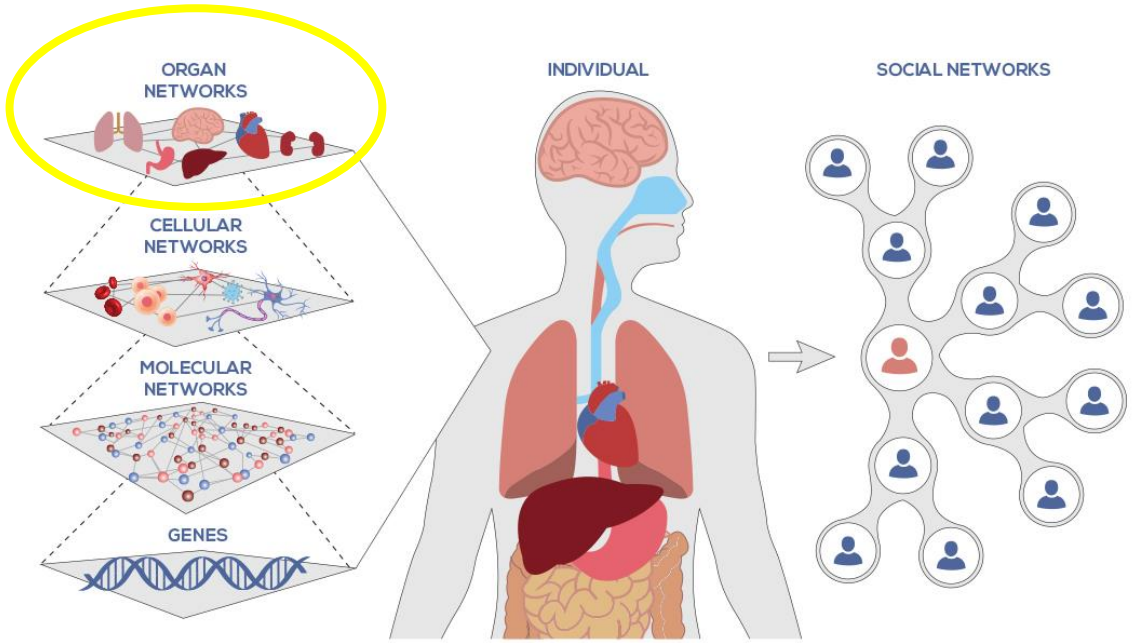
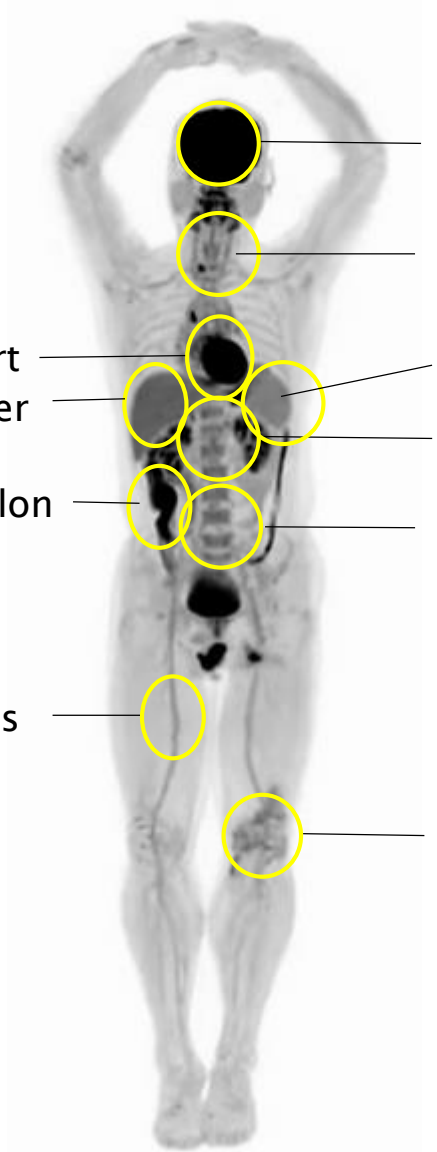
Stress and Lung Cancer

Univ.-Prof. Dr. Med. Marcus Hacker

Total Body FDG-PET in Network Medicine





Multiple brain regions
(like amygdala, pituitary gland,…)

Thyroid

Heart

Liver

Spleen, bone marrow

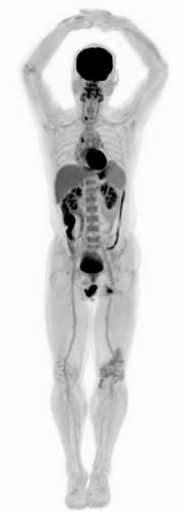
Adrenal glands

Bowel/colon

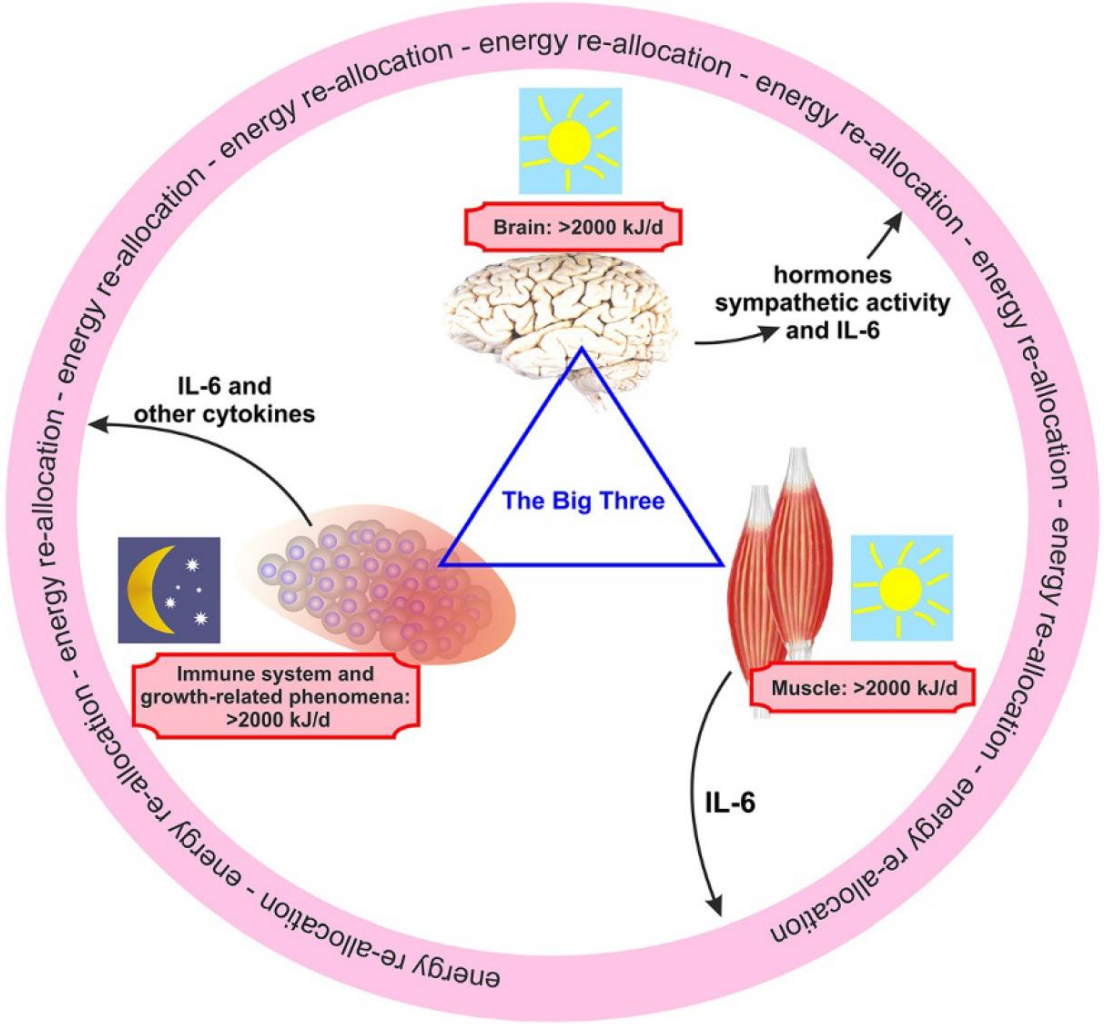
Muscle, fat

Arteries

Joints

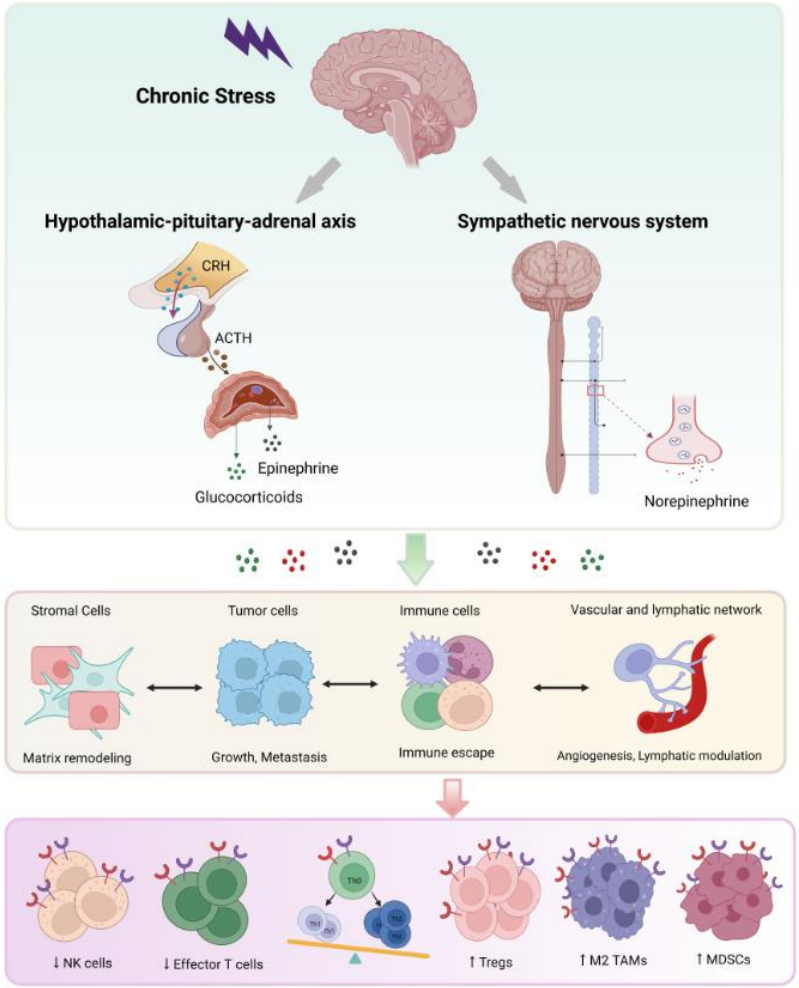


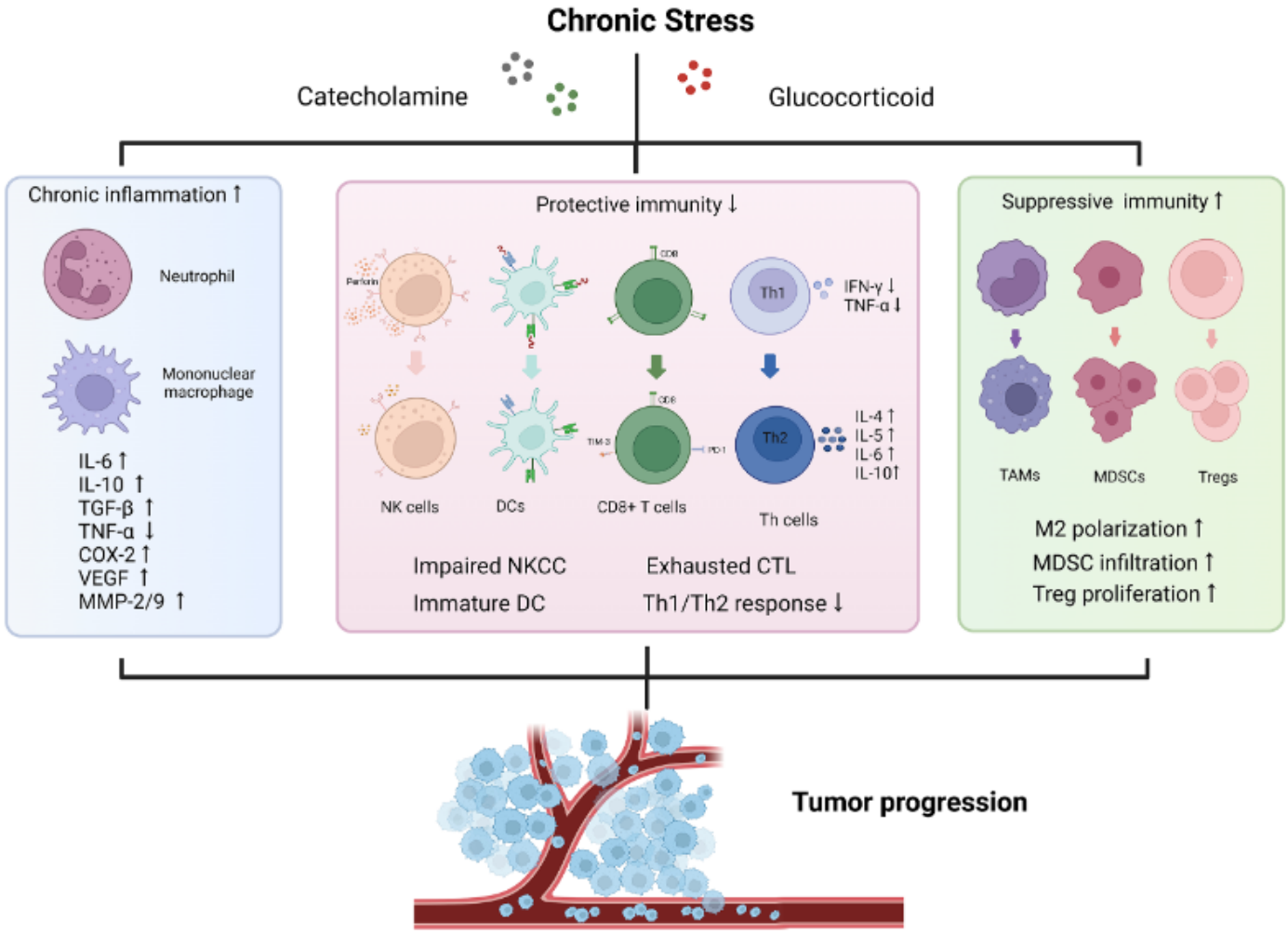
Energy Consumption of the Body: „the big three“



System/organ	Energy expenditure per day (kJ/day)
Basal metabolic rate	7000
Total body with usual activity	10,000
Total body of a *Tour de France* bicyclist	30,000[a]
Total body during minor surgery	11,000
Total body with multiple bone fractures	11,500–13,000
Total body with sepsis	15,000
Total body with extensive burns	20,000
Immune system under normal conditions	1600[b]
Immune system moderately activated	1750–2080[b]
Central nervous system	2000
Muscles at rest	2500
Muscles activated	2500 to more than 6000
Thoracic organs (together)	1600–2400
Abdominal organs (together)	3000–3700

Stress, Cancer and the Immune System





„Emotional“ **Stress** and Treatment Naïve Lung Cancer

1,148 lung cancer patients with 2-[18F]FDG PET/CT scans

928 patients excluded:
-811 previous treatment
-50 not lung cancer
-32 equivocal findings
-35 missing studies

220 study population of treatment naive patients

24 patients excluded:
-brain not in the field of View (FoV)

196 patients for evaluation

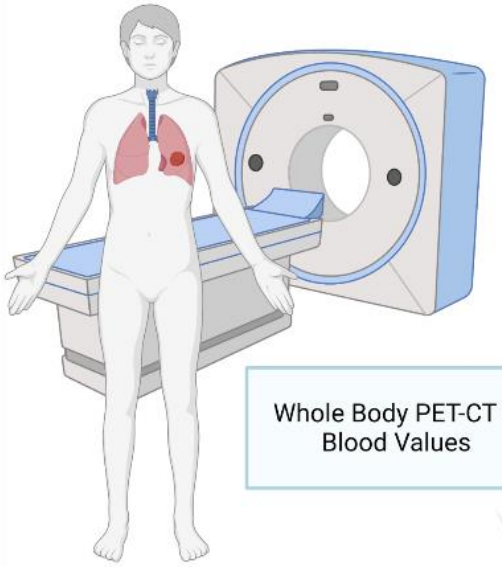
12 patients excluded:
-poor imaging quality

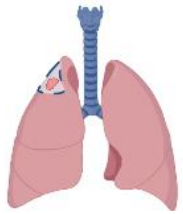
184 final study population

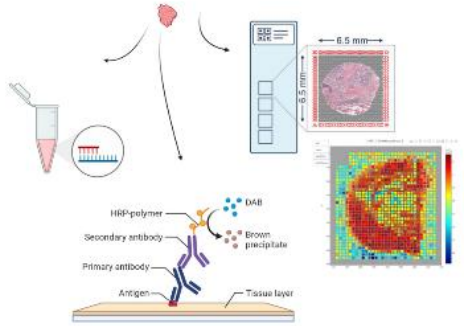
55 patients underwent surgical resection

4 patients excluded:
- 2 histological samples unavailable (surgery at different hospital)
- 2 patients underwent preoperative (radio)chemotherapy

20 representative FFPE tissue samples from surgery:
- 10 amygdala high samples
-10 amygdala low samples





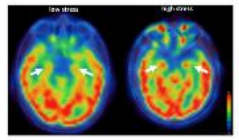


Whole Body PET-CT & Blood Values

Surgery

Genetics, MP-IHC, ST

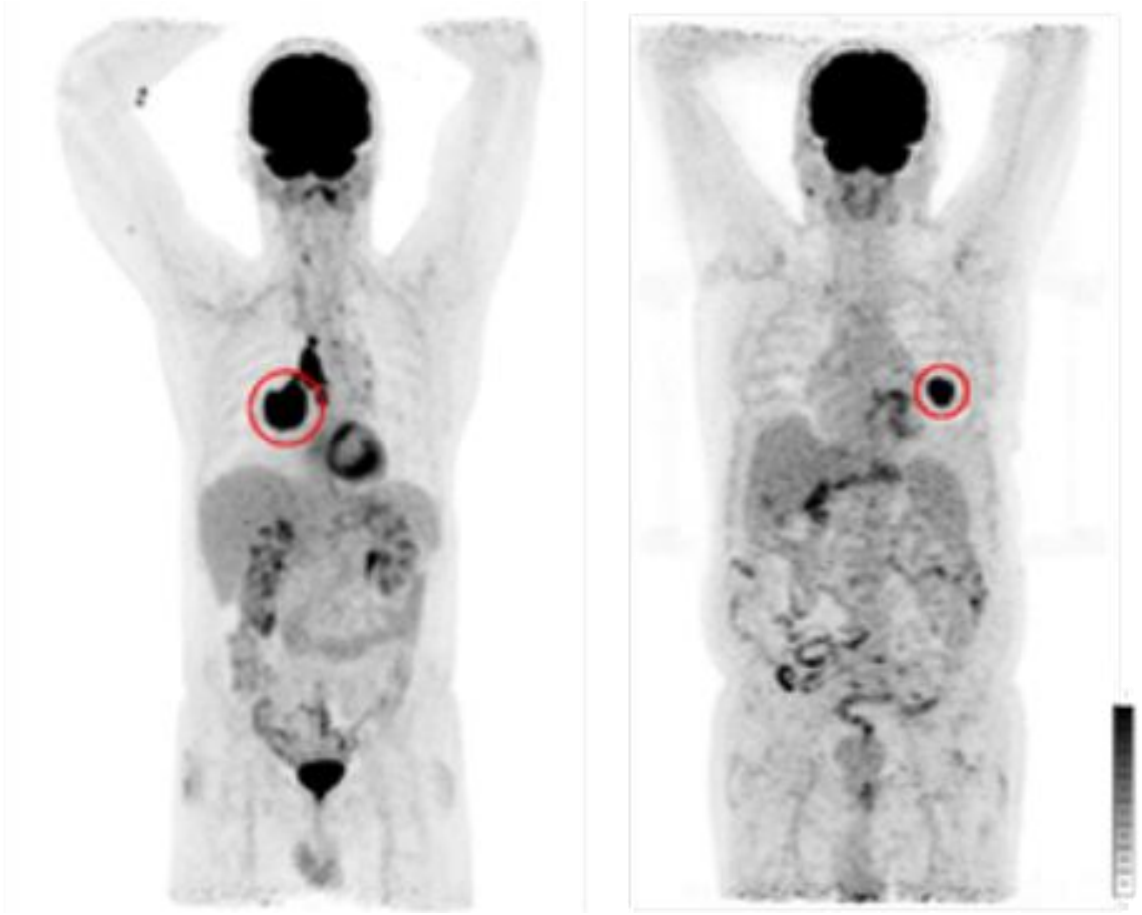
Blood Values, Demographics, Patient Characteristics, Follow-Up Data, Survivial Data and other Health Parameters

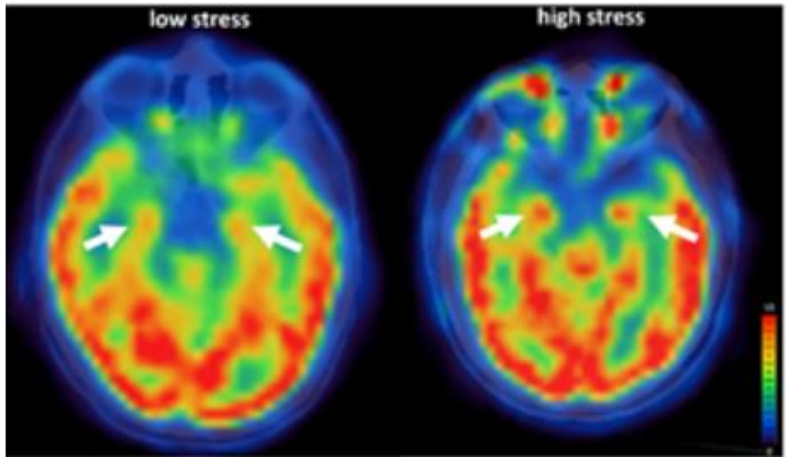


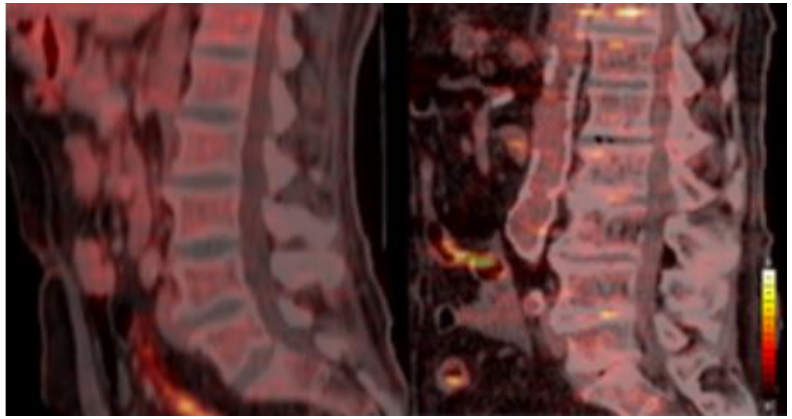
Stress Group Assignment

Statistics & Survival Analysis

„Emotional“ **Stress** and Treatment Naïve Lung Cancer







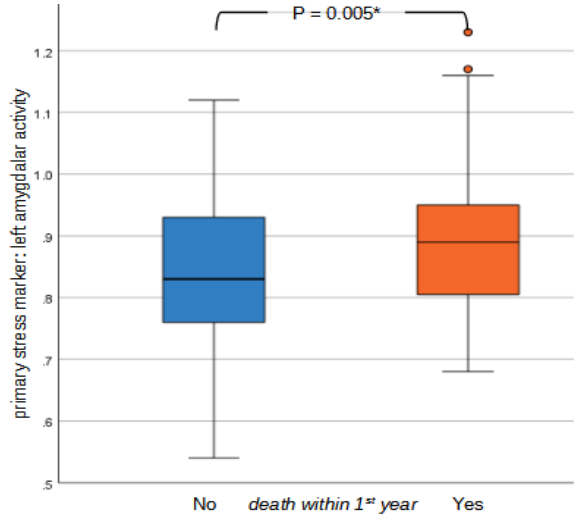
„Emotional“ **Stress** and Treatment Naïve Lung Cancer

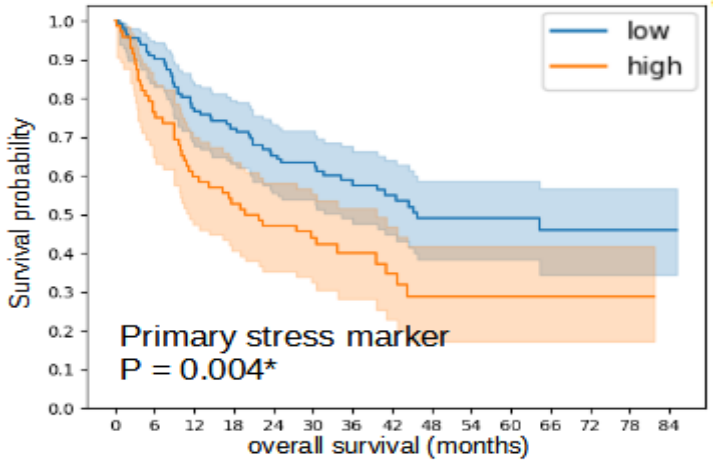
	Full cohort	AMAhigh	AMAlow	P-value
Full cohort (percent cohort)	184	72 (67 %)	112 (33 %)	
Male (percent male)	101 (55%)	40 (56 %)	61 (54 %)	0.86
Age in years (SD)	65.4 (10)	65.7 (10)	65.1 (10)	0.72
BMI in kg/m² (SD)	25.9 (5)	25.7 (5)	26.0 (5)	0.67
Smoking status				
No history of smoking	15 (8%)	5 (3%)	10 (5%)	0.8
Current/former smoker	163 (89%)	65 (90%)	98 (88%)	0.8
Package years (SD) of smokers	39 (27)	41 (28)	37 (26)	0.41
Histology				
AC	97 (53 %)	37 (52 %)	60 (54 %)	0.88
SCC	53 (29 %)	22 (31 %)	31 (28 %)	0.74
NSCLC	17 (9 %)	5 (7 %)	12 (11 %)	0.44
SCLC	11 (6 %)	4 (6 %)	7 (6 %)	1.00
Stage				
I-II	52 (28%)	18 (25%)	34 (30%)	0.50
III-IV	132 (72%)	54 (75%)	78 (70%)	0.50

	Full cohort	AMAhigh	AMAlow	P-value
Treatment				
Surgery	55 (30 %)	20 (28 %)	35 (31 %)	0.74
Chemotherapy	78 (42 %)	27 (38 %)	51 (46 %)	0.34
Radiotherapy	60 (30 %)	24 (33 %)	36 (32 %)	0.87
Immunotherapy	15 (8 %)	10 (14 %)	5 (4 %)	0.04*
Inflammation markers:				
Leukocytes [G/l] (SD)	9.2 (2.8)	9.5 (3.0)	9.0 (2.6)	0.31
Neutrophile/lymphocyte ratio (SD)	4.1 (2.7)	4.5 (2.9)	3.9 (2.5)	0.25
CRP [mg/dl] (SD)	3.4 (7.0)	5.0 (9.5)	2.4 (4.6)	0.02*
Bone marrow SNR_{max} (SD)	1.5 (1.3)	1.8 (1.3)	1.4 (1.3)	0.02*
Tumor metabolism marker:				0.27
TLG (SD)	553 (882)	496 (784)	642 (1015)	0.27

TLG: Tumor Lesion Glycolysis

„Emotional“ **Stress** and Treatment Naïve Lung Cancer

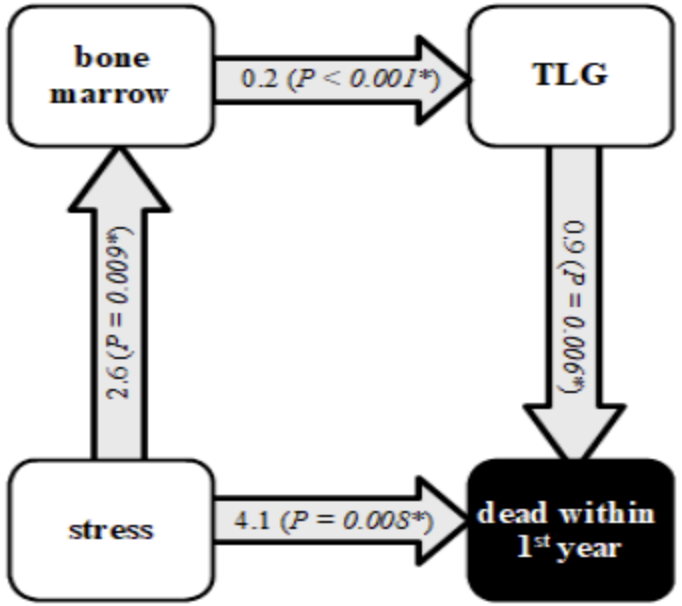




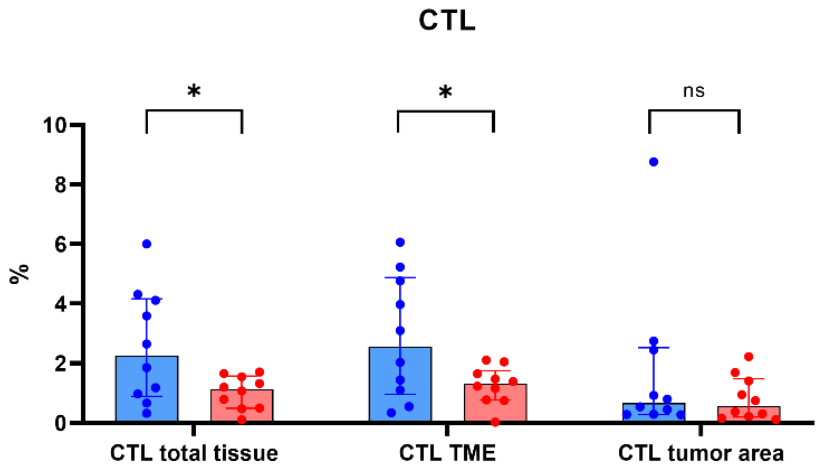
	Univariate			Multivariate		
Parameter	HR	95 % CI	P-value	HR	95 % CI	P-value
Primary stress marker: left mean Amygdala activity	29.7	3.4 - 257.4	0.002*	67.7	7.3 - 625.2	< 0.001*
Secondary stress marker: left maximum Amygdala activity	4.7	1.2 - 17.4	0.02*	6.4	1.9 - 22.0	0.003*
Leucocytes	1.0	0.9 - 1.1	0.9			
CRP	1.0	0.97 - 1.04	0.8			
Bone marrow activity	1.1	0.95 - 1.2	0.2			
BMI	1.0	0.9 - 1.1	0.9			
Age	1.0	0.97 - 1.03	0.96			
Sex	1.0	0.6 - 1.7	0.97			
Smoker	2.7	0.6 - 10.9	0.18			
Package years	1.0	0.98 - 1.01	0.99			
TLG	1.1	1.04 - 1.09	< 0.001*	1.1	1.03 - 1.08	< 0.001*

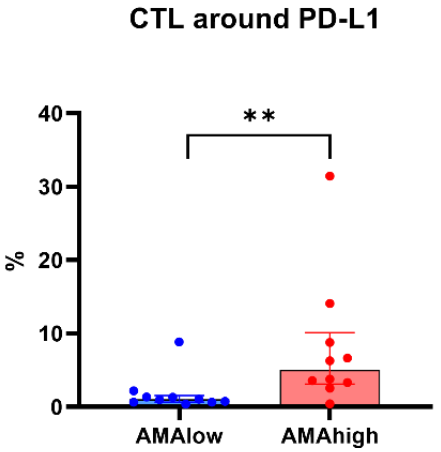
„Emotional“ **Stress** and Treatment Naïve Lung Cancer

Mediation Analysis



Multiplexing IHC

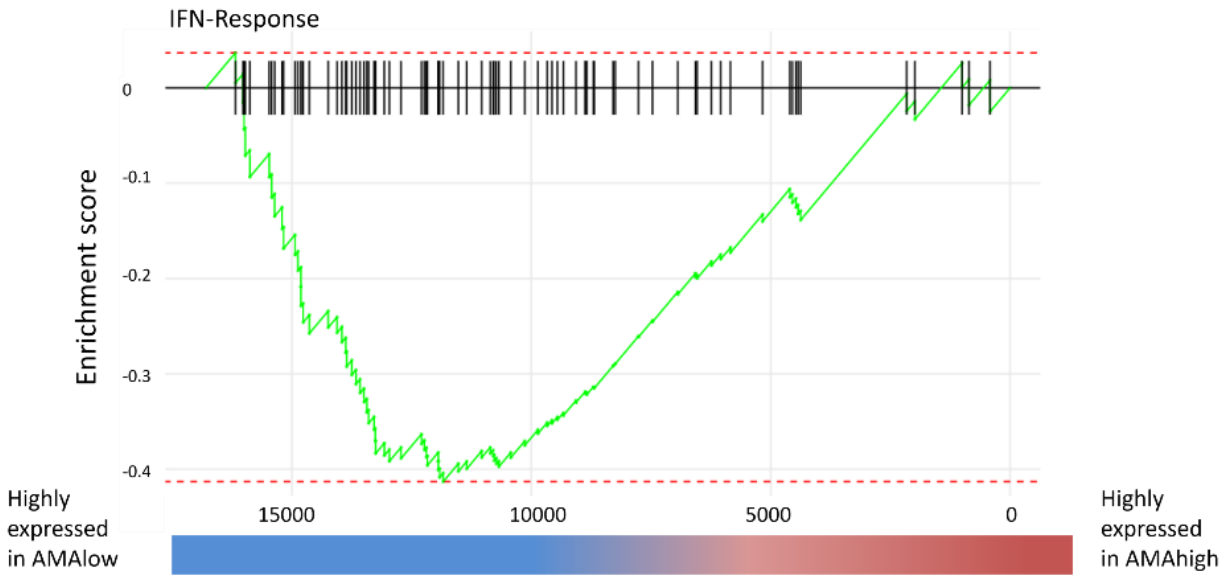




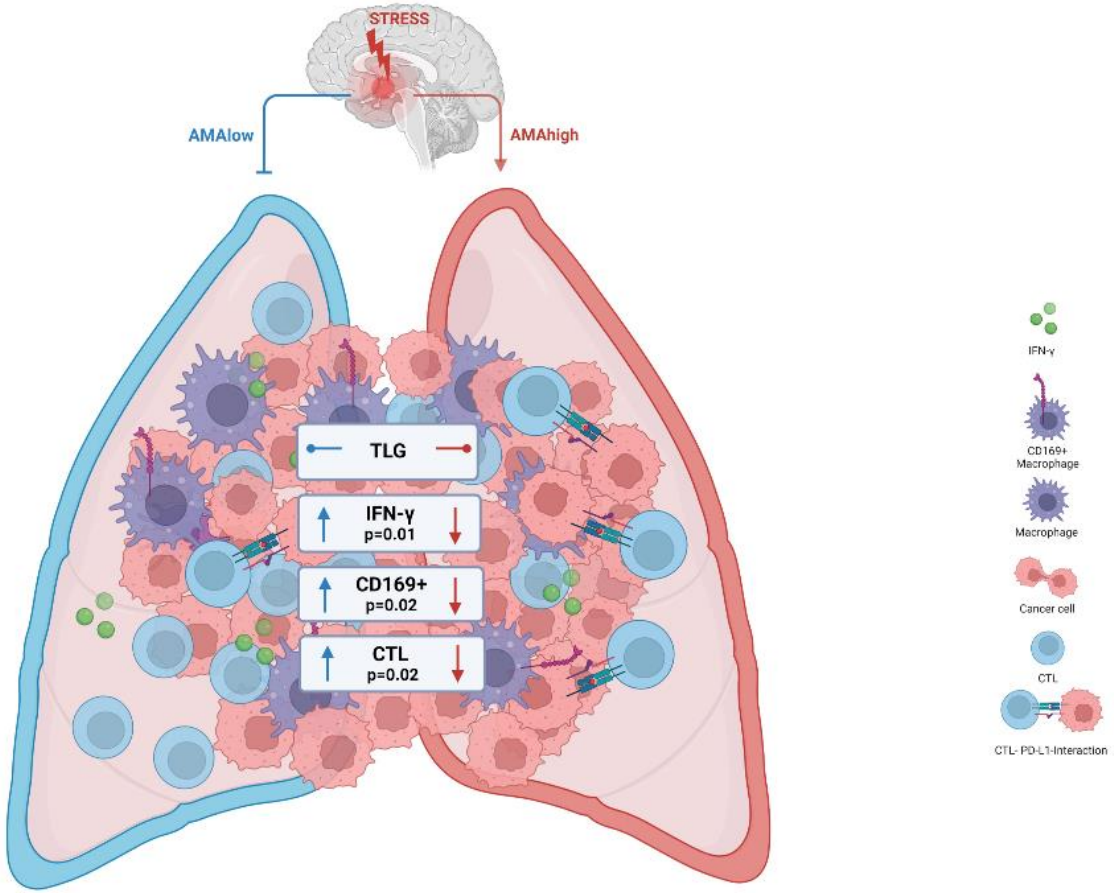
red: AMAhigh
blue: AMAlow

„Emotional“ **Stress** and Treatment Naïve Lung Cancer

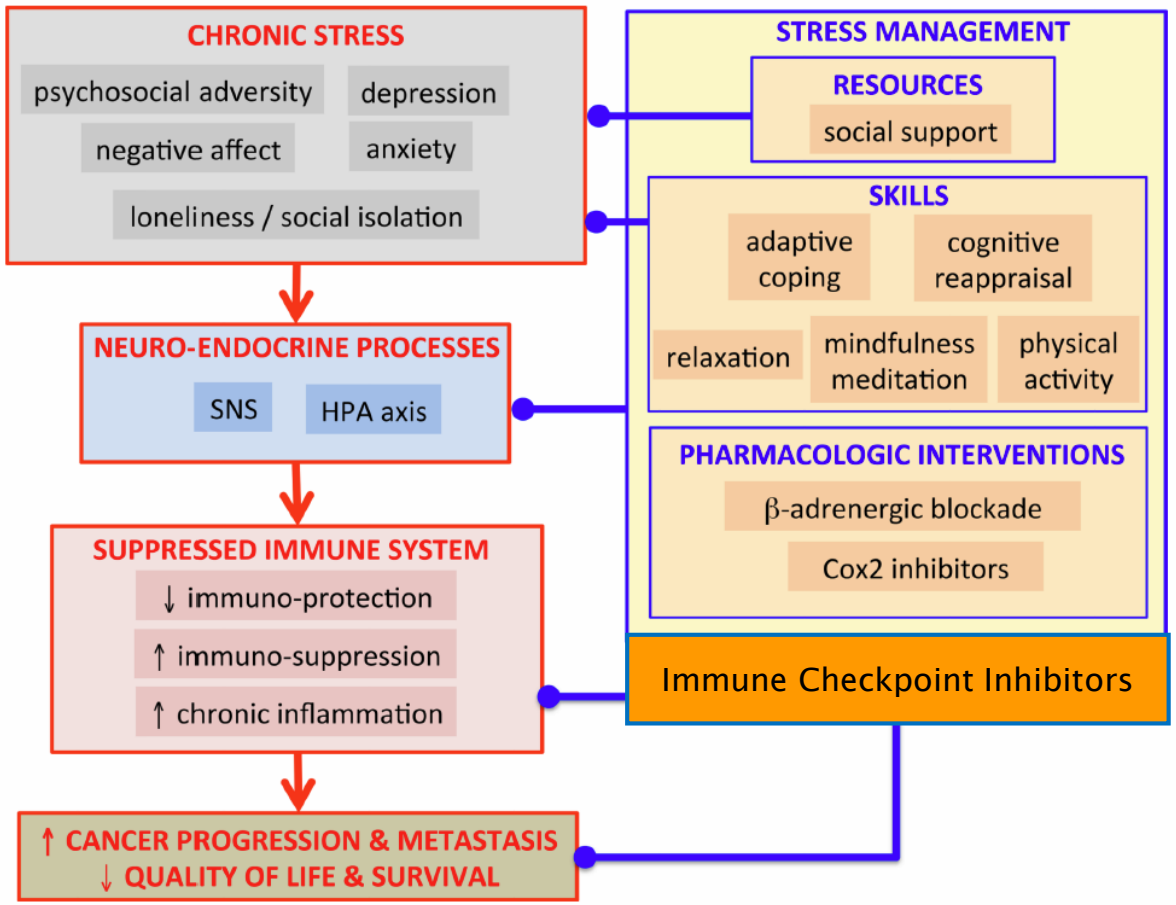
Gene Set Enrichment Analysis

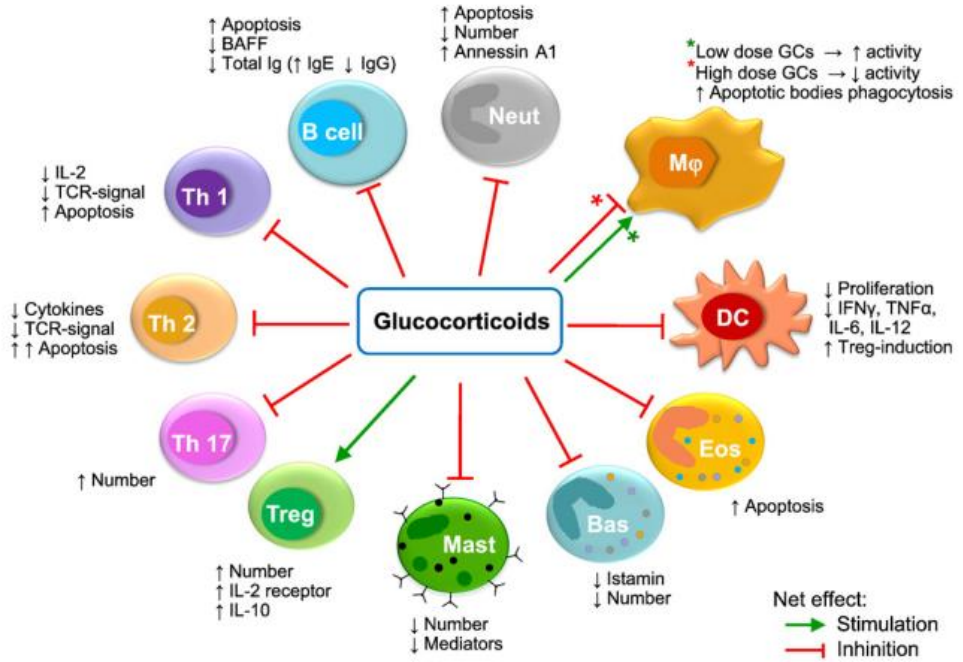


Summary MP-IHC and Spatial Transcriptomics



Chronic Stress, Stress Management and Cancer-Relevant Immune Responses





ARTICLES
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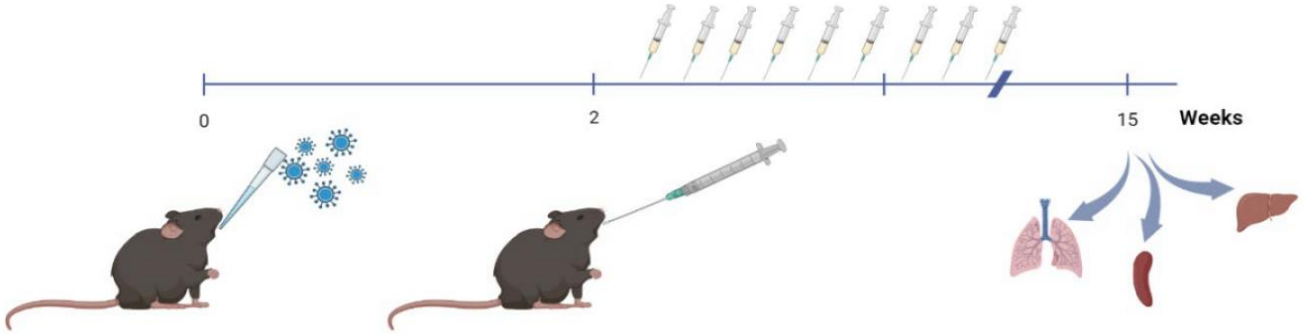
Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity

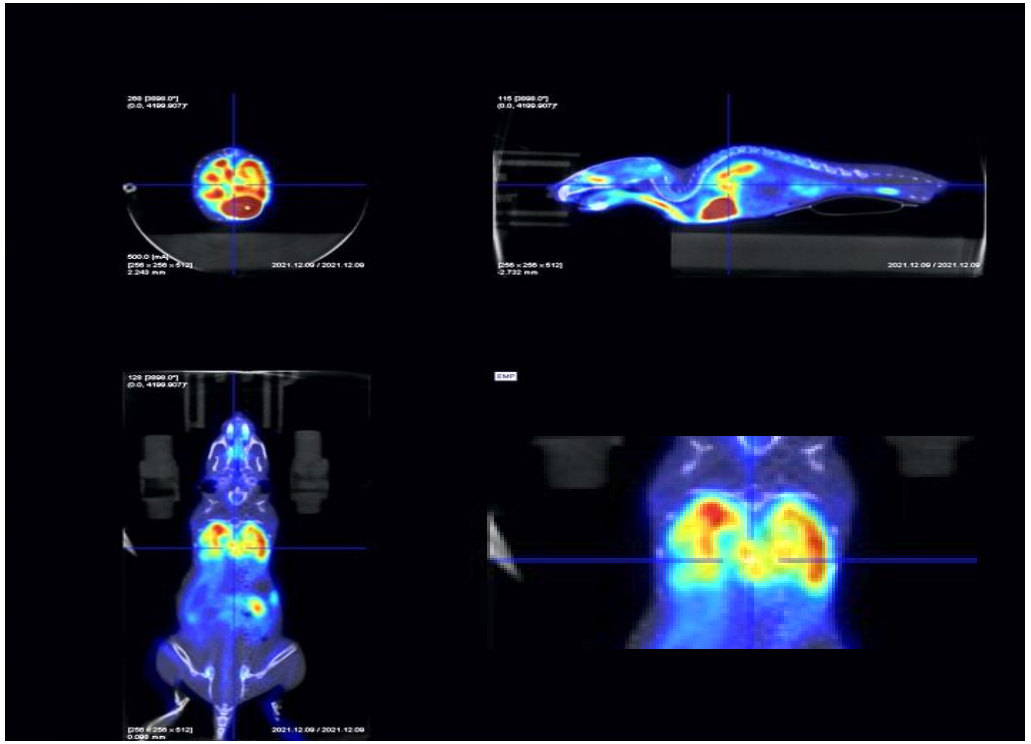
Heng Yang[1,2,22], Lin Xia[1,2,22], Jian Chen[3,22], Shuqing Zhang[1,2], Vincent Martin[4], Qingqing Li[1,2], Shangqing Lin[1,2], Jinfeng Chen[1,2], Joseph Calmette[5], Min Lu[6], Lingyi Fu[7], Jie Yang[7], Zhizhong Pan[7], Kuai Yu[7], Jingjing He[7], Eric Morand[8], Géraldine Schlecht-Louf[5], Roman Krzysiek[5,9], Laurence Zitvogel[1,2,10,11,12], Boxi Kang[13], Zeming Zhang[13], Andrew Leader[14], Penghui Zhou[7], Laurence Lanfumey[4], Minxin Shi[3], Guido Kroemer[1,2,15,16,17,18,19,20,21,23*] and Yuting Ma[1,2,23*]

Dexametasone (DEX) Treatment in Lung Cancer

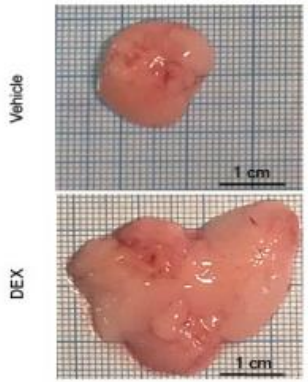
Experimental Workflow; KP mouse model (n=4/group)

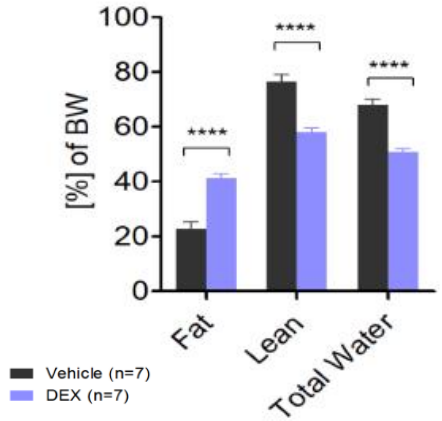


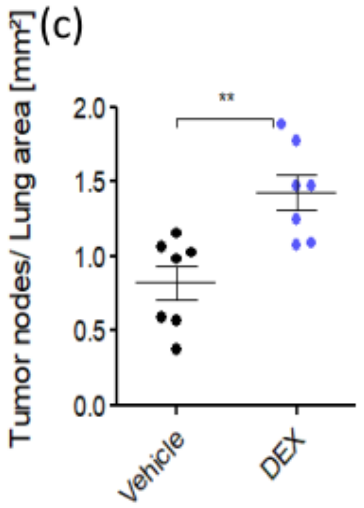
from week 2: DEX (4 mg/kg) or vehicle gavage 3x per week

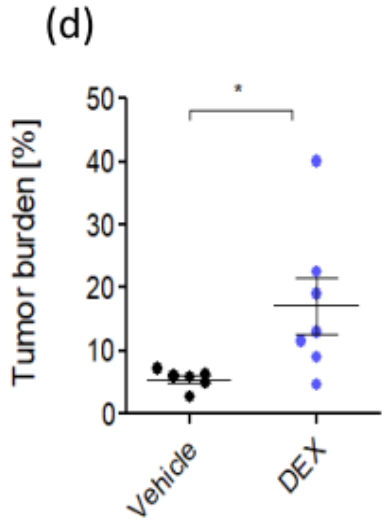


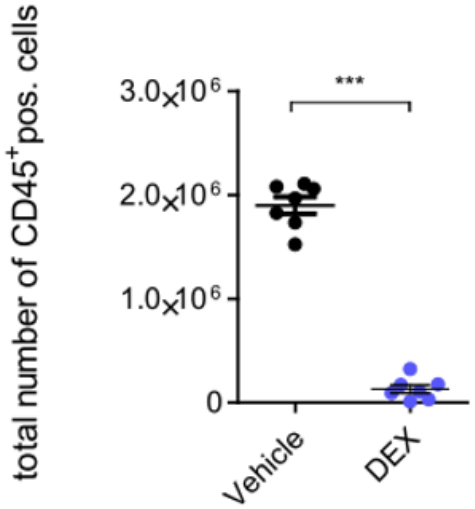
Cortisol Treatment Effects

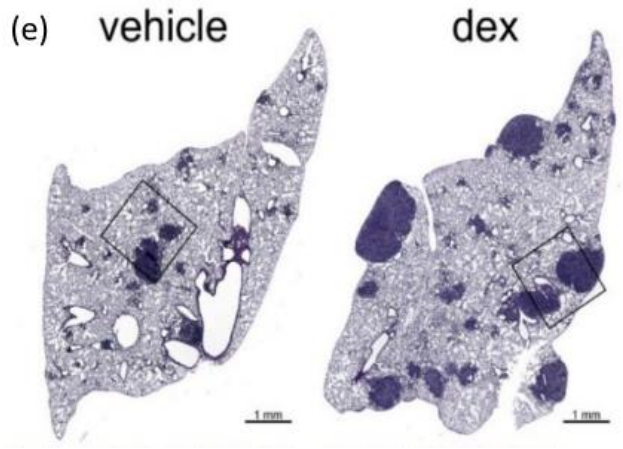


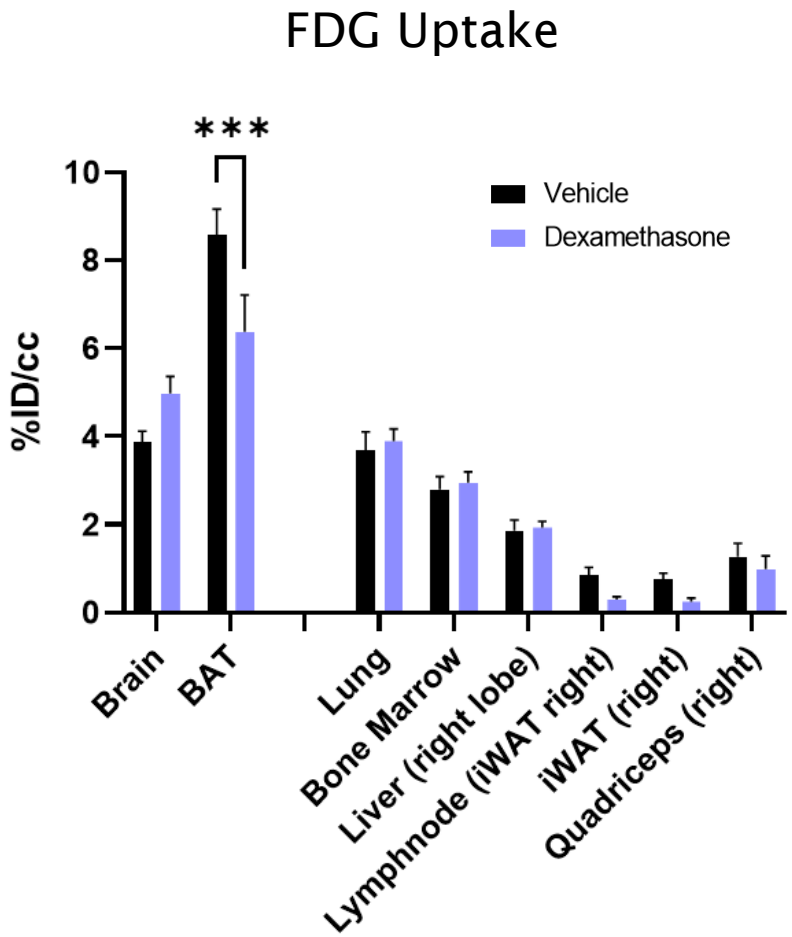




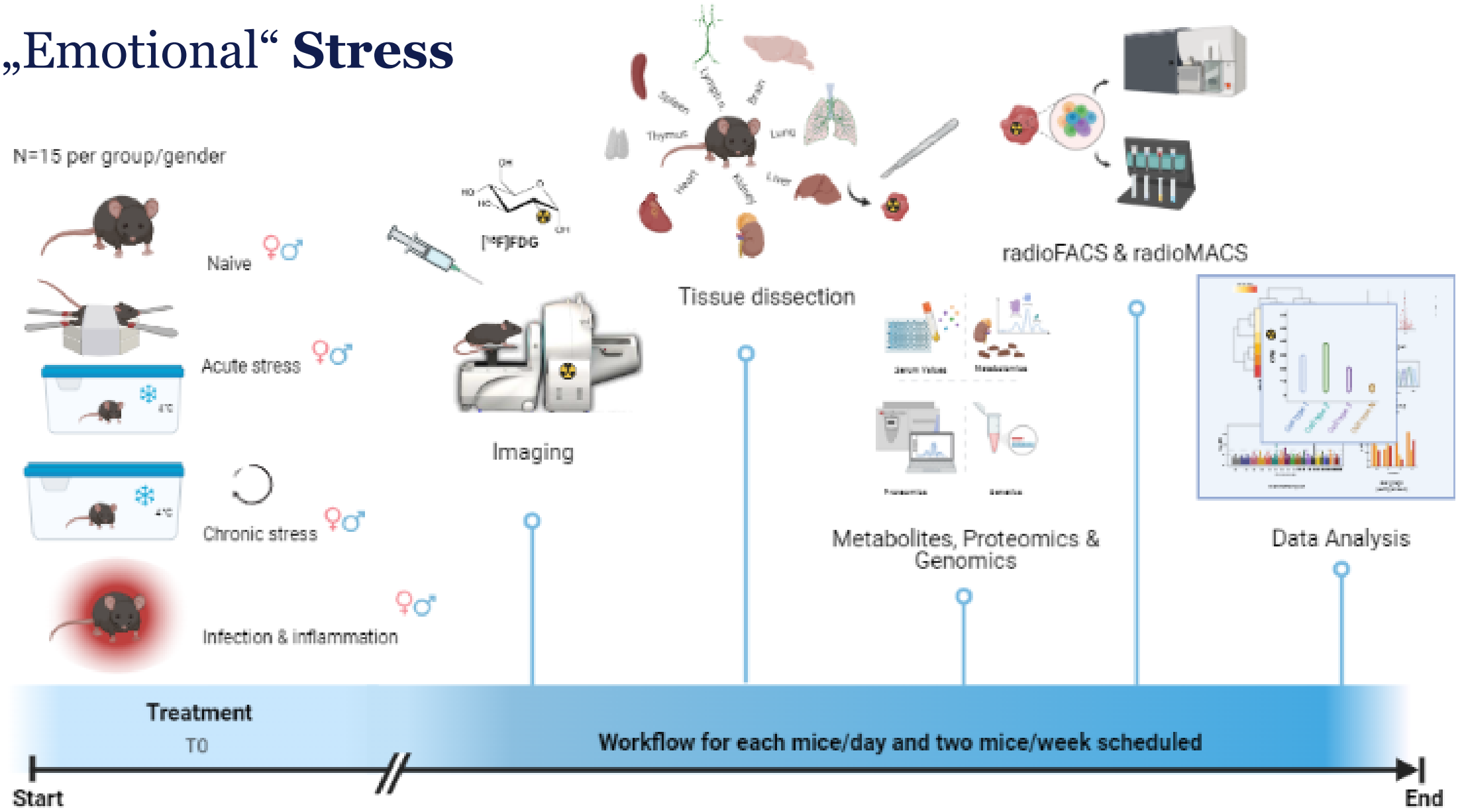




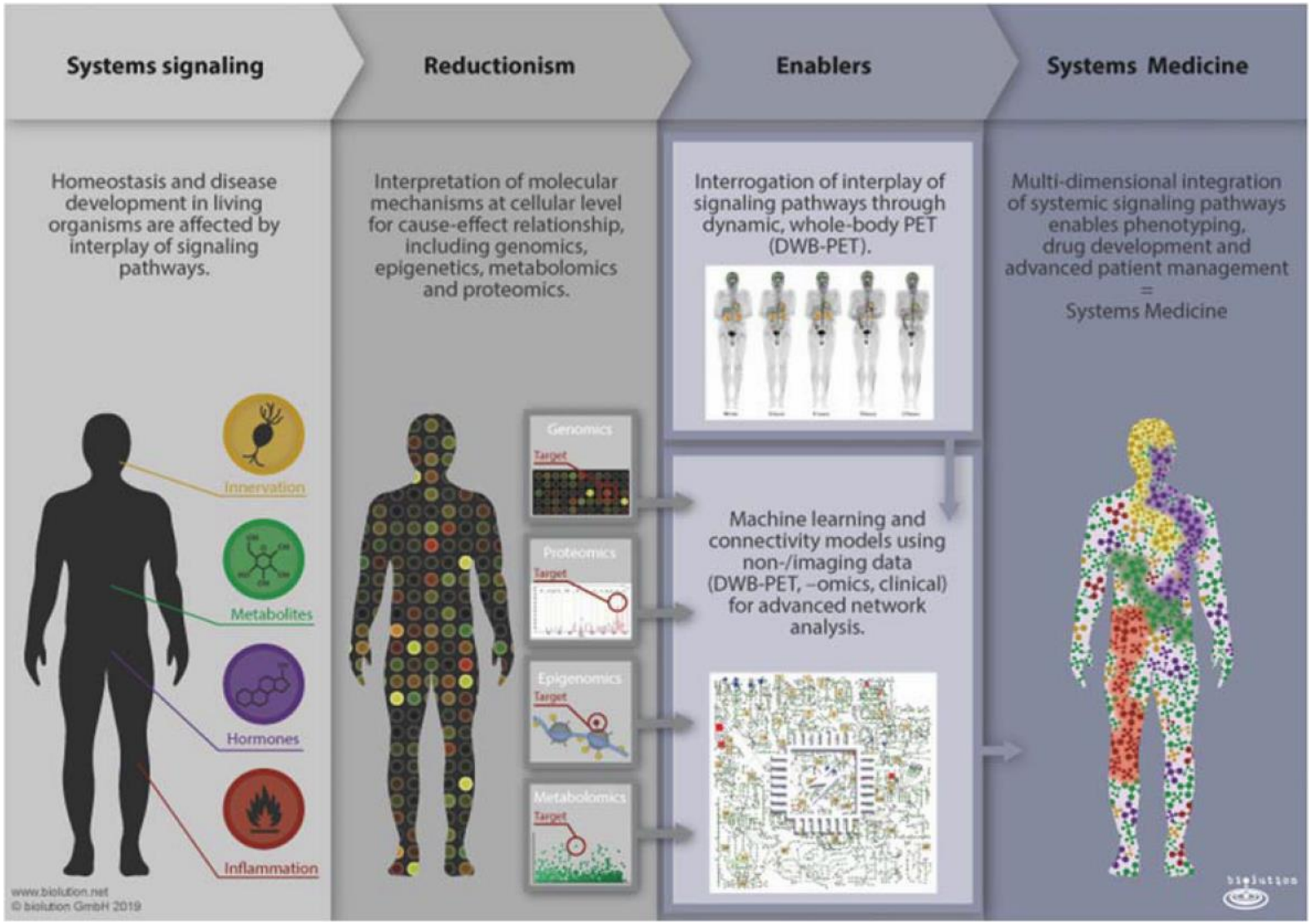


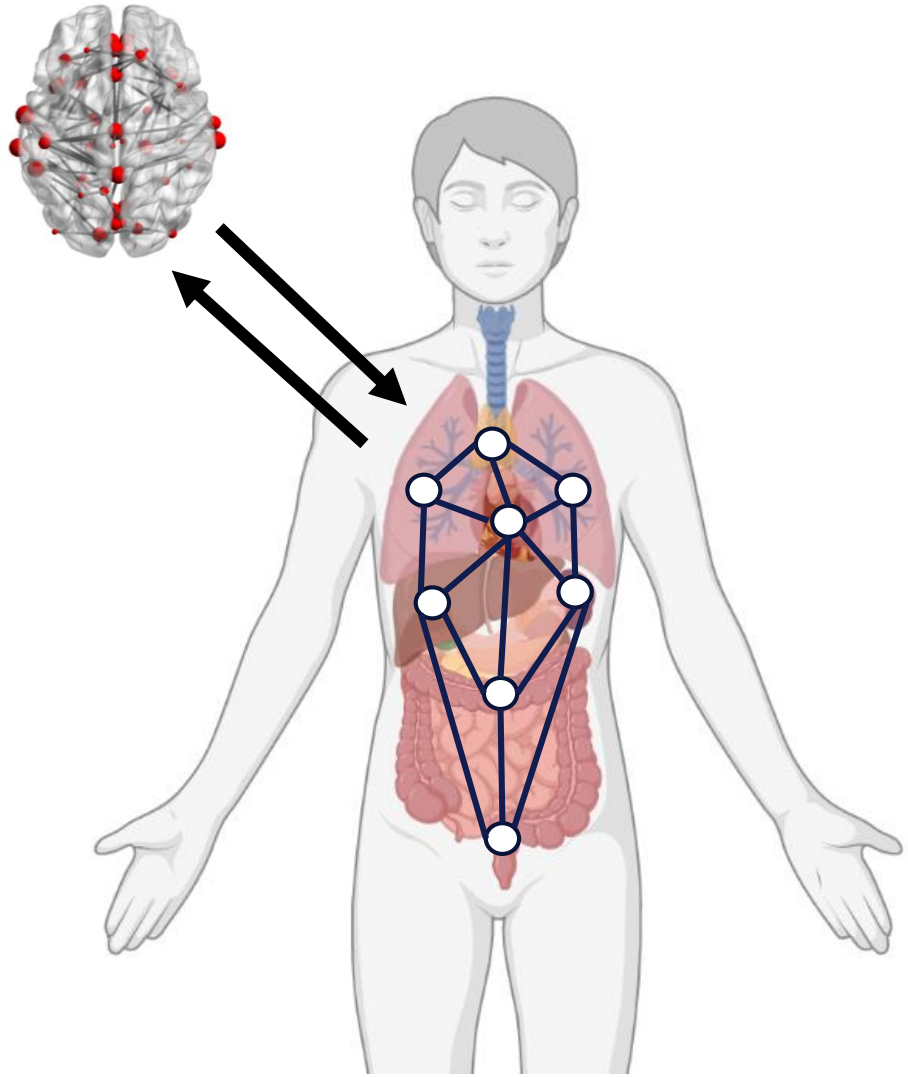


„Emotional“ **Stress**

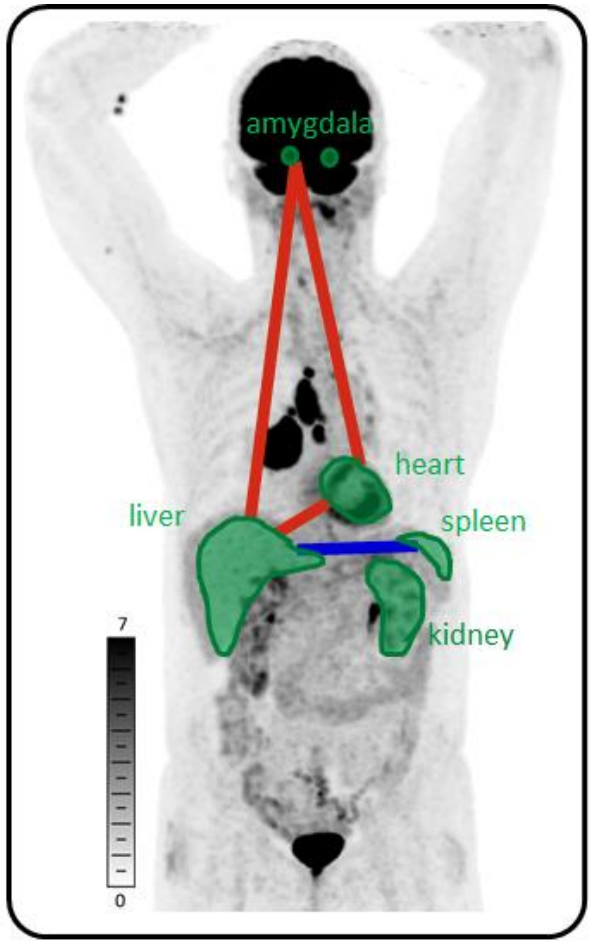


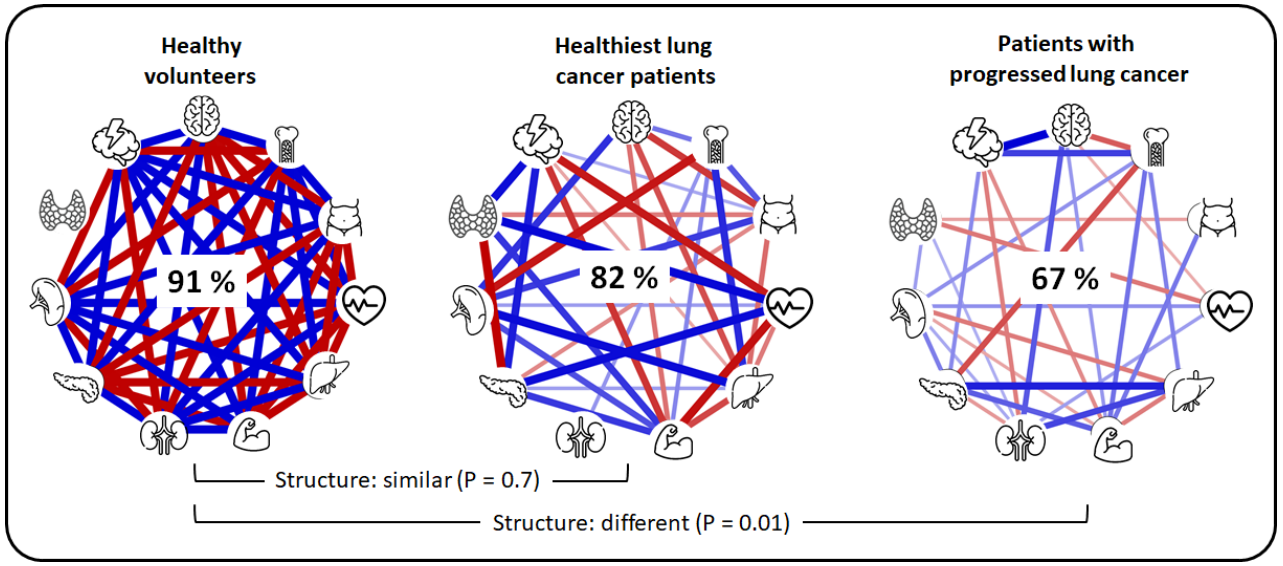
Total Body PET and Network Medicine





Treatment naïve lung cancer – Inter-organ Networks



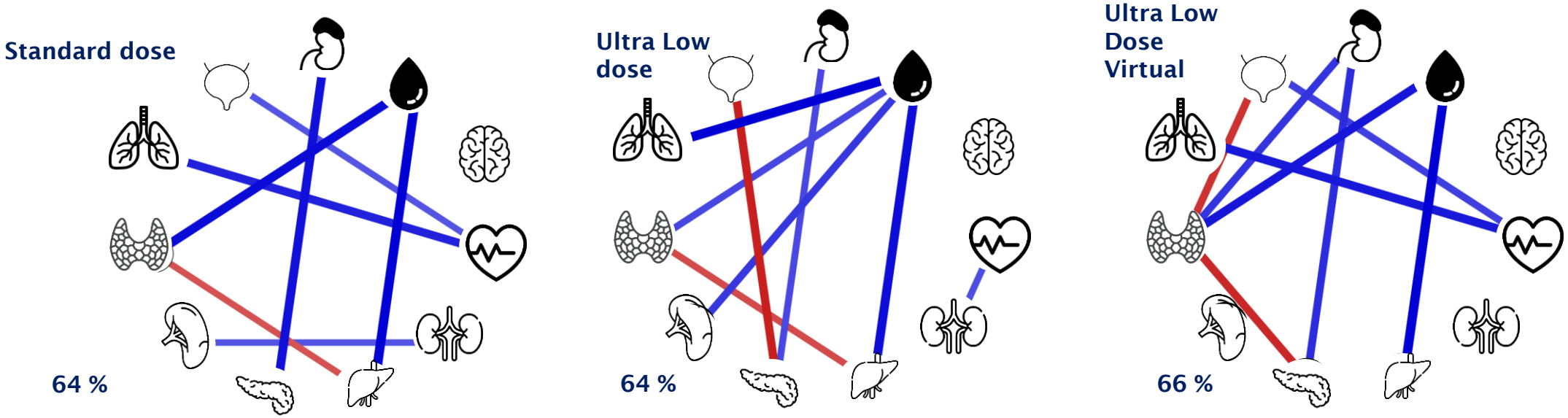


Dichotomization parameters	Group	Density		Similarity
CRP	Normal range: CRP = (0.2 ± 0.2) mg/dl, n = 20	65 %	P = 0.002	Similar
	Increased CRP = (3.1 ± 2.6) mg/dl, n = 20	38 %		(P = 0.3)
Tumor load	Low: total lesion glycolysis = (70 ± 65) mg/dl, n = 92	74 %	P = 0.006	Identical
	High: tot les glyc = (1000 ± 1000) mg/dl, n = 92	52 %		(P = 0.8)
CRP and survival	CRP = (0.2 ± 0.2) mg/dl, survived > 2 years (n = 40)	68 %	P = 0.003	Different
	CRP = (4.7 ± 5.2) mg/dl, , survived < 1 year (n = 40)	42 %		(P = 0.03)
Healthiness	Healthy volunteers with normal BMI (n=12)	91 %	P = 0.002	Different
	Progressed lung cancer (n=12)	67 %		(P = 0.01)

Similar Networks

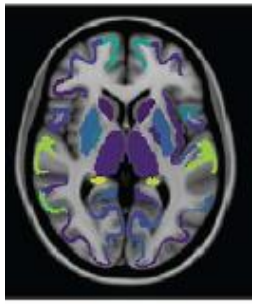
Similar networks for

- Different doses (P > 0.3)
- Different glucose metabolism quantifications (P > 0.3)
- Male / Female (P = 0.8)

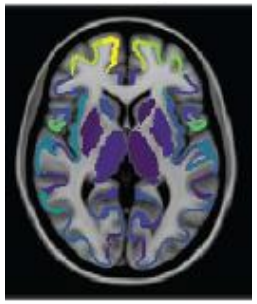


Inter-organ Networks – Covariance vs. Connectivity

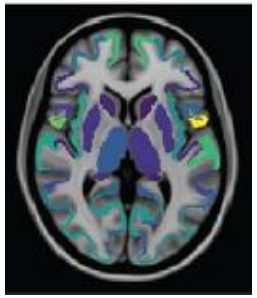
Static PET (sPET)

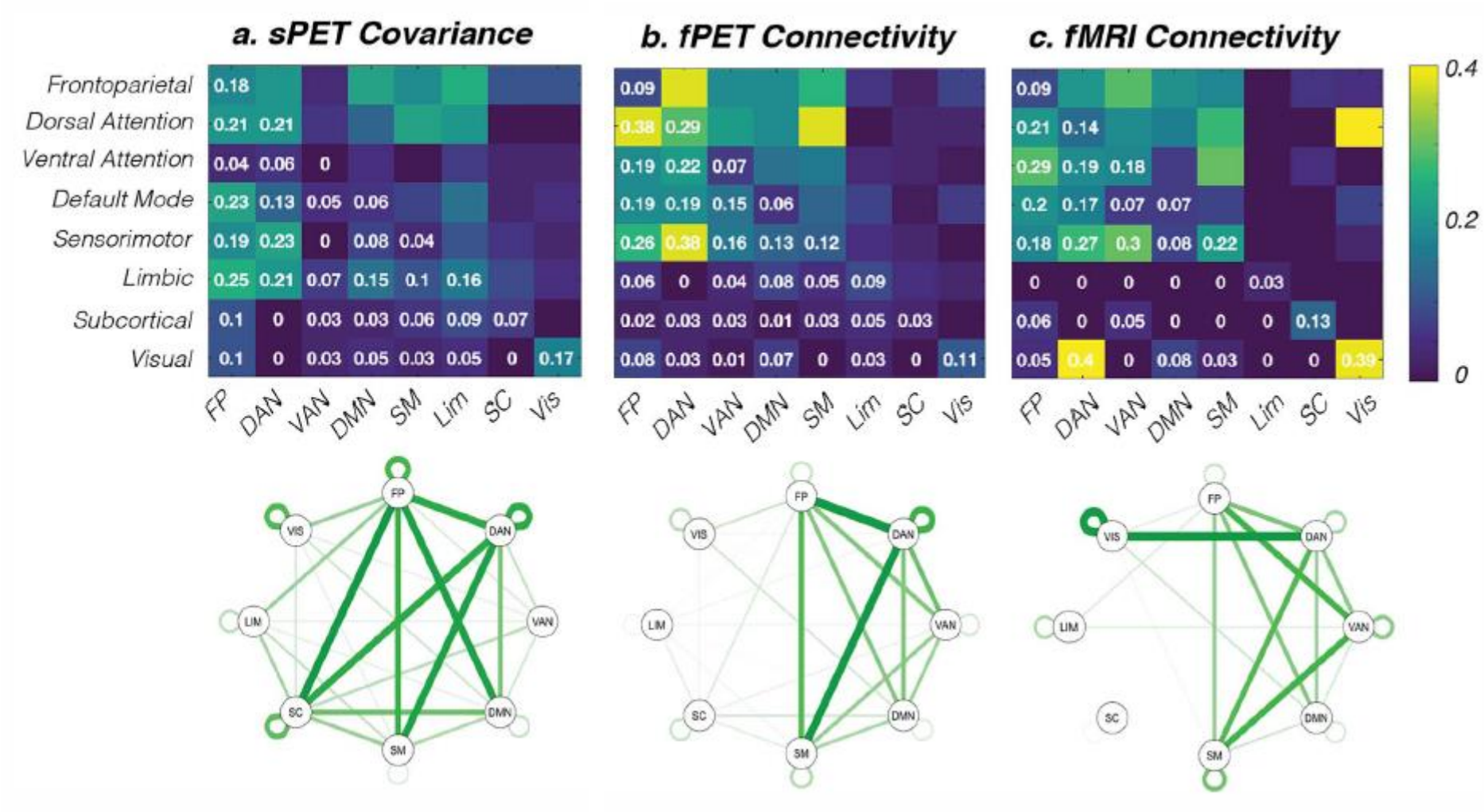


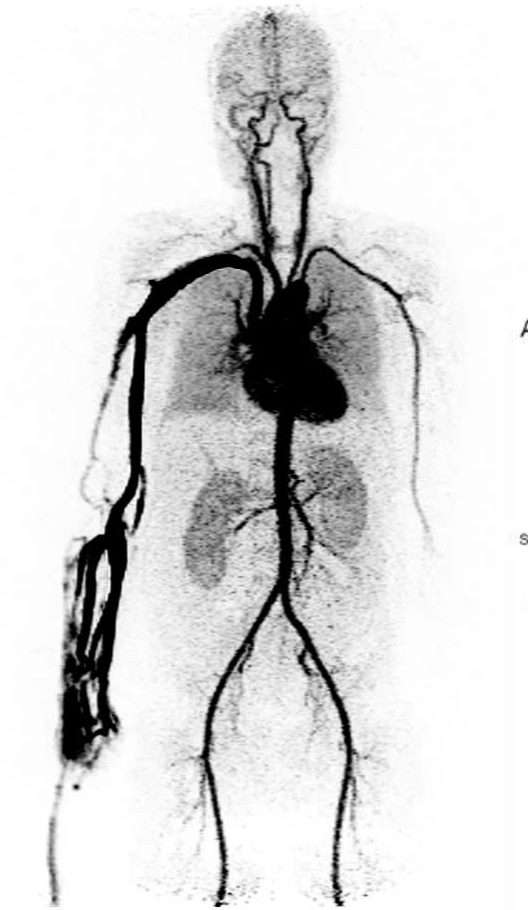
fPET



fMRI







Neuroimaging Lab Head
Univ.-Prof. R. Lanzenberger

NeuroImage 271 (2023) 120030

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Whole-body metabolic connectivity framework with functional PET

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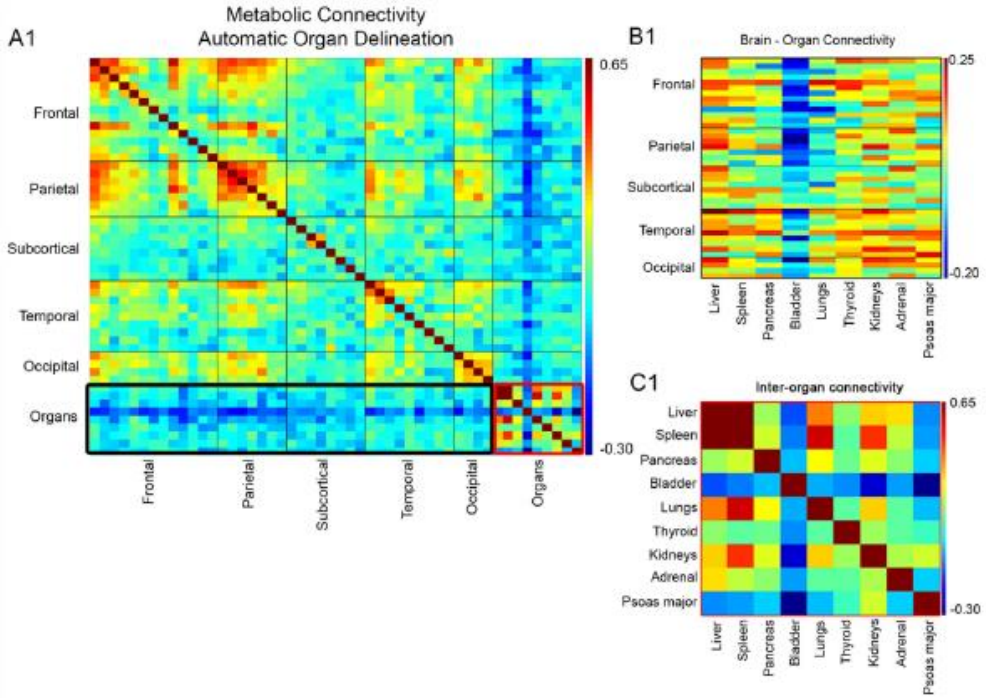
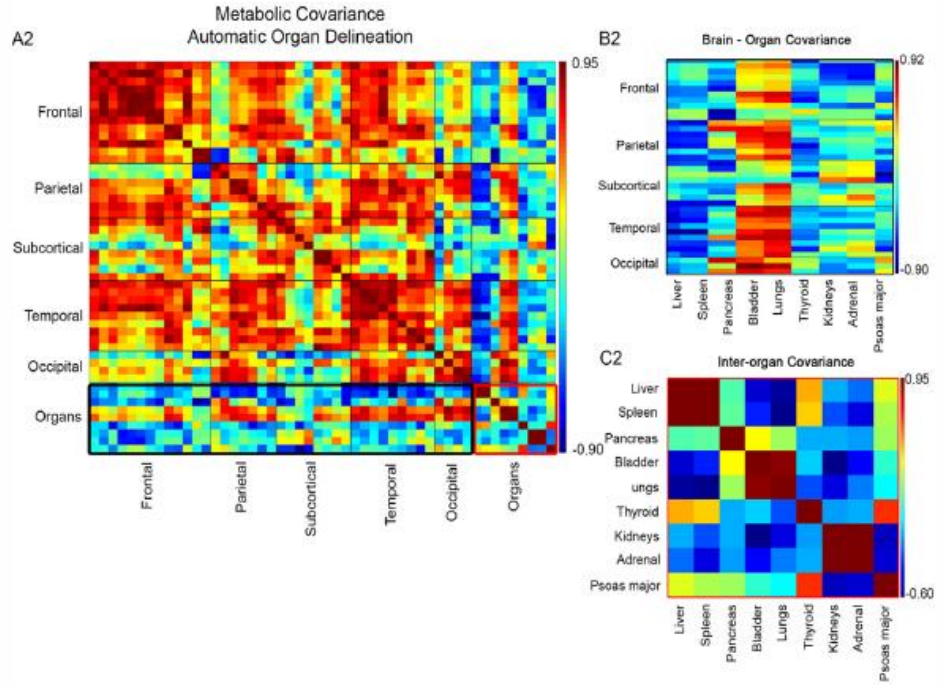


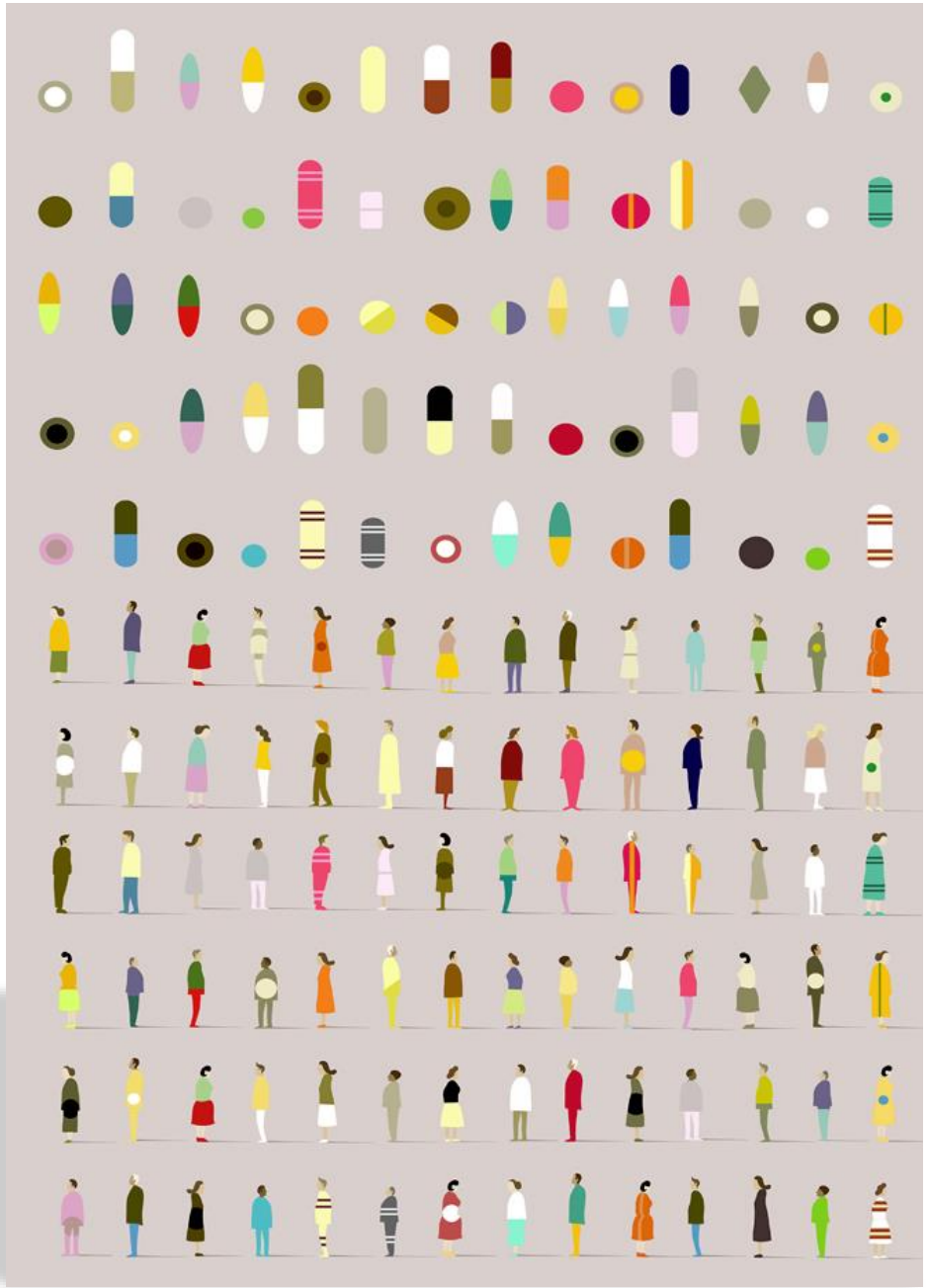


Summary

- Metabolic processes in the whole body can be visualized and quantified by PET/CT in humans and small animals
- Network analysis and analysis of organ communication possible
- Patient stratification into high/low stress possible based on routine FDG PET
- Potentially therapeutic approaches can be guided using FDG (e.g. beta adrenergic blockade)

→ A precondition is to understand our in-vivo signals and the underlying signalling mechanisms

→ Human tissue probes and small animal disease models can be used to explore the radioactive sources of whole body signalling on a cellular level



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