeta	- PRKCZ may contribute to the development of cardiomyopathy [93] - Patients with AECOPD showed a dynamic gene expression in an up-up pattern [94]
ALS2	alsin Rho guanine nucleotide exchange factor	- Alsin has neuroprotective activity against ALS-related insults [95] - ALS2-KO neurons are reported to be predisposed to oxidative stress [96]
GNAO1	G protein subunit alpha o1	
GNB1	Guanine nucleotide binding protein (G protein) beta polypeptide 1	- It is discussed that PS1 can interact and regulate G protein activity [97] - Aβ can influence function of G-proteins and its receptors directly or indirectly [98] - G proteins are related to cardiovascular diseases [99] - first signal transduction cascade in response to oxidative stress includes G proteins
GNB2	Guanine nucleotide binding protein (G protein) beta polypeptide 2	
EP300	E1A (adenovirus early region 1A) binding protein p300	- Ep300 is dysregulated in AD brains compared to healthy controls [100] - alterations of histone acetylation on PS1- and BACE1 promoters were described to be mediated by EP300 [101] - EP300 was linked to the development of recurrent cardiovascular events [102]
HDAC1	Histone deacetylase 1	- in AD patients the level of HDAC1 is significantly attenuated [103] - the HDAC activity reflects the severity of COPD [104] - HDACs are regulators that are playing a role in certain cellular processes e.g. apoptosis, fibrosis, oxidative stress and inflammation [105]

Aβ- and tau pathology & inflammation		
CDKL1	Cyclin-dependent kinase-like 1	- Cdkl1 is a kinase involved in the pathologic phosphorylation of tau, a neuropathological feature of AD [106]
GAP43	Growth associated protein 43	- increased GAP43 mRNA and protein level were reported in AD brains [107,108]
GSK3a	Glycogen synthase kinase 3 alpha	- GSK3 is a key kinase contributing to abnormal tau-phosphorylation causing neurofibrillary tangles in AD [109,110]
GSK3b	Glycogen synthase kinase 3 beta	- GSK3 is discussed as potential therapeutic target for myocardial diseases [111] - GSK3b mediates ROS-induced glucocorticoid unresponsiveness in COPD [112]
APBA1	APP binding, family A, member 1	- APBA proteins fine-tune APP trafficking and processing [113,114] - regulation of APP processing [115]
APBA3	APP binding, family A, member 3	- interaction of APP with APP-BP1 is required for activation of DNA synthesis and apoptosis in neurons [116]
APBB1	APP binding, family B, member 1	- APP and its processing products are reported to be present in artherosclerotic plaques, which are part of the pathomechanism of cardiovascular diseases [117,118]
APBB2	APP binding, family B, member 2	- circulating Aβ40 levels were predictive of cardiovascular mortality in patients with coronary heart disease (CHD) as reported in a retrospective cohort study [119]
APPBP1/NAE1	APP binding protein 1	- serum levels of Aβ40, Aβ42 and total Aβ are significantly increased in patients with chronic obstructive pulmonary disease compared to healthy controls [120]
UBQLN1	ubiquitilin 1	- UBQLN1 expression was decreased in human temporal cortex in relation to the early stages of AD related neurofibrillary pathology [121] - Ubqln1-CKO mice showed an increase in myocardial ubiquitinated proteins, leading to late-onset cardiomyopathy and reduced life span [122] - bioinformatical analysis showed UBQLN1 as an DEG in cases with severe COPD [123]
APH1a	aph1 homolog A, gamma secretase subunit	- encodes a component of the gamma secretase complex [124-126] - the pathogenesis of different lung diseases has been linked to the regulation of the Notch signaling, a substrate of γ-secretase [127]
APH1b	aph1 homolog B, gamma secretase subunit	- Notch is suggested to be involved in the aetiology of different cardiovascular diseases and discussed as therapeutic target [128] - the γ-secretase is discussed to mediate the oxidative stress-induced increase of the beta-secretase enzyme [129]
CASP3	caspase 3	in AD cases there is a high degree of co-localization of activated caspases and neurofibrillary tangles / senile plaques (see also CASP4)
CTSB	cathepsin B	- Cathepsin was described to play a role in APP metabolism [130]
CTSL	cathepsin L	- in AD impairments in the cathepsin family have been observed [131] - Plasma cathepsins are potential biomarkers for cardiovascular disease in humans [132] - Cathepsin L is discussed to degrade an alternative APP c-terminal fragment [133]
PSENEN	presenilin enhancer, gamma secretase subunit	- encodes a component of the gamma secretase complex [126] (see also APH1a and APH1b)
A2M	alpha-2-macroglobulin	- A2m is associated with cerebrospinal fluid (CSF) markers of neuronal injury in preclinical AD [134] - A2M gene polymorphism is associated with Parkinson´s disease [135] - up-regulated in a model of dyssynchrony heart failure (DHF) [136] - up-regulated protein expression in ST-elevation myocardial infarction [137]
ECE1	endothelin converting enzyme 1	- Aβ-degrading enzymes [138] (see also "APP binding and transport" section)
ECE2	endothelin converting enzyme 2	
LRP1	low density lipoprotein receptor-related protein 1	- LRP is associated with the transport, the production and the clearance of Abeta [139] - Inactivation of LRP1 leads to a higher risk of atherosclerosis and could result in aneurysm formation [140]
MMP2	matrix metallo-peptidase 2	- Aβ-Degradation [141] - functional polymorphisms of MMPs were related to arterial stiffness and CAD [142]

		- MMP members are up-regulated during acute or chronic phase of lung diseases [143]
PKP4	plakophilin 4	- interaction with presenilin 1 [144]
PRNP	prion protein	- Significantly altered levels of PRNP mRNA levels in ventricular autopsy samples from children and young adults which were exposed to high concentrations of air pollutants indicating increased myocardial inflammation [145] - Significant association with COPD was found only in smokers [146]
SNCA	synuclein, alpha	- up-regulated expression of SNCA in AD subjects than in control subjects [147] - link between alpha-synuclein levels in the blood and insulin resistance in SNCA knock-out mice; SNCA association to diabetes indirectly links it to CVD as diabetes is a risk factor [148]
SNCB	synuclein, beta	- levels of beta-synuclein were decreased in AD [149]
CASP4	Caspase 4	- in AD cases there is a high degree of co-localization of activated caspases and neurofibrillary tangles / senile plaques [150,151] - anti-apoptotic approaches seem to be an effective therapeutic strategy for cardiovascular diseases [152] - in the pathogenesis of COPD apoptosis of structural lung cells might possibly be an important event [153]
IL1A	Interleukin 1, alpha	- Altered expression is observed in AD [154,155] - IL-1 cytokines and the inflammasome are linked to the pathogenesis of cardiovascular diseases [156] - IL-1 alpha is secreted via alveolar macrophages and leads to subsequent lung inflammation [157]
SH2D3C/CHAT	SH2 domain containing 3C	- SH2D3C is reported to be overexpressed in Aß-enriched fractions [158] - expression of SH2D3C was found to correlate negatively with smoking, a risk factor for COPD, in a transcriptomic study in lymphocytes [159]

neuronal genes		
MAP2	Microtubule-associated protein 2	- Map2 is negative correlated to the pathomechanism of AD [160] - As a part of the MAPK-Cascade Map2 is involved in pulmonary cell adhesion and cell motility [161]
MAPT	Microtubule-associated protein tau	- hyperphosphorylated tau → neurofibrillary tangle [162,163] - top gene identified in COPD patients vs control group in a sherlock analysis [164]
PLAU	Plasminogen activator, urokinase	- Polymorphism in PLAU gene could increase the risk of AD [165] - Gene variations of the PLAU gene were significantly associated with an increased risk of MI [166] - via activation of TGF-beta1 inhibition of SERPINE2, PLAU could be linked to COPD [167]
PLAT	Plasminogen activator, tissue	- t-PA is associated with Abeta degradation [168] - t-PA protein level were significantly lower for healthy control patients than CAD patients [169]
ACHE	Acetylcholinesterase	- decreased AChE activity in AD brains [170,171] - Treatment with acetylcholinesterase inhibitors was linked to a reduced risk of acute coronary syndrome in patients with dementia [172] - Alterations in AChE activities can be associated with development and severity of COPD [173] - AChE was reported to regulate lipid metabolism in the brain via transcriptional influence on lipid-related genes [174]
BDNF	Brain-derived neurotrophic factor	- declined BDNF level in AD leads to poorly differentiated neurons, synapse loss and cognitive dysfunction [175-177] - A direct interplay of oxidative stress indicators and the levels of BNDF is suggested in the brain [178] - BDNF is indicated as important biomarker associated with parameters of COPD severity [179] - reduced plasma BDNF concentration is suggested to be linked to coronary heart disease pathogenesis [180]

Supplement S2. Selection of stable housekeeping genes. *The table listed the selected housekeeping genes and their expression stability calculated by NormFinder in SH-SY5Y-, HEPG2- and Calu-3 cells treated with different xanthine derivatives. The figure shows the expression levels of the selected genes for normalization given as quantitative real-time PCR cycle treshold (Cq) values in Calu-3(A) and HEPG2 (C) cells. Expression stability values for 19 analyzed genes calculated by NormFinder algorithm. Housekeeping genes are ranked from the least to the most stable one from the left to right and the five most stable genes selected for normalization in Calu-3 (B) and HEPG2 (D) cells are highlighted in a box.*

gene	gene name	SH-SY5Y	HEPG2	Calu-3
ACTB	Actin Beta	0.165	0.133	0.159
ATP5B	ATP synthase F1 subunit beta, mitochondrial	0.149	0.117	0.188
B2M	Beta-2-Microglobulin	0.218	0.207	0.359
C1ORF43	Chromosome 1 open reading frame 43	0.407	0.137	0.237
EIF4A2	Eukaryotic translation initiation factor 4A2	0.177	0.103	0.242
EMC7	ER membrane protein complex subunit 7	0.131	0.122	0.284
GAPDH	Glyceraldehyde-3-phosphate-dehydrogenase	0.106	0.179	0.233
GPI	Glucose-6-phospate isomerase	0.120	0.154	0.273
HPRT1	Hypoxanthine phosphoribosyltransferase 1	0.168	0.133	0.222
MPRIP	Myosine phosphatase Rho interacting protein	0.149	0.466	0.445
POLR2F	RNA polymerase II,I and III subunit F	0.139	0.146	0.297
PSMB4	Proteasome 20F subunit beta 4	0.130	0.116	0.169
RN18S1	18S ribosomal RNA	0.126	0.163	0.259
RPL13A	Ribosomal protein L13a	0.178	0.163	0.295
SDHA	Succinate dehydrogenase complex flavoprotein subunit A	0.136	0.121	0.218
SNRPD3	Small nuclear ribonucleoprotein D3 polypeptide	0.127	0.106	0.318
TBP	TATA-box binding protein	0.132	0.143	0.246
TOP1	DNA topoisomerase 1	0.109	0.133	0.326
YWHAZ	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta	0.107	0.146	0.130

A

Calu-3 cells

B

C

HEPG2 cells

D
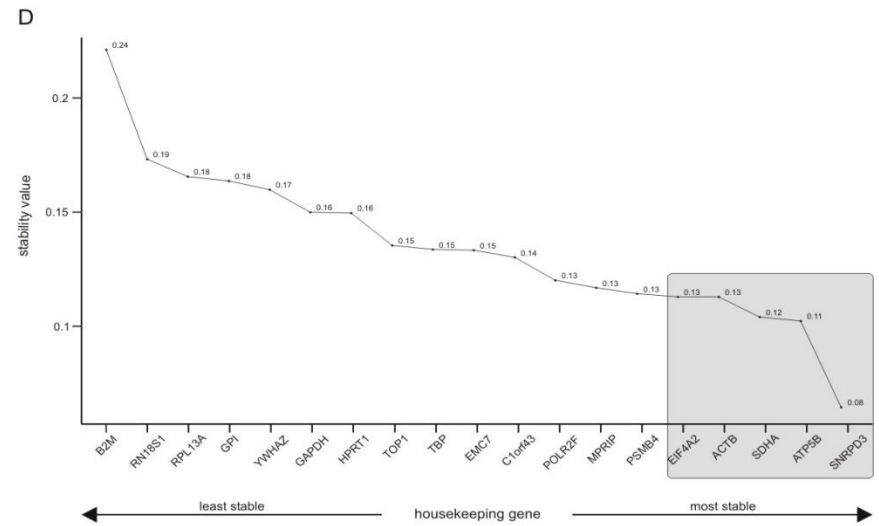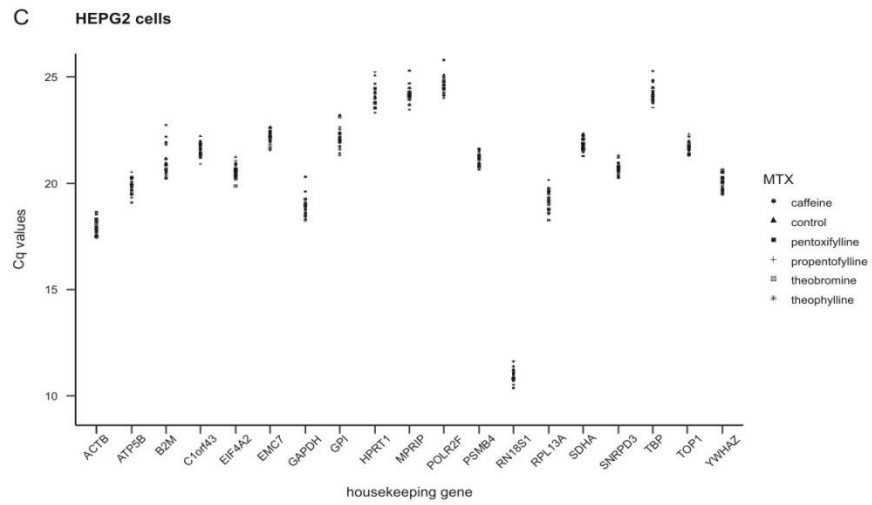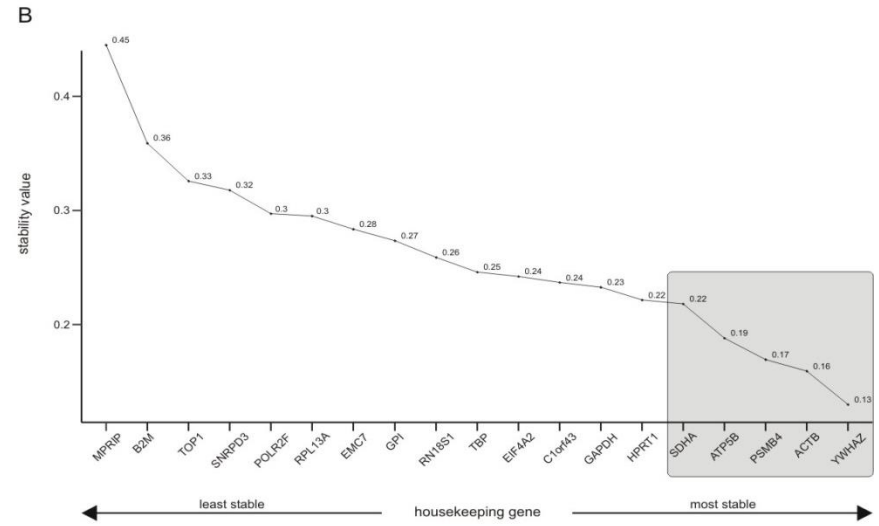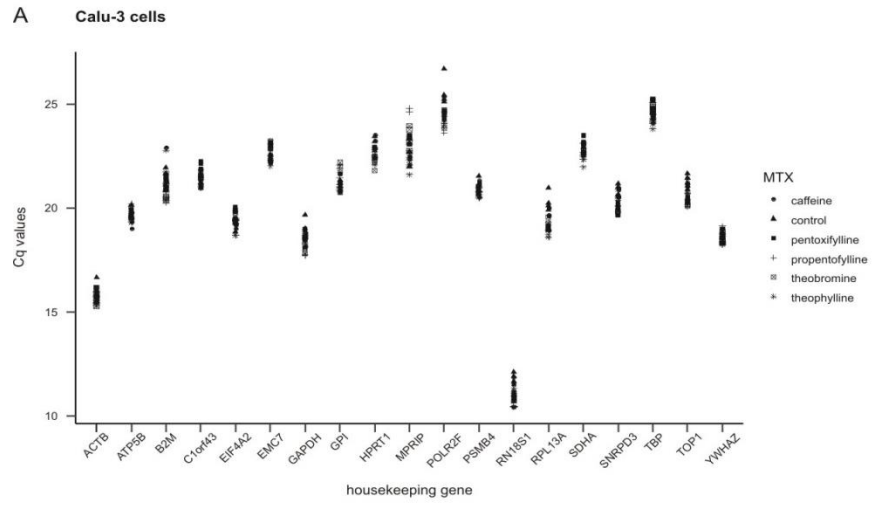
Supplement S3. Rawdata after incubation in SH-SY5Y cells. Detailed overview of transcriptional changes after treatment with caffeine, theobromine, theophylline, pentoxifylline, and propentofylline in SH-SY5Y cells compared to treatment with water as solvent control. Included are the mean expression changes ± standard error of the mean (SEM) after normalization using the five most stable housekeeping genes (RN18S1, GPI, TOP1, YWHAZ, and GAPDH). P values for ANOVA analysis, false discovery rate adjusted p values ("ANOVA adj.") and p values for Dunnett´s Test (each methylxanthine in comparison to the solvent control) are shown.

gene	mean expression changes ± standard error of the mean (SEM) [%]						p values						
	control	caffeine	theobromine	theophylline	pentoxifylline	propento-fylline	ANOVA	ANOVA adj.	Ctrl vs. C	Ctrl vs. TB	Ctrl vs. TP	Ctrl vs. P	Ctrl vs. PF
CAT	100 ± 6.96	130.07 ± 13.76	105.52 ± 16.49	97.07 ± 19.6	93.87 ± 26.82	100.54 ± 26.68	0.8205	0.8407					
GPX1	100 ± 4.64	114.58 ± 4.78	80.41 ± 2.13	83.78 ± 10.11	108.88 ± 6.99	77.58 ± 8.35	0.0012	0.0038					
GPX3	100 ± 18.95	153.5 ± 10.69	86.97 ± 5.54	97.38 ± 21.94	118.42 ± 28.29	98.46 ± 19.69	0.2976	0.3828					
GPX7	100 ± 10.69	119.98 ± 2.38	92.73 ± 8.12	100.99 ± 6.86	96.56 ± 11.83	83.71 ± 11.75	0.1421	0.2184					
NQO1	100 ± 8.99	157.56 ± 26.24	94.45 ± 5.29	117.05 ± 3.69	97.76 ± 25.43	105.93 ± 7.77	0.2962	0.3828					
NUDT15	100 ± 8.72	118.38 ± 4.79	104.7 ± 7.95	103 ± 2.35	95.56 ± 5.92	80.58 ± 8.71	0.0227	0.0449					
PARK7	100 ± 5.85	132 ± 2.39	93.58 ± 5.54	82.79 ± 10.47	103.2 ± 9.4	67.67 ± 4.53	0.0000	0.0003	0.0104	0.2507	0.9961	0.9277	0.0098
PPP1R15B	100 ± 5	115.76 ± 14.3	97.2 ± 3.55	94.73 ± 1.48	105.72 ± 5.37	90.33 ± 5.62	0.2997	0.3828					
PRDX1	100 ± 7.25	141.78 ± 5.73	168.39 ± 9.27	114.23 ± 16.05	163.31 ± 10.56	169.88 ± 6.96	0.0063	0.0160	0.1606	0.9168	0.0182	0.0104	0.0088
PRDX2	100 ± 9.97	96.14 ± 6.65	107.91 ± 3.78	97.04 ± 3.36	120.79 ± 7.02	92.91 ± 3.49	0.0645	0.1071					
PRDX6	100 ± 14.17	124.25 ± 7.12	169.35 ± 7.04	137.95 ± 16.42	202.09 ± 6.14	185.26 ± 5.22	0.0005	0.0021	0.6276	0.2404	0.0003	0.0109	0.0020
SOD1	100 ± 5.97	96.13 ± 9.41	69.06 ± 8.37	76.85 ± 10.4	82.38 ± 5.58	69.75 ± 9.84	0.0181	0.0396	0.9931	0.1044	0.2814	0.0208	0.0241
TXNIP	100 ± 8.23	61.45 ± 31.93	77 ± 7.88	47 ± 9.56	109.24 ± 15.95	60.54 ± 11.75	0.0113	0.0253	0.1284	0.0238	0.9733	0.5383	0.1162
TXNRD2	100 ± 2.18	125.01 ± 2.79	80.3 ± 5.82	92.42 ± 4.97	112.07 ± 8.7	71.7 ± 4.64	0.0000	0.0001	0.0142	0.7623	0.3766	0.0626	0.0056
UCP3	100 ± 8.65	95.62 ± 18.31	106.26 ± 3.89	80.02 ± 4.18	110.46 ± 4.13	97.3 ± 10.38	0.3260	0.4042					
UQCRC1	100 ± 16.98	116.92 ± 10.24	113.55 ± 33.19	82.45 ± 31.22	125.7 ± 36.45	85.6 ± 28.95	0.8721	0.8721					
UQCRC2	100 ± 13.14	92.99 ± 5.65	94.25 ± 7.65	91.12 ± 7.29	95.81 ± 13.58	74.36 ± 13.36	0.5394	0.6133					
CDK5	100 ± 10.36	134.03 ± 5.4	81.63 ± 26.92	87.44 ± 3.1	115.11 ± 2.01	99.47 ± 9.55	0.0410	0.0708					
DUOX1	100 ± 9.67	70.95 ± 33.5	95.67 ± 8.77	105.04 ± 12.93	99.89 ± 26.56	72.87 ± 25.15	0.6432	0.6933					

IDH1	100 ± 12.75	103.92 ± 15.89	132.82 ± 6.52	84.64 ± 11	126.44 ± 13.45	147.64 ± 4.66	0.0203	0.0422	0.9995	0.8505	0.4479	0.2614	0.0563
ERCC2	100 ± 9.65	159.67 ± 5.94	69.13 ± 5.56	56.64 ± 7.42	73.4 ± 9.64	51.86 ± 11.07	0.0000	0.0000	0.0000	0.0017	0.0606	0.0252	0.0007
ERCC6	100 ± 19.21	122.49 ± 16.47	42.71 ± 19.37	55.13 ± 19.68	54.24 ± 28.28	46.77 ± 18.25	0.0043	0.0116	0.7143	0.1517	0.1403	0.0477	0.0705
XPA	100 ± 13.76	99.95 ± 15.86	81.8 ± 10.57	84.09 ± 8.27	63.22 ± 19.1	77.36 ± 14.78	0.2664	0.3625					
ABCA1	100 ± 13.09	66.3 ± 37.1	44.78 ± 7.5	62.84 ± 11.71	115.31 ± 4.43	35.26 ± 7.86	0.0011	0.0038	0.2175	0.1531	0.8366	0.0189	0.0058
ACAT1	100 ± 4.12	85.53 ± 10.67	90.99 ± 6.85	96.19 ± 5.14	95.36 ± 10.32	79.74 ± 7.85	0.3787	0.4491					
APOA1	100 ± 13.82	71.75 ± 23.65	237.71 ± 12.65	226.95 ± 19.76	127.97 ± 12.98	209.87 ± 9.7	0.0006	0.0023	0.9022	0.0122	0.9057	0.0066	0.0320
HMGCR	100 ± 13.95	99.64 ± 12.39	111.18 ± 12.78	82.69 ± 9.35	102.47 ± 10.09	117.27 ± 4.16	0.3774	0.4491					
APOE	100 ± 9.26	130.89 ± 11.4	119.13 ± 10.18	86.62 ± 17.77	99.9 ± 11.28	125.5 ± 13.12	0.1954	0.2845					
HADH2	100 ± 6.85	155.45 ± 9.14	80.25 ± 5.49	72.37 ± 6.69	96.62 ± 5.43	67.01 ± 2.85	0.0000	0.0000	0.0002	0.0608	0.9972	0.2435	0.0210
LRP6	100 ± 16.73	146.35 ± 10.85	99.38 ± 12.02	95.19 ± 11.22	134.5 ± 5.27	91.43 ± 7.56	0.0188	0.0401					
LPL	100 ± 11.06	216.3 ± 9.25	219.24 ± 13.59	190.86 ± 7.38	132.87 ± 22.68	125.92 ± 22.52	0.0064	0.0160	0.0107	0.0532	0.7821	0.0090	0.8963
INSR	100 ± 27.26	126.57 ± 5.41	105.16 ± 22.84	112.63 ± 23.63	144.84 ± 33.68	132.17 ± 13.63	0.8611	0.8716					
PRKAA1	100 ± 16.41	111.83 ± 6.39	113.16 ± 8.29	92.5 ± 17.53	119.56 ± 16.86	122.71 ± 9.37	0.6532	0.6950					
PRKAA2	100 ± 25.87	113.39 ± 12.07	119.15 ± 11.84	146.81 ± 17.85	138.09 ± 34.82	95.27 ± 18.05	0.7167	0.7530					
ERN1	100 ± 11.13	183.32 ± 24.06	52.23 ± 13.12	47.46 ± 14.63	61.26 ± 7.84	55.8 ± 17.34	0.0007	0.0026	0.0292	0.2431	0.5061	0.3197	0.3871
CLU	100 ± 2.26	395.02 ± 42.33	164.31 ± 30.71	195.75 ± 10.68	117.02 ± 16.02	176.3 ± 16.98	0.1126	0.1763					
AASS	100 ± 7.72	82.97 ± 30.06	149.37 ± 3.16	75.49 ± 4.79	89.89 ± 11.49	106.28 ± 10.71	0.0089	0.0211	0.8019	0.5254	0.9685	0.0491	0.9960
PRKCA	100 ± 16.51	95.47 ± 9.29	124.36 ± 4.33	114.13 ± 8.93	125.05 ± 27.8	89.56 ± 6.99	0.5631	0.6231					
PRKCD	100 ± 14.51	71.96 ± 5.43	139.64 ± 4.89	135.58 ± 8.19	134.46 ± 12.5	144.86 ± 8.24	0.0018	0.0052					
PRKCE	100 ± 11.45	140.67 ± 7.91	121.26 ± 5.06	99.58 ± 2.47	113.08 ± 10.82	120.9 ± 5.49	0.0426	0.0721					
PRKCG	100 ± 7.71	94.34 ± 12.69	123.81 ± 7.02	137.9 ± 6.55	105.56 ± 22.63	160.53 ± 11.39	0.0352	0.0648					
PRKCQ	100 ± 13.62	256.87 ± 28.7	83.65 ± 5.42	161.16 ± 10.94	112.88 ± 25.06	130.2 ± 3.47	0.0222	0.0448	0.0162	0.5834	0.9988	0.9964	0.9505
PRKCZ	100 ± 11.66	104.22 ± 10.27	119.01 ± 7.41	105.07 ± 11.9	114.34 ± 5.55	119.74 ± 7.13	0.6266	0.6843					
ALS2	100 ± 3.94	89 ± 2.58	235.42 ± 9.92	189.81 ± 8.47	144.09 ± 10.06	252.76 ± 4.64	0.0000	0.0000	0.9708	0.0011	0.1385	0.0001	0.0000
GNAO1	100 ± 25.06	136.21 ± 3.57	77.18 ± 7.81	58.92 ± 13.25	83.42 ± 22.03	87.24 ± 12.09	0.0240	0.0462					

GNB1	100 ± 46.06	116 ± 25.57	212.07 ± 15.27	107 ± 42.55	209.8 ± 38.13	298.29 ± 4.08	0.0392	0.0703					
GNB2	100 ± 4.42	132.14 ± 3.47	72.14 ± 4.31	79.14 ± 4.84	60.6 ± 13.35	75.99 ± 4.39	0.0000	0.0000	0.0008	0.0284	0.0001	0.0034	0.0108
EP300	100 ± 5.39	168.04 ± 4.81	72.09 ± 5.43	76.11 ± 2.91	84.24 ± 7.92	75.76 ± 5.98	0.0000	0.0000	0.0000	0.0256	0.1948	0.0086	0.0232
HDAC1	100 ± 14.74	116.09 ± 1.79	127.66 ± 6.49	84.07 ± 12.78	112.68 ± 16.11	119.04 ± 5.76	0.1526	0.2302					
CDKL1	100 ± 30.06	139.3 ± 11.46	123.66 ± 24.67	99.86 ± 23.64	121.66 ± 25.84	145.96 ± 24.15	0.8041	0.8342					
GAP43	100 ± 23	178.87 ± 7.57	89.16 ± 11.31	68.57 ± 8.87	80.16 ± 17.32	89.68 ± 9.5	0.0003	0.0014	0.0029	0.3730	0.7566	0.9696	0.9752
GSK3a	100 ± 8.41	131.06 ± 3.09	118.59 ± 7.57	99.24 ± 10.15	128.19 ± 11.02	124.07 ± 6.82	0.1023	0.1633					
GSK3b	100 ± 35.67	177.47 ± 14.66	146.04 ± 12.41	107.17 ± 24.76	156.78 ± 20.2	214.92 ± 25.99	0.2155	0.2981					
APBA1	100 ± 9.05	123.72 ± 13.24	100.53 ± 11.8	96.21 ± 10.51	116.87 ± 17.53	95.7 ± 4.12	0.5546	0.6220					
APBA3	100 ± 8.94	127.53 ± 6.05	84.44 ± 14.18	103.32 ± 7.99	125.94 ± 11.47	104.55 ± 9.56	0.0720	0.1172					
APBB1	100 ± 18.6	136.32 ± 4.54	139.57 ± 17.3	124.1 ± 22.53	168.39 ± 26.3	171.1 ± 9.41	0.3944	0.4553					
APBB2	100 ± 4.59	163.7 ± 6.55	89.68 ± 24.61	96.23 ± 11.31	85.09 ± 4.66	88.57 ± 9.41	0.0013	0.0041	0.0050	0.9995	0.8352	0.9546	0.9331
APPBP1	100 ± 12.44	135.96 ± 3.63	118.68 ± 14.66	102.03 ± 9.13	116.2 ± 26.43	84.73 ± 3.74	0.3263	0.4042					
UBQLN1	100 ± 12.65	138.66 ± 5.91	86.23 ± 2.97	84.09 ± 3.67	99.19 ± 4.13	86.92 ± 4.19	0.0002	0.0008	0.0031	0.3526	1.0000	0.4818	0.5285
APH1a	100 ± 6.61	124.11 ± 8.08	61.15 ± 3.03	54.08 ± 5.42	55.78 ± 13.35	61.91 ± 7.23	0.0000	0.0000	0.0517	0.0003	0.0004	0.0018	0.0018
APH1b	100 ± 3.58	141.08 ± 8.72	61.04 ± 19.27	60.08 ± 6.73	69.3 ± 4.82	62.76 ± 16.81	0.0000	0.0001	0.0135	0.0167	0.0788	0.0197	0.0265
CASP3	100 ± 13.66	172.59 ± 9.92	62.93 ± 22.17	66.89 ± 6.54	89.15 ± 6.86	76.32 ± 3.59	0.0000	0.0001	0.0009	0.1715	0.9321	0.1083	0.4413
CTSB	100 ± 7.97	114.94 ± 4.69	84.86 ± 10	95.01 ± 10.05	87.31 ± 18.31	64.01 ± 13.49	0.0398	0.0703					
CTSL	100 ± 9.63	136.7 ± 7.8	64.73 ± 19.38	77.65 ± 6.34	91.07 ± 11.56	61.53 ± 18.35	0.0006	0.0023					
PSENEN	100 ± 7.53	143.11 ± 10.9	74.08 ± 5.41	69.19 ± 5.97	100.88 ± 4.38	61.31 ± 8.31	0.0000	0.0001	0.0050	0.0520	1.0000	0.1204	0.0121
A2M	100 ± 13.67	69.58 ± 19.04	576.6 ± 20.29	445.48 ± 13.64	169.52 ± 19.46	451.01 ± 10.09	0.0000	0.0001	0.9953	0.0027	0.8703	0.0004	0.0024
ECE1	100 ± 16.03	73.71 ± 12.58	61.72 ± 22.42	112.92 ± 22.37	94.85 ± 34.2	55.56 ± 35.03	0.3459	0.4222					
ECE2	100 ± 16.17	150.04 ± 3.8	54.4 ± 13.25	60.26 ± 10.37	84.74 ± 14.71	50.91 ± 6.35	0.0000	0.0001	0.0069	0.0353	0.6923	0.0142	0.0082
LRP1	100 ± 8.94	117.13 ± 12.85	50.23 ± 20.72	80.94 ± 6.94	91.21 ± 9.11	72.62 ± 13.45	0.0038	0.0105	0.6415	0.5509	0.9561	0.0110	0.2375
MMP2	100 ± 15.48	132.24 ± 6.29	74.3 ± 7.42	81.52 ± 12.27	63.2 ± 9.62	54.8 ± 8.94	0.0001	0.0007	0.0840	0.4896	0.0420	0.2110	0.0107
PKP4	100 ± 5.41	122.49 ± 7.22	106.3 ± 4.25	105.14 ± 6.88	105.1 ± 9.83	97.1 ± 2.03	0.2094	0.2946					

PRNP	100 ± 14.59	102.2 ± 7.09	154.6 ± 9.38	159.86 ± 9.45	85.13 ± 13.13	162.92 ± 9.61	0.0009	0.0031	1.0000	0.0219	0.8931	0.0388	0.0155
SNCA	100 ± 15.06	105.36 ± 4.06	101.69 ± 7.8	92.43 ± 12.59	103.85 ± 19.45	63.96 ± 8.07	0.1921	0.2845					
SNCB	100 ± 12.79	131.41 ± 20.02	58.34 ± 8.74	71.52 ± 9.36	87.55 ± 20.49	51.38 ± 8.15	0.0109	0.0251					
CASP4	100 ± 8.07	150.49 ± 6.57	80.81 ± 17.27	83.26 ± 5.06	110.84 ± 5.17	86.42 ± 12.92	0.0005	0.0020	0.0056	0.6042	0.8799	0.4840	0.7622
IL1A	100 ± 5.05	119.17 ± 5.31	756.46 ± 14.51	835.5 ± 15.27	102.71 ± 7.19	818.49 ± 3.93	0.0000	0.0000	0.9998	0.0000	1.0000	0.0002	0.0000
SH2D3C	100 ± 18.59	121.91 ± 7.12	83.8 ± 26.91	100.6 ± 16.24	119.72 ± 26.2	60.19 ± 19.84	0.2757	0.3691					
MAP2	100 ± 8.84	97.16 ± 8.22	112.66 ± 8.18	111.72 ± 12.97	116.92 ± 4.44	91.82 ± 10.26	0.3950	0.4553					
MAPT	100 ± 4.3	119.89 ± 8.16	153.39 ± 3	141.78 ± 12.13	83.47 ± 16.91	142.22 ± 6.99	0.0017	0.0050	0.5910	0.0589	0.7361	0.0126	0.0555
PLAU	100 ± 3.87	138.9 ± 6.29	94.51 ± 7.63	119.94 ± 4.13	93.31 ± 4.2	78.66 ± 10.44	0.0001	0.0003	0.0020	0.1513	0.9165	0.9604	0.1141
PLAT	100 ± 14.66	135.67 ± 11.1	108.59 ± 5.01	95.86 ± 5.91	99.25 ± 18.03	96.1 ± 5.92	0.2007	0.2871					
ACHE	100 ± 14.93	125.35 ± 22.22	165.64 ± 4.95	224.64 ± 8.61	130.02 ± 25.38	164.85 ± 5.25	0.0087	0.0211	0.8558	0.0022	0.7624	0.1391	0.1458
BDNF	100 ± 4.13	159.65 ± 22.93	187.3 ± 19.86	183.29 ± 6.71	92.58 ± 16.36	170.92 ± 7.45	0.0298	0.0563					

Supplement S4. Analysis of significant differences between the transcriptional effects of the analyzed methylxanthine variants in SH-SY5Y cells. P values of ANOVA, adjusted ANOVA and Tukey HSD post-hoc test used for multi comparison analysis are listed.

gene	p values											
	ANOVA	ANOVA adj.	C vs. TP	C vs. P	C vs. TB	C vs. PF	TP vs. P	TP vs. TB	TP vs. PF	P vs. TB	P vs. PF	TB vs. PF
PARK7	0.0001	0.0002	0.0007	0.0487	0.0067	0.0000	0.2327	0.7715	0.5035	0.8351	0.0122	0.0862
PRDX1	0.0789	0.0834	0.6814	0.8357	0.7077	0.6661	0.1806	0.1200	0.1058	0.9991	0.9976	1.0000
PRDX6	0.0071	0.0093	0.9552	0.0100	0.2059	0.0508	0.0378	0.5281	0.1721	0.4893	0.9106	0.9256
SOD1	0.0871	0.0895	0.3401	0.6469	0.0973	0.1098	0.9795	0.9316	0.9499	0.6727	0.7123	1.0000
TXNIP	0.0308	0.0368	0.9235	0.1052	0.9029	1.0000	0.0234	0.4731	0.9385	0.4056	0.0961	0.8838
TXNRD2	0.0000	0.0001	0.0078	0.5133	0.0004	0.0001	0.1561	0.5728	0.1249	0.0095	0.0012	0.8185
IDH1	0.0208	0.0257	0.8051	0.7055	0.4932	0.1454	0.1744	0.0937	0.0194	0.9958	0.7474	0.9125
ERCC2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.3840	0.6497	0.9832	0.9890	0.1757	0.3562
ERCC6	0.0043	0.0063	0.0209	0.0191	0.0059	0.0089	1.0000	0.9632	0.9914	0.9718	0.9944	0.9995
ABCA1	0.0025	0.0040	0.9995	0.0682	0.7055	0.3836	0.0466	0.8159	0.4947	0.0059	0.0020	0.9779
APOA1	0.0028	0.0042	0.0099	0.6224	0.0058	0.0229	0.1409	0.9986	0.9919	0.0877	0.2800	0.9521
HADH2	0.0000	0.0000	0.0000	0.0004	0.0000	0.0000	0.1956	0.9409	0.9850	0.5433	0.0818	0.7176
LPL	0.0454	0.0494	0.9507	0.1884	1.0000	0.1366	0.5072	0.9286	0.4010	0.1647	0.9996	0.1186
ERN1	0.0013	0.0024	0.0026	0.0064	0.0035	0.0045	0.9890	0.9998	0.9984	0.9978	0.9997	0.9999
AASS	0.0104	0.0132	0.9943	0.9957	0.0224	0.7333	0.9377	0.0104	0.5030	0.0449	0.9046	0.2050
PRKCQ	0.0374	0.0433	0.3759	0.0839	0.0291	0.1508	0.8766	0.5719	0.9724	0.9776	0.9969	0.8899
ALS2	0.0000	0.0000	0.0023	0.1287	0.0001	0.0000	0.2597	0.2618	0.0673	0.0054	0.0012	0.9247
GNB2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.1094	0.8507	0.9905	0.4885	0.2306	0.9803
EP300	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.8293	0.9843	1.0000	0.5397	0.8075	0.9888
GAP43	0.0000	0.0001	0.0000	0.0001	0.0003	0.0003	0.9392	0.6702	0.6502	0.9750	0.9694	1.0000
APBB2	0.0024	0.0040	0.0139	0.0042	0.0069	0.0061	0.9694	0.9958	0.9923	0.9989	0.9996	1.0000

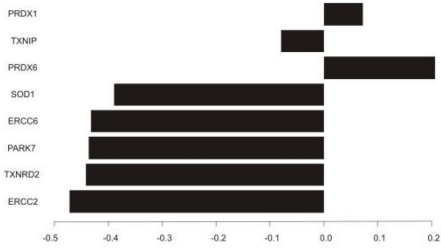|											
UBQLN1	0.0000	0.0000	0.0000	0.0003	0.0000	0.0000	0.2170	0.9975	0.9927	0.3465	0.3977	1.0000
APH1a	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9996	0.9216	0.8915	0.9696	0.9518	1.0000
APH1b	0.0001	0.0001	0.0001	0.0005	0.0002	0.0002	0.9524	1.0000	0.9996	0.9677	0.9862	0.9999
CASP3	0.0000	0.0000	0.0000	0.0004	0.0000	0.0001	0.5783	0.9988	0.9668	0.4270	0.9057	0.8918
PSENEN	0.0000	0.0001	0.0001	0.0150	0.0002	0.0000	0.0858	0.9920	0.9548	0.1799	0.0235	0.7912
A2M	0.0002	0.0005	0.0068	0.8049	0.0004	0.0060	0.0555	0.6130	1.0000	0.0035	0.0496	0.6488
ECE2	0.0000	0.0000	0.0000	0.0002	0.0000	0.0000	0.2061	0.9809	0.9036	0.0816	0.0449	0.9973
LRP1	0.0054	0.0077	0.1466	0.4197	0.0028	0.0531	0.9522	0.2669	0.9774	0.0828	0.7090	0.5562
MMP2	0.0000	0.0001	0.0014	0.0001	0.0004	0.0000	0.4120	0.9516	0.1168	0.8105	0.9193	0.3537
PRNP	0.0014	0.0024	0.0483	0.8848	0.0812	0.0354	0.0083	0.9984	0.9998	0.0143	0.0060	0.9908
CASP4	0.0006	0.0011	0.0015	0.0708	0.0011	0.0023	0.3048	0.9997	0.9993	0.2337	0.4163	0.9934
IL1A	0.0000	0.0000	0.0001	0.9999	0.0003	0.0001	0.0001	0.9466	0.9998	0.0002	0.0001	0.9773
MAPT	0.0066	0.0091	0.6965	0.2468	0.3182	0.6815	0.0248	0.9559	1.0000	0.0066	0.0236	0.9615
PLAU	0.0001	0.0003	0.3340	0.0023	0.0029	0.0001	0.0938	0.1166	0.0053	0.9999	0.5726	0.5005
ACHE	0.0392	0.0439	0.0392	0.9999	0.6922	0.7067	0.0521	0.3528	0.3408	0.7761	0.7894	1.0000

Supplement S5. Analysis of cell type independent effects. *Detailed overview of pooled transcriptional changes after treatment with caffeine (C), theobromine (TB), theophylline (TP), pentoxifylline (P), and propentofylline (PF) in SH-SY5Y, Calu-3 and HEPG2 cells. Included are the mean expression changes ± standard error of the mean (SEM) after normalization using the five most stable housekeeping genes for each cell line. P values for ANOVA analysis, false discovery rate adjusted p values ("ANOVA adj.") and p values for Dunnett´s Test are shown.*

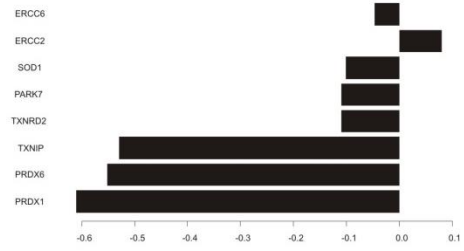| gene	mean expression changes ± standard error of the mean (SEM) [%]						p value						
	Ctrl	C	TP	P	TB	PF	ANOVA	ANOVA adj.	Crtl vs. C	Ctrl vs. TP	Ctrl vs. P	Ctrl vs. TB	Ctrl vs. PF
PARK7	100 ± 8.24	116.56 ± 12.14	99 ± 10.89	97.73 ± 16.29	101.72 ± 16.71	104.61 ± 30.55	0.7914	0.8186	0.6582	1.0000	0.9999	1.0000	0.9975
TXNRD2	100 ± 5.96	116.56 ± 8.58	95.73 ± 7.53	102.96 ± 15.08	77.87 ± 13.85	89.87 ± 15	0.0047	0.0218	0.2880	0.9891	0.9980	0.0887	0.7285
ERCC2	100 ± 6.79	128.92 ± 16.78	86.36 ± 14.04	87.25 ± 14.71	87.51 ± 12.75	92.87 ± 23.34	0.0095	0.0259	0.0997	0.7234	0.7706	0.7840	0.9716
HADH2	100 ± 7.92	119.48 ± 16.44	82.93 ± 6.58	101.3 ± 11.6	85.37 ± 15.16	92.73 ± 15.09	0.0104	0.0259	0.2268	0.3408	1.0000	0.4869	0.9315
ALS2	100 ± 10.32	83.8 ± 10.18	115.57 ± 29.88	97.89 ± 21.54	161.06 ± 40.1	151.13 ± 41.45	0.0064	0.0218	0.9339	0.9432	1.0000	0.0449	0.1204
PRDX6	100 ± 16.31	123.1 ± 20.7	123.96 ± 20.16	113.82 ± 35.93	128.07 ± 25.36	131.17 ± 31.47	0.7120	0.7628	0.7117	0.6828	0.9478	0.5443	0.4448
GNB2	100 ± 5.29	117.17 ± 7.55	95.07 ± 8.48	86.41 ± 11.92	91.65 ± 8.55	97.08 ± 13.77	0.0065	0.0218	0.1255	0.9563	0.3007	0.7355	0.9955
EP300	100 ± 5.49	121.53 ± 19.69	82.04 ± 8.25	91.15 ± 13.41	83.65 ± 10.39	74.57 ± 12.9	0.0003	0.0048	0.1446	0.2818	0.8553	0.3666	0.0617
APBB2	100 ± 5.6	118.34 ± 18.96	95.65 ± 9.37	86.98 ± 9.05	87.95 ± 13.6	89.55 ± 6.02	0.0114	0.0263	0.1911	0.9872	0.4963	0.5689	0.6908
UBQLN1	100 ± 13.5	114.01 ± 23.29	104.85 ± 14.48	103.02 ± 32.91	95.02 ± 30.61	95.28 ± 27.77	0.9420	0.9420	0.9360	0.9994	0.9999	0.9994	0.9995
Casp3	100 ± 14.65	141.37 ± 24.02	104.92 ± 18.29	97.12 ± 15.65	102.29 ± 28.39	116.06 ± 27.5	0.1510	0.2059	0.0971	0.9989	0.9999	1.0000	0.8421
PRDX1	100 ± 10.47	131.41 ± 17.42	117.96 ± 12.94	141.91 ± 16.68	136.76 ± 21.53	148.56 ± 24.91	0.0192	0.0411	0.1355	0.6190	0.0249	0.0598	0.0069
APH1a	100 ± 4.46	110.16 ± 10.61	84.5 ± 12.5	97.38 ± 17.12	91.53 ± 18.72	96.14 ± 17.48	0.3844	0.4805	0.8552	0.5483	0.9996	0.9235	0.9974
A2M	100 ± 17.02	109.19 ± 25.89	247.01 ± 82.57	152.02 ± 37.69	294.07 ±126.18	243.94 ± 84.71	0.0053	0.0218	0.9999	0.0670	0.8541	0.0084	0.0754
IL1A	100 ± 14.21	94.12 ± 15.27	336.34 ±196.16	104.35 ± 17.98	359.2 ± 160.33	344.56 ±176.88	0.0080	0.0240	1.0000	0.0986	1.0000	0.0591	0.0822
PLAU	100 ± 10.74	169.61 ± 28.83	139.77 ± 34.19	194.78 ± 60.16	143.6 ± 26.4	181.85 ± 55.52	0.0611	0.0965	0.1345	0.6183	0.0211	0.5346	0.0574
ACHE	100 ± 10.01	107.03 ± 19.46	139.26 ± 35.21	133.85 ± 23.36	174.95 ± 31.1	161.67 ± 22.93	0.0025	0.0152	0.9968	0.2089	0.3346	0.0024	0.0156
AASS	100 ± 6.59	89.54 ± 17.76	76.98 ± 12.63	92.96 ± 8.17	94.07 ± 24.27	84.71 ± 10.87	0.4871	0.5549	0.8518	0.2090	0.9660	0.9835	0.5803
ABCA1	100 ± 9.79	99.37 ± 18.59	85.36 ± 19.2	104.92 ± 8.34	77.4 ± 14.87	76.7 ± 18.76	0.1067	0.1600	1.0000	0.6691	0.9945	0.2712	0.2456

APH1b	100 ± 5.72	125.04 ± 9.43	83.86 ± 11.99	89.64 ± 10.36	85.08 ± 14.36	78.19 ± 13.67	0.0000	0.0011	0.0352	0.2860	0.6900	0.3568	0.0823
APOA1	100 ± 15.15	113.49 ± 34.16	173.79 ± 38.88	141.78 ± 29.91	166.67 ± 38.21	157.66 ± 39.43	0.0507	0.0845	0.9841	0.0384	0.4167	0.0721	0.1480
CASP4	100 ± 7.14	108.98 ± 16.81	74.87 ± 4.98	93.94 ± 8.16	83.77 ± 11.26	78.12 ± 9.05	0.0006	0.0058	0.7270	0.0167	0.9236	0.2037	0.0461
ERCC6	100 ± 10.78	99.75 ± 16.32	66.89 ± 15.84	103.51 ± 26.4	96.7 ± 28.31	108.88 ± 26.05	0.2325	0.3032	1.0000	0.2287	0.9998	0.9998	0.9823
IDH1	100 ± 11.61	104.67 ± 10.12	85.05 ± 19.99	114.86 ± 21.7	133 ± 18.46	141.66 ± 22.55	0.0025	0.0152	0.9978	0.7650	0.7691	0.1094	0.0263
LRP1	100 ± 6.68	100.02 ± 12.31	87.33 ± 9.17	115.96 ± 21.53	94.91 ± 26.33	103.87 ± 20.64	0.4994	0.5549	1.0000	0.8471	0.6996	0.9963	0.9990
MAPT	100 ± 11.83	97.95 ± 14.92	118.84 ± 18.94	135.91 ± 41.36	153.65 ± 14.46	138.59 ± 29.76	0.0349	0.0649	1.0000	0.8051	0.2550	0.0357	0.1978
PRKCQ	100 ± 10.93	166.45 ± 52.62	137.86 ± 24.56	100.93 ± 29.5	101.54 ± 14.95	126.8 ± 22.76	0.0368	0.0649	0.0288	0.3727	1.0000	1.0000	0.6883
PRNP	100 ± 9.72	101.97 ± 12.03	119.65 ± 22.01	96.36 ± 10.86	122.5 ± 16.75	133.57 ± 17.76	0.0231	0.0463	0.9999	0.3936	0.9986	0.2705	0.0408
PSENEN	100 ± 6.66	113.42 ± 15.6	85.31 ± 8.74	101.73 ± 11.04	92.61 ± 15.87	92.91 ± 15.96	0.1450	0.2059	0.5793	0.4945	0.9999	0.9308	0.9407
SOD1	100 ± 4.15	91.52 ± 10.31	86.71 ± 9.15	84.88 ± 8.72	82.55 ± 14.11	90.15 ± 15.12	0.4415	0.5298	0.8032	0.4308	0.3106	0.1926	0.7004

Supplement S6. Loading plots corresponding to the principal component analysis.
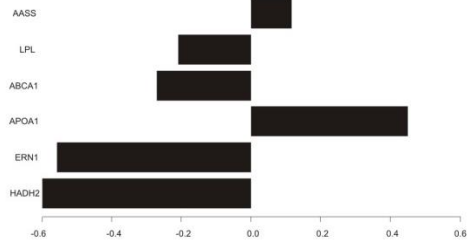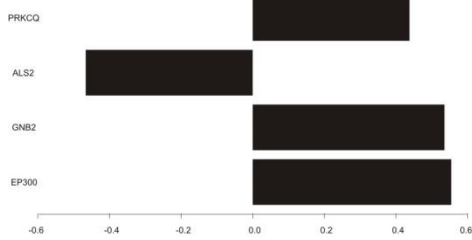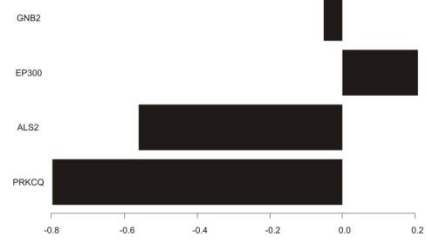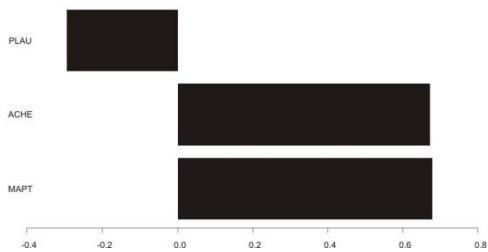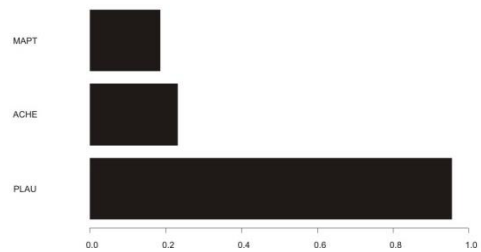
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