3rd International Danube Symposium
Vienna

Sex and Gender in Medicine

The brain-hormone connection: investigating the Influence of sex (hormones) and gender

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Department of Cardiology, Inselspital University Hospital Bern
Department of Nuclear Medicine, University Hospital Zurich

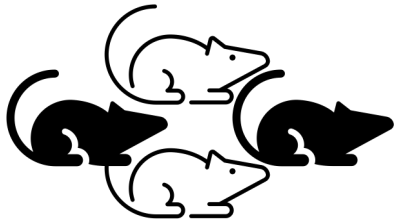
INSELSPITAL

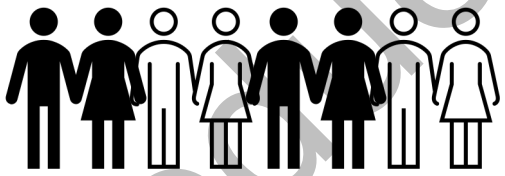
USZ Universitäts Spital Zürich

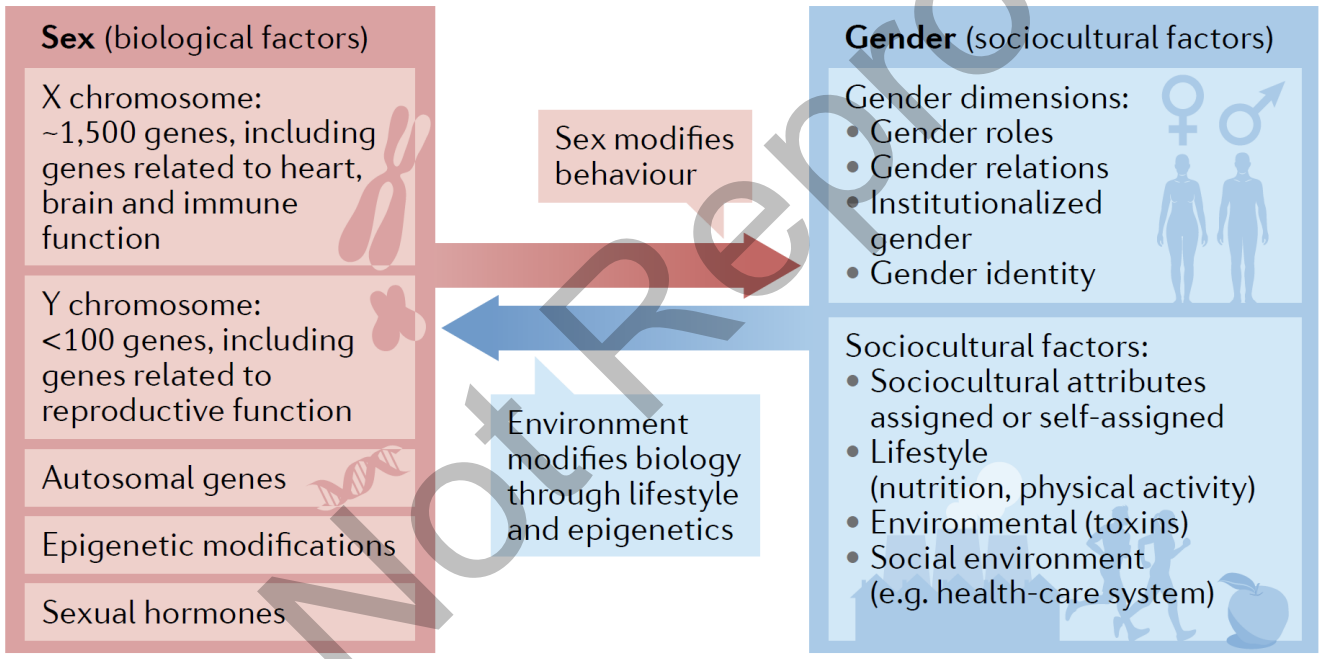
Sex AND Gender Impact Health and Disease

Sex

Biological differences such as genes, sex hormones, anatomy, and physiology





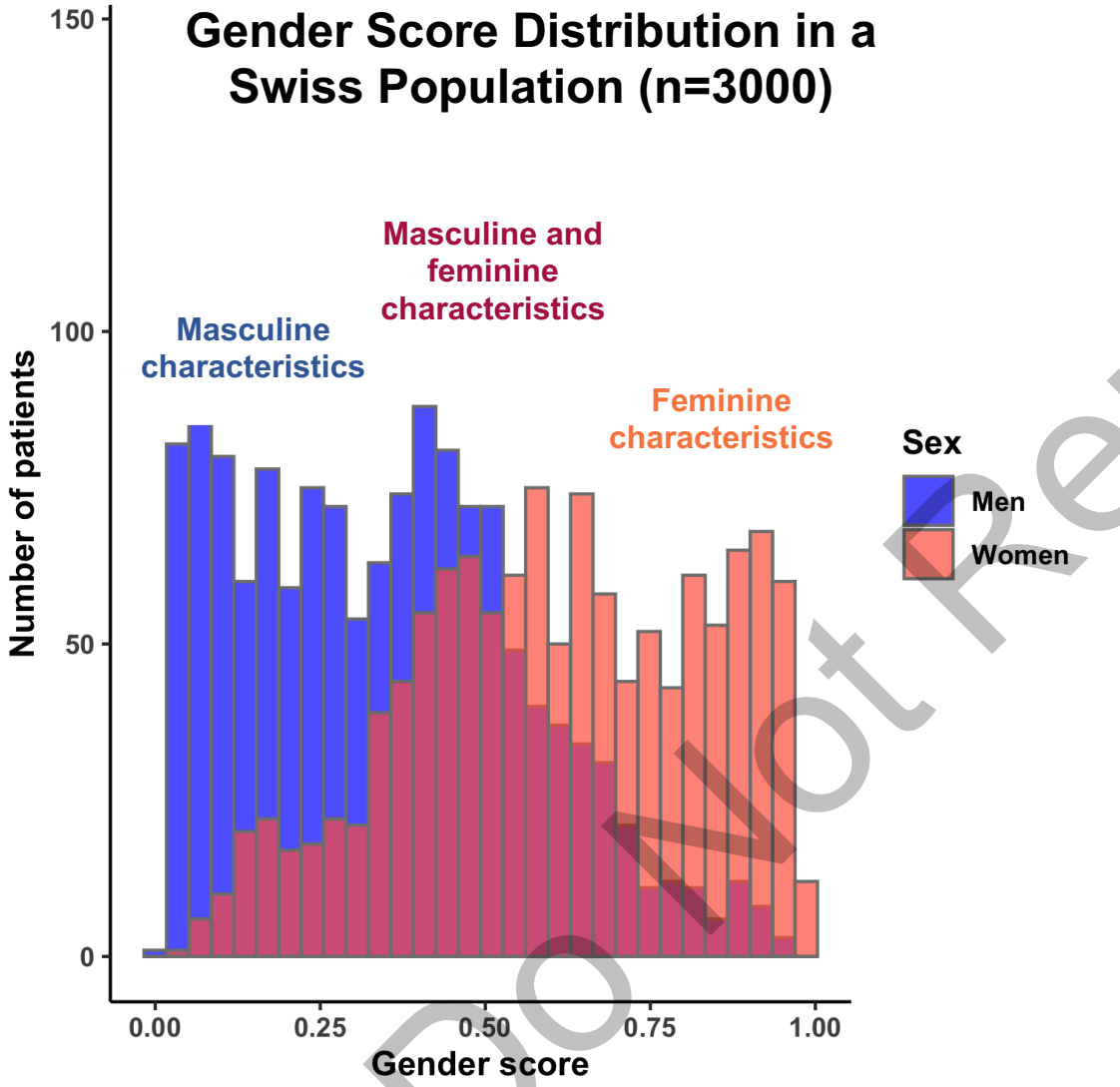


Gender

Socially constructed characteristics of women and men

Gebhard C et al. Nat Rev Cardiol. 2022

How to Assess Gender?



Definition of Gender:

- **Gender roles**
- (e.g. child care)

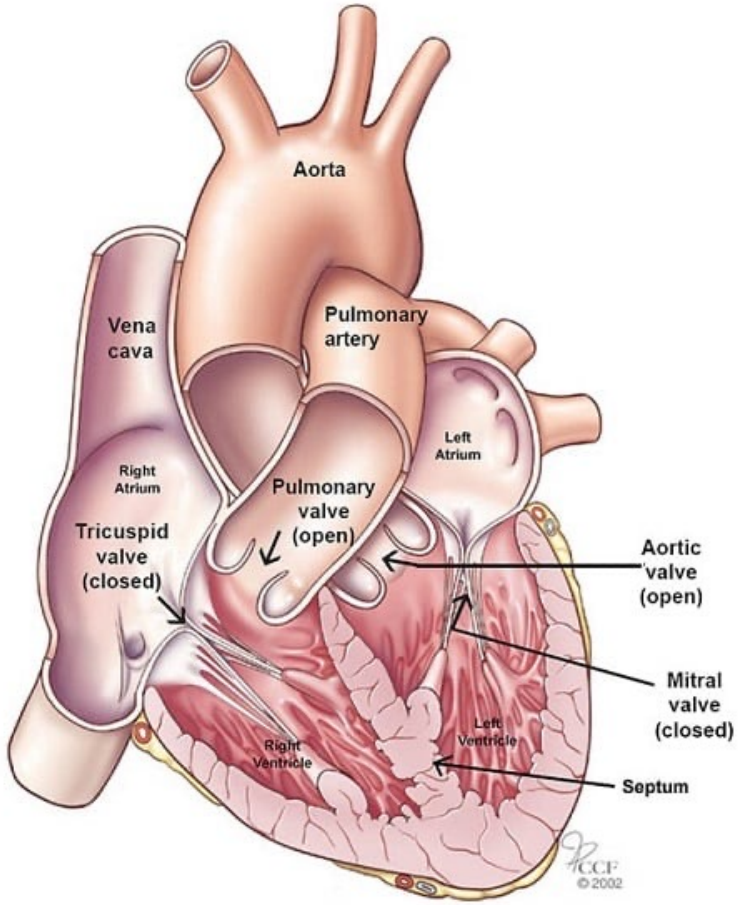
- **Gender identity**
- (a personal conception of oneself as man or woman)

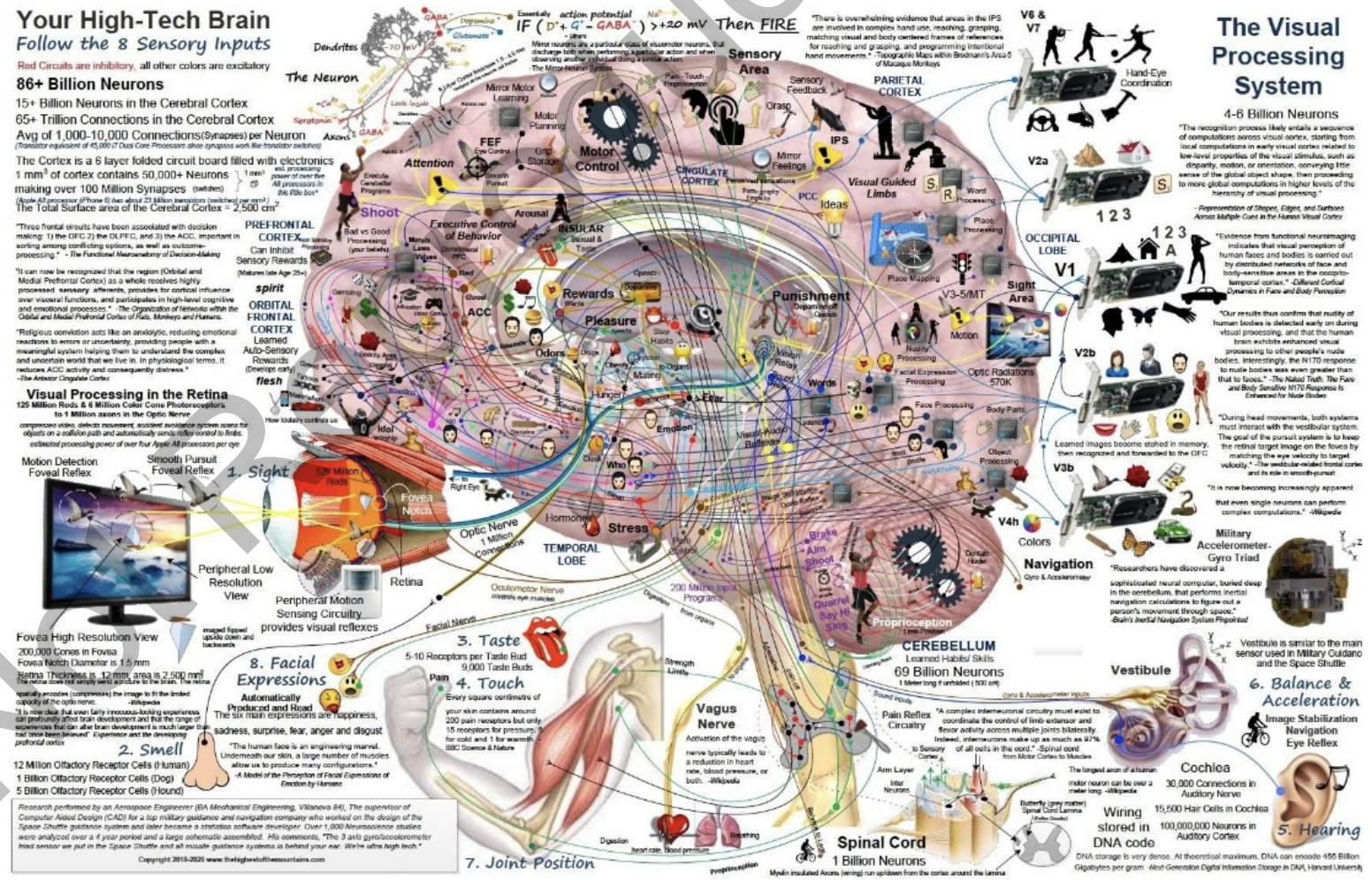
- **Gender relationships**
- (e.g. social support)

- **Institutionalized gender**
- (e.g. education level, personal income)

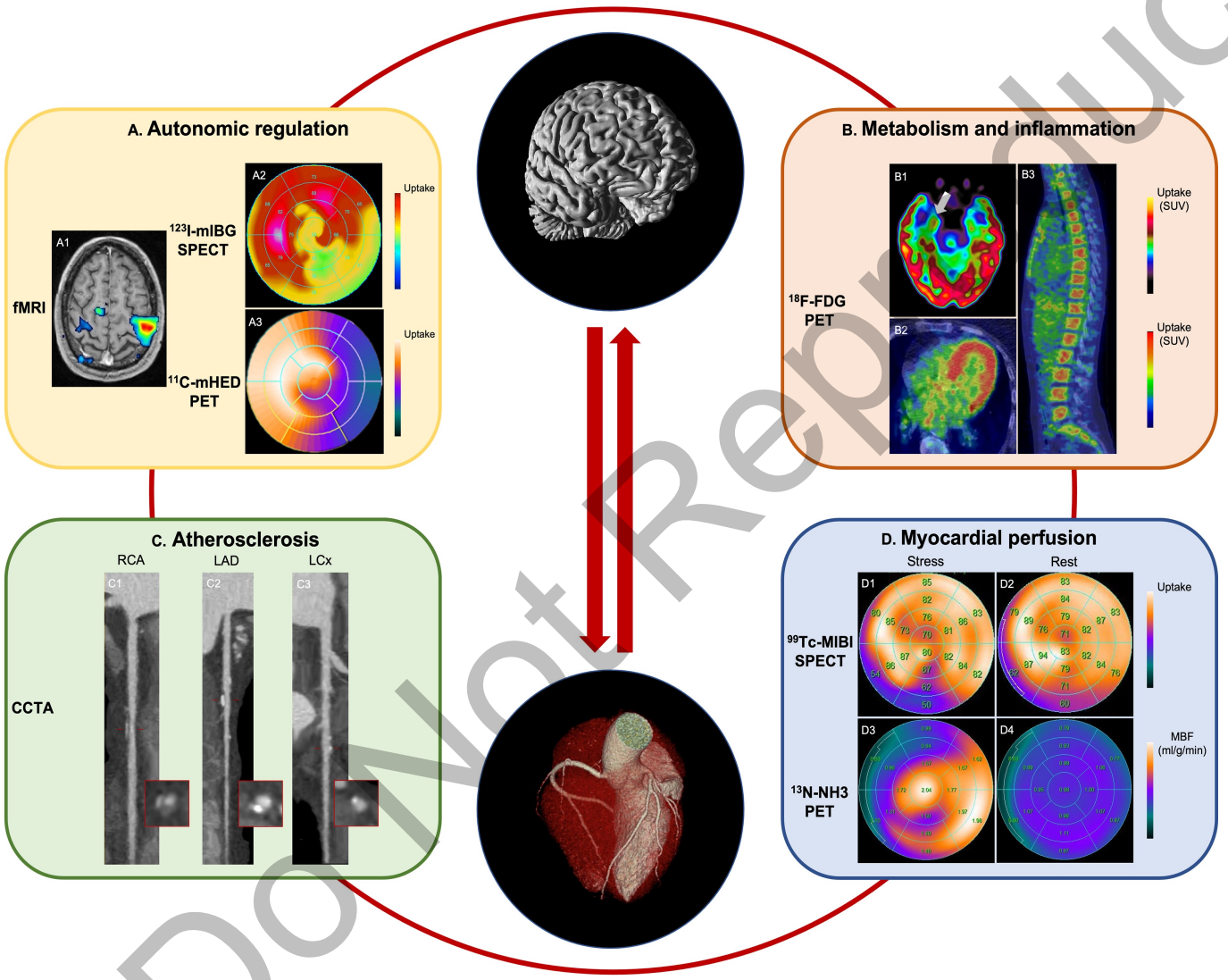
Gebhard C et al. Intensive Care Med. 2022

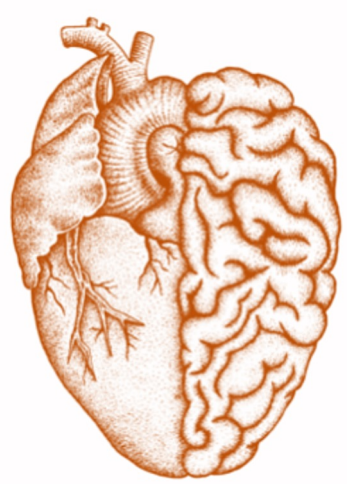
Heart versus Brain





The Brain-Heart Connection





Rossi A […] Gebhard C. Eur Heart J. 2022

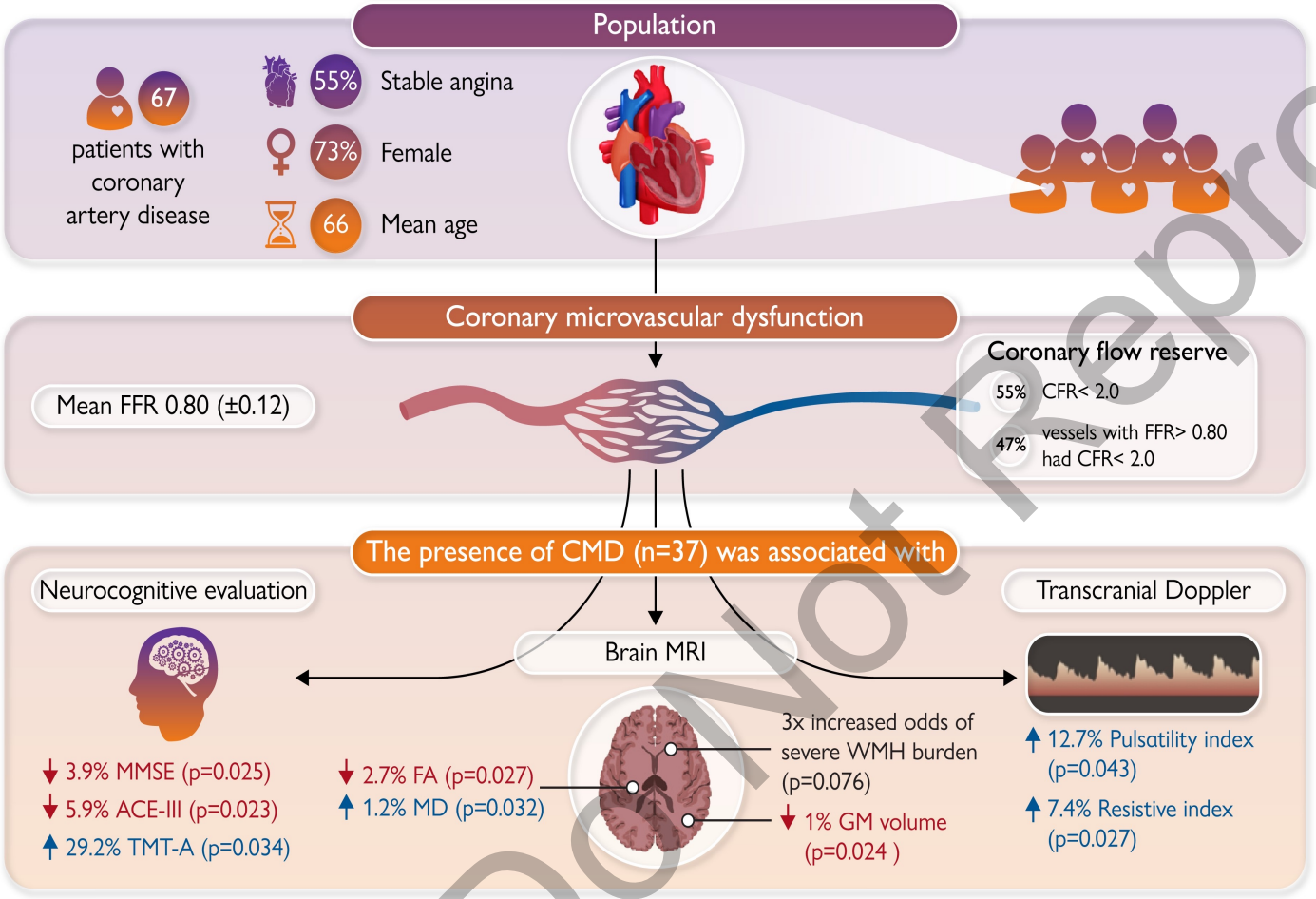
Heart Brain Interactions: Role of Sex and Gender

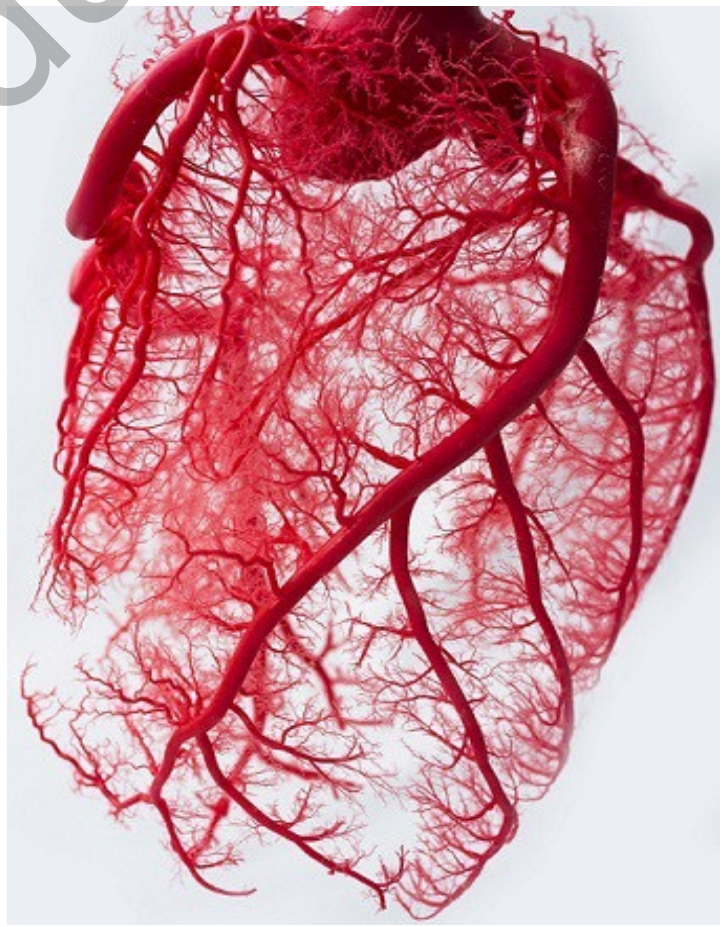
- **Stroke**
  - Stroke due to atrial fibrillation is more common in women than in men
  - Women with stroke have a higher incidence of MACE, cardiovascular mortality, and heart failure than men, mechanism unknown

- **Dementia**
  - Dementia affects women twice as often as men
  - Women suffering from hypertension have worse cognitive performance than normotensive women

Akyea RK et al. Stroke 2021; Livingston G et al. Lancet 2020; Zilberman JM et al. J Clin Hypertens 2015; 173. Voss A et al. Prog Neuropsychopharmacol Biol Psychiatry 2011; Koch C et al. Psychol Med 2019

Coronary Microvascular Dysfunction is Associated with Impaired Cognitive Function





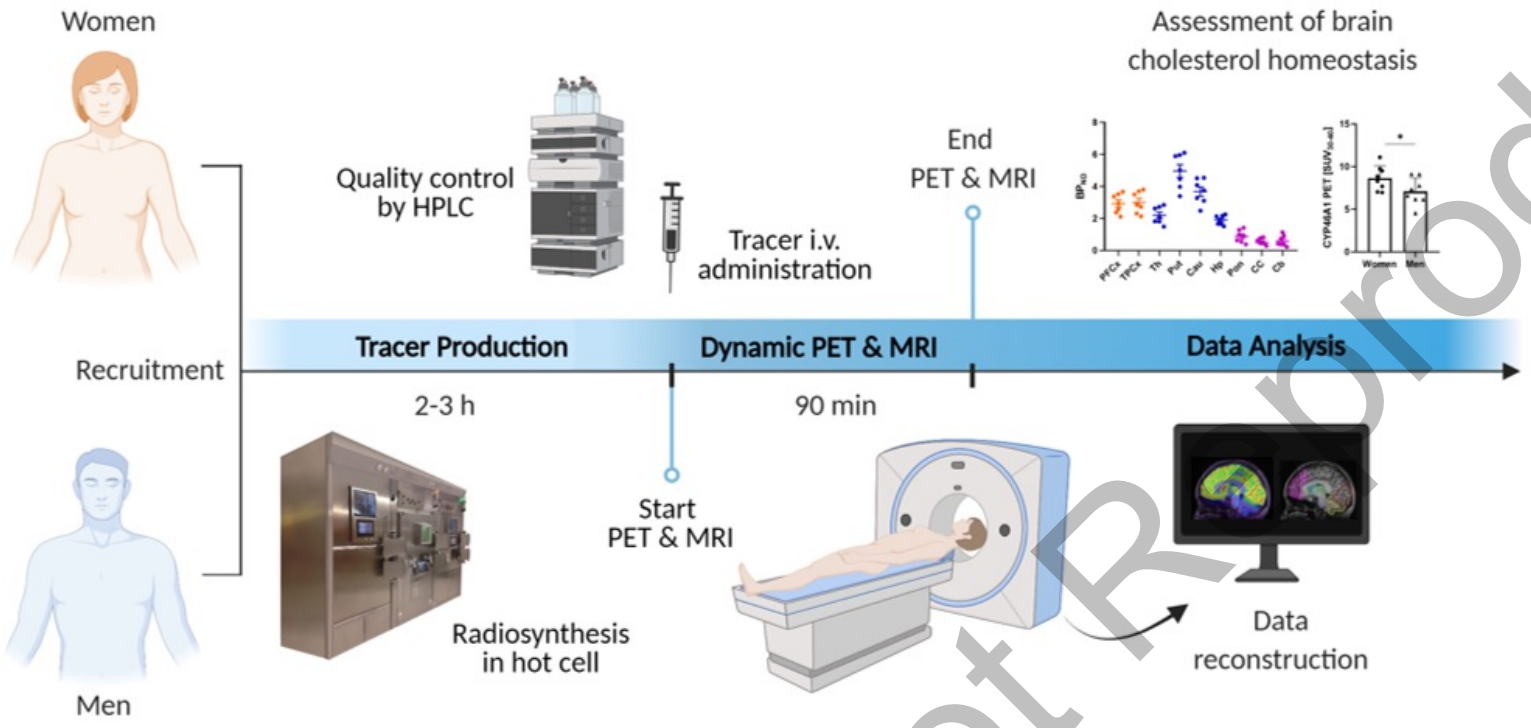
Mejia-Renteria H. et al. Eur Heart J. 2022

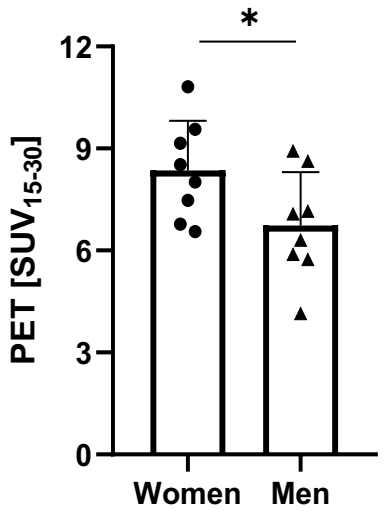
Heart Brain Interactions: Role of Sex and Gender

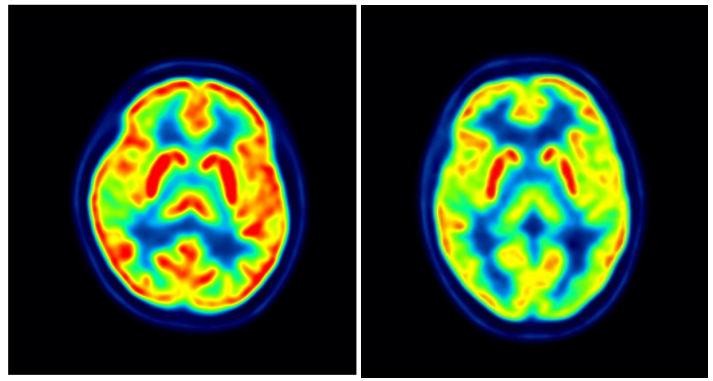
- **Depression**
  - The prevalence of depression after MI is higher in women than men
  - Depression is a stronger cardiovascular risk factor in women than in men
  - Greater activation of the sympathetic nervous system in women with depression
  - Cholesterol and estrogen

Akyea RK et al. Stroke 2021; Livingston G et al. Lancet 2020; Zilberman JM et al. J Clin Hypertens 2015; 173. Voss A et al. Prog Neuropsychopharmacol Biol Psychiatry 2011; Koch C et al. Psychol Med 2019

Depression and Cholesterol Clearance



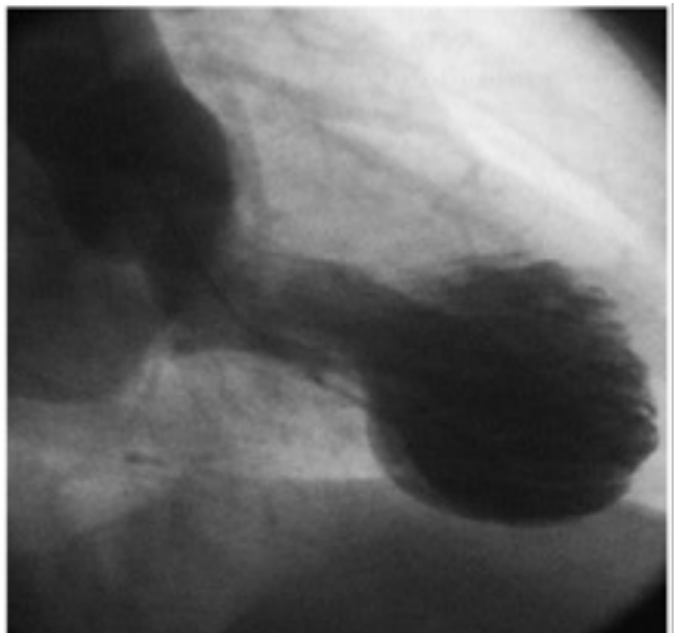




- Cholesterol clearance is enhanced in healthy women compared to men
- **Low brain cholesterol is associated with depression**
- Cholesterol (= substrate for steroid hormone synthesis) -> reduced local biosynthesis of estrogen

Haider A, Gebhard C et al. Science Transl Med. 2022

Heart Brain Interactions: Takotsubo Syndrome



Predominantly affects postmenopausal women (9x more often than men)

Agdamag AC et al. J Womens Health. 2020

Takotsubo-Mechanisms?

Male animals only

Immobilization Stress With α_2-Adrenergic Stimulation Induces Regional and Transient Reduction of Cardiac Contraction Through Gi Coupling in Rats

Ryohei KURODA,[1] MD, Kaori Shintani-ISHIDA,[1] PhD, Kana UNUMA,[2] MD, *and* Ken-ichi YOSHIDA,[1] MD

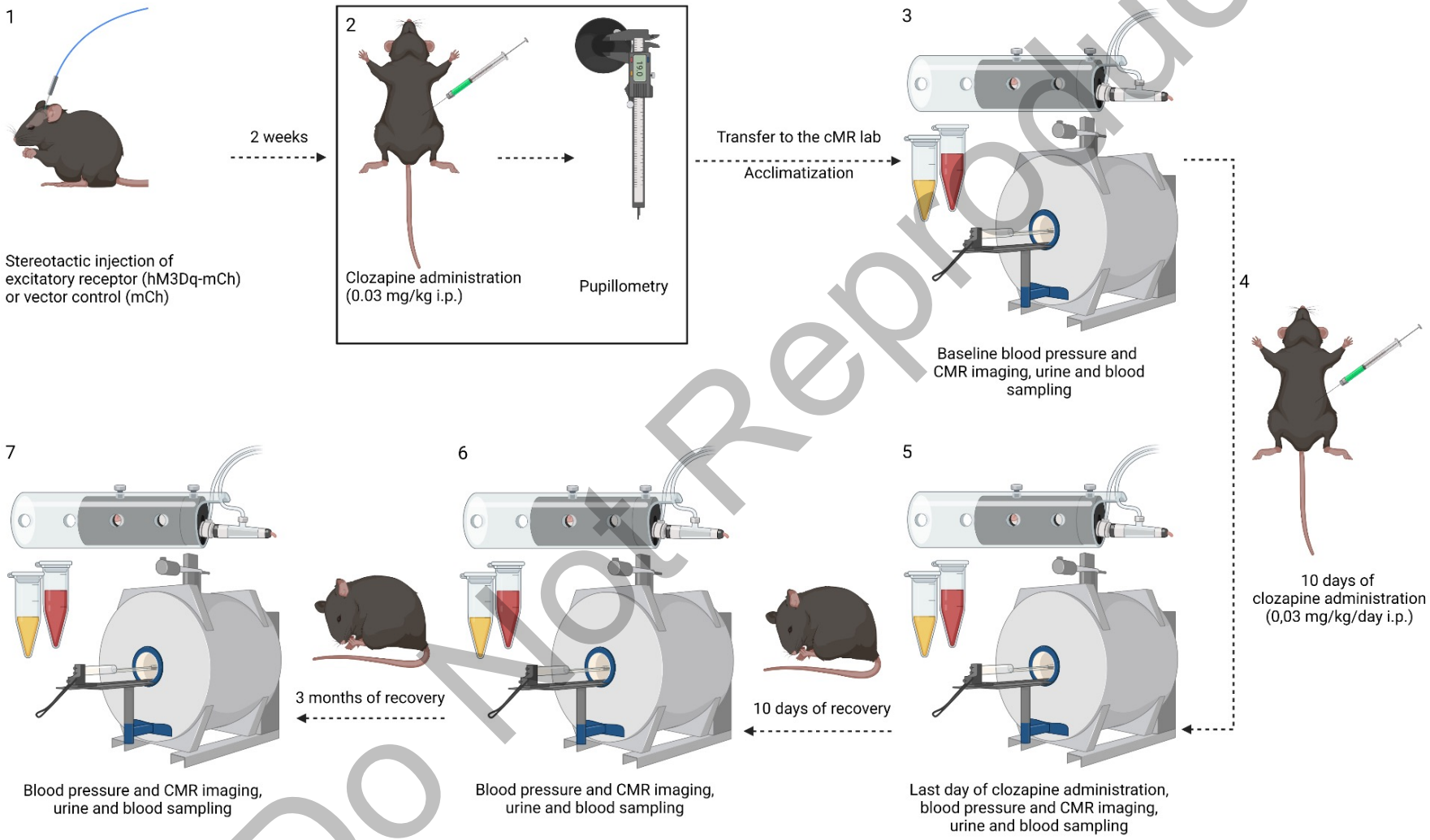
Novel rat model reveals important roles of β-adrenoreceptors in stress-induced cardiomyopathy☆

Yangzhen Shao [a,1], Bjorn Redfors [a,*,1], Margareta Scharin Täng [a], Helge Möllmann [b,c], Christian Troidl [b,c], Sebastian Szardien [b], Christian Hamm [b,c], Holger Nef [b,c], Jan Borén [a], Elmir Omerovic [a]

[a] *Wallenberg Laboratory at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[b] *Department of Cardiology, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany*
[c] *University of Giessen, Department of Cardiology, Giessen, Germany*

Kuroda R et al. Int Heart J. 2015; Shao Y et al. Int J Cardiol. 2013

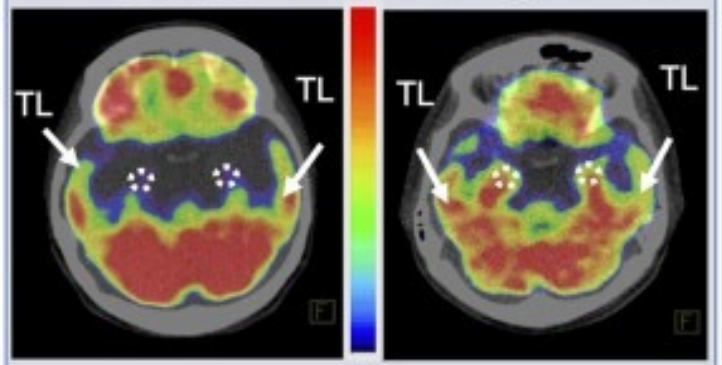
Mouse Model Mimicking the Response of the Central Nervous System to Stress



Ministrini S […] Gebhard C. 2023. Manuscript submitted

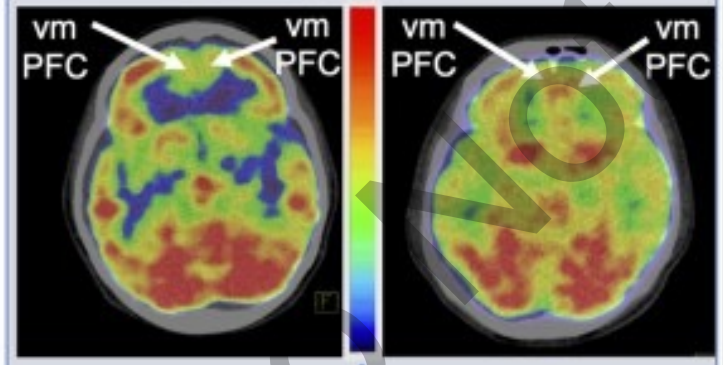
Takotsubo Syndrome and Amygdala Activity

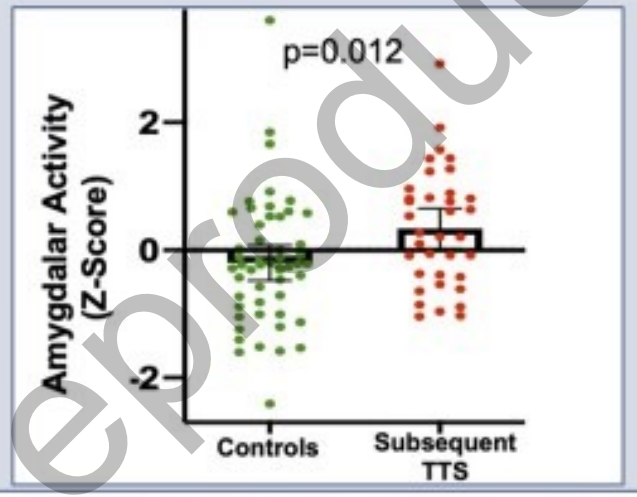
^{18}F-FDG-PET/CT Imaging of Stress-Associated Neurobiological Activity (as Amygdalar Activity)



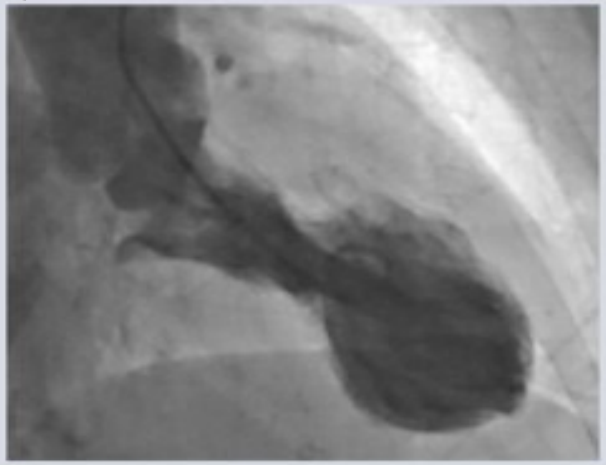
Level of the Amygdala and Temporal Lobe

Level of the Ventromedial Prefrontal Cortex





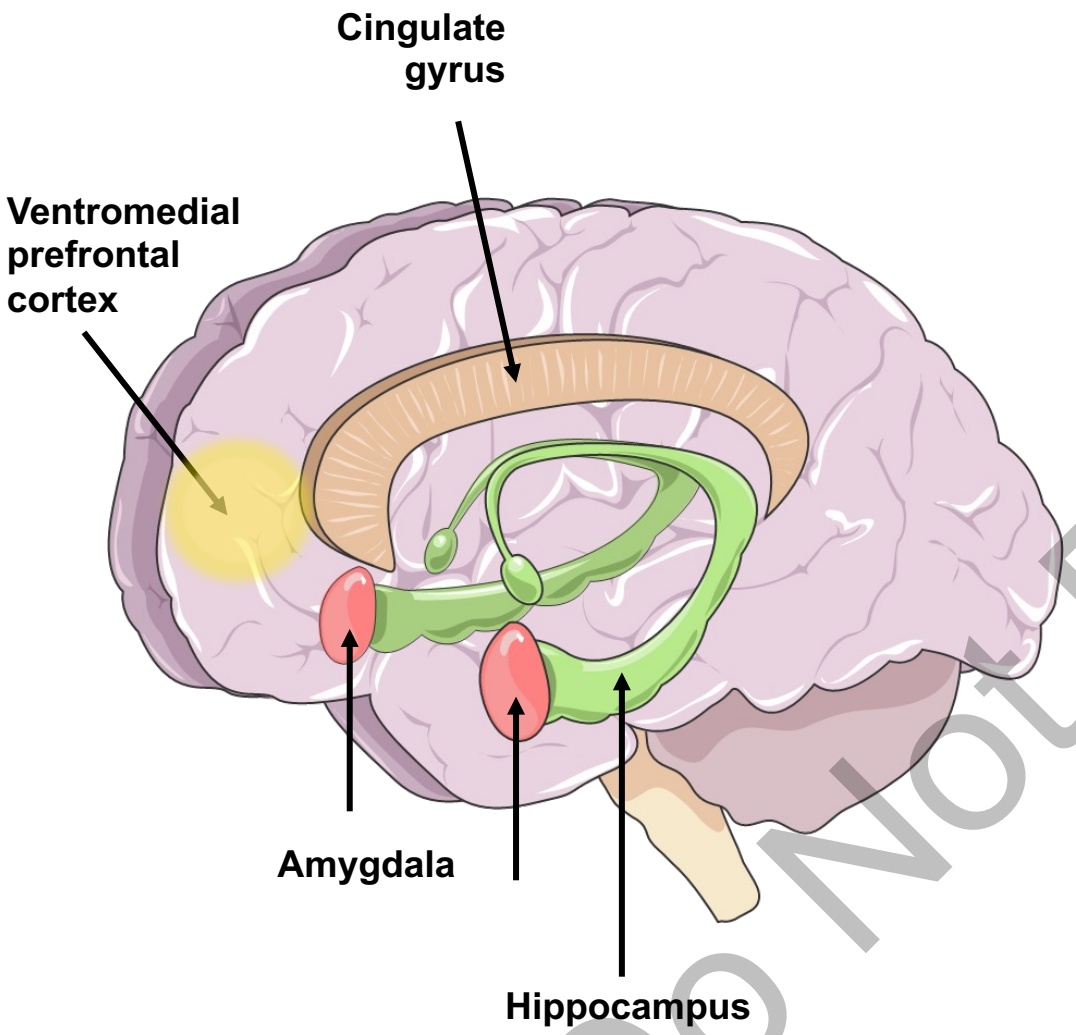
Amygdalar Activity is Higher Among Individuals Who Subsequently Develop TTS



Development of Takotsubo Syndrome after Imaging

Radfar A et al. Eur Heart J. 2021

The Amygdala: Sexual Dimorphism

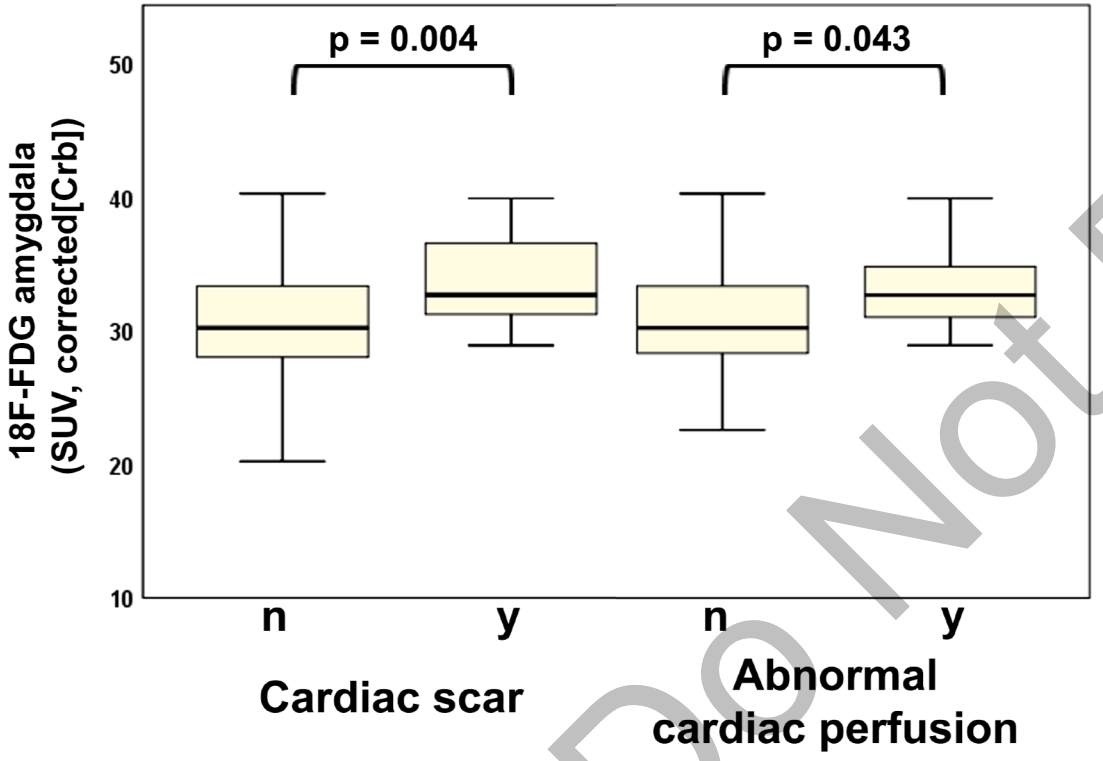


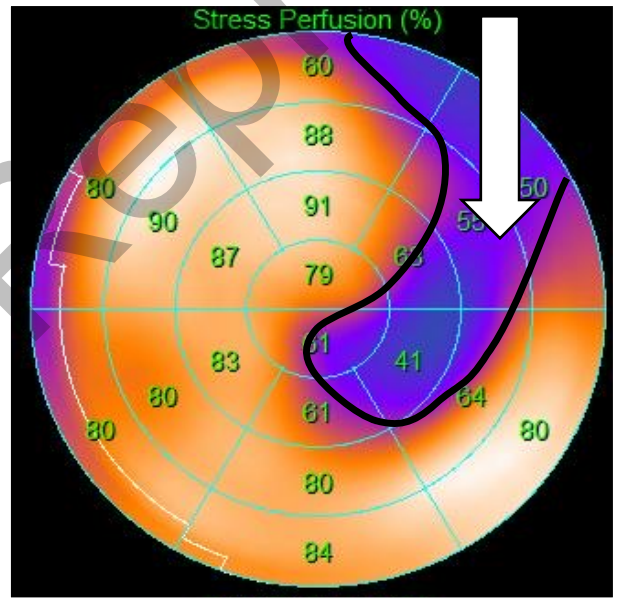
- Expression of estrogen and testosterone receptors in the amygdala and related structures
- Decrease in Amygdala activity in healthy, aged men, but not in women
- Men have larger volumes of the amygdala
- Socioeconomic and lifestyle variables, which differ between women and men ('Gender'), are associated with amygdala activity

Haider A et al. J Nucl Cardiol. 2021; Milner TA et al. Endocrinology. 2008; van Wingen G et al. Psychoneuroendocrinology. 2010; Goldstein JM et al. Cereb Cortex. 2001; Mezue K et al. J Am Coll Cardiol. 2023; Dar T et al. Circ Cardiovasc Imaging. 2020

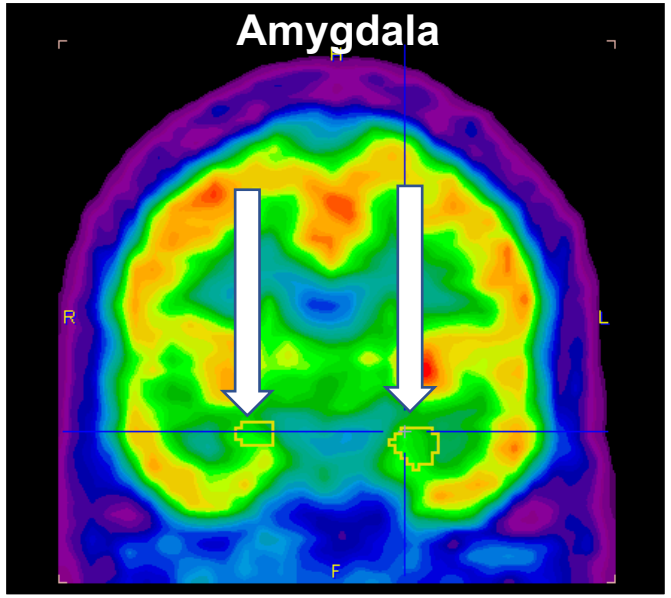
Sex and Gender Differences in Neuronal Stress Responses

Association between neuronal stress responses and myocardial injury in women, but not in men – ^{18}F-FDG-PET





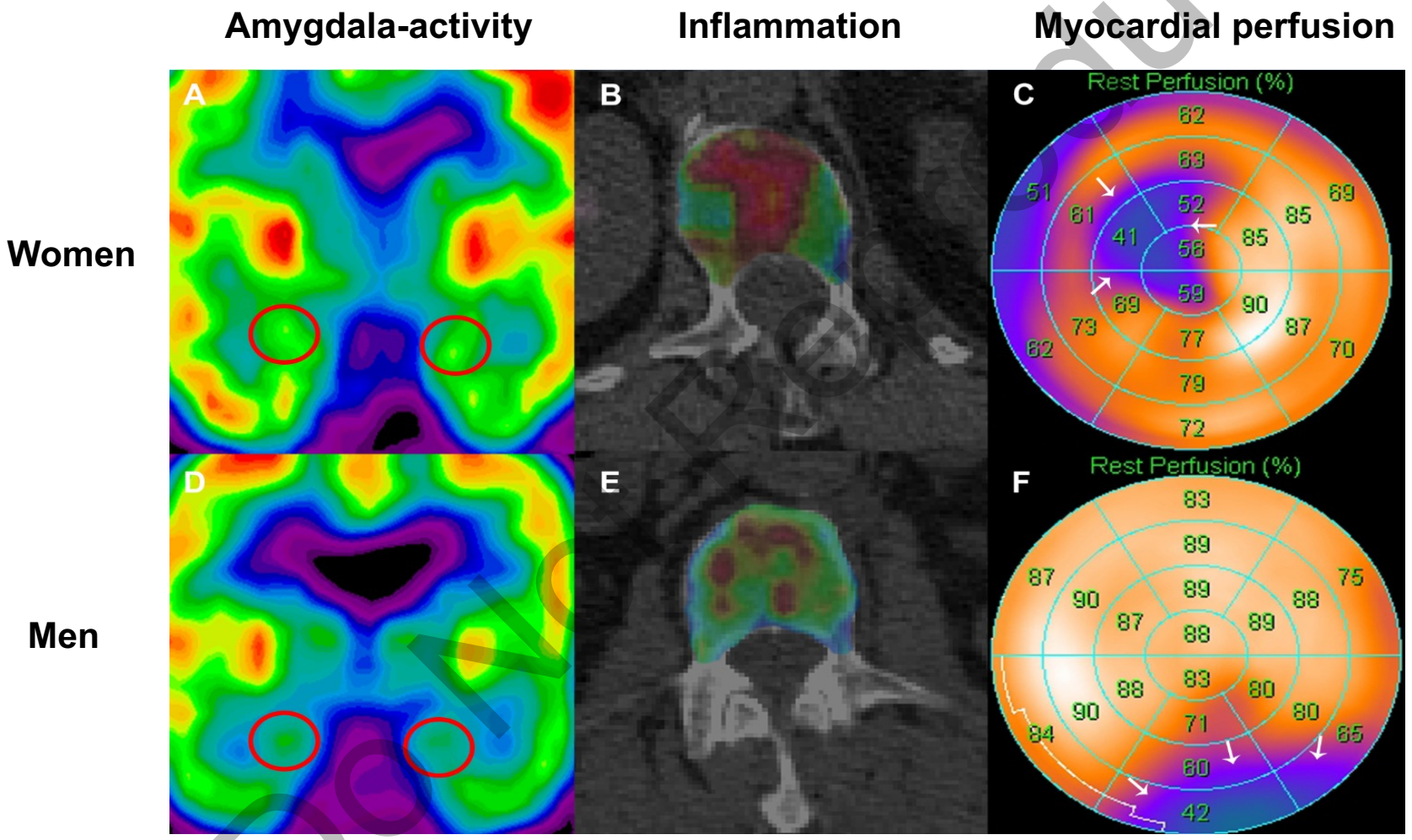
Myocardial perfusion defect



Increased amygdalar metabolic activity

Fiechter M […] Gebhard C. Eur Heart J:Cardiovasc Imaging. 2019

Gender Differences in Neuronal Stress Responses: Role of Inflammation



Fiechter M [...] Gebhard C. Eur J Nucl Med Mol Imaging. 2020

Gender Differences in Neuronal Stress Responses: Clinical Implications

ESC European Society of Cardiology

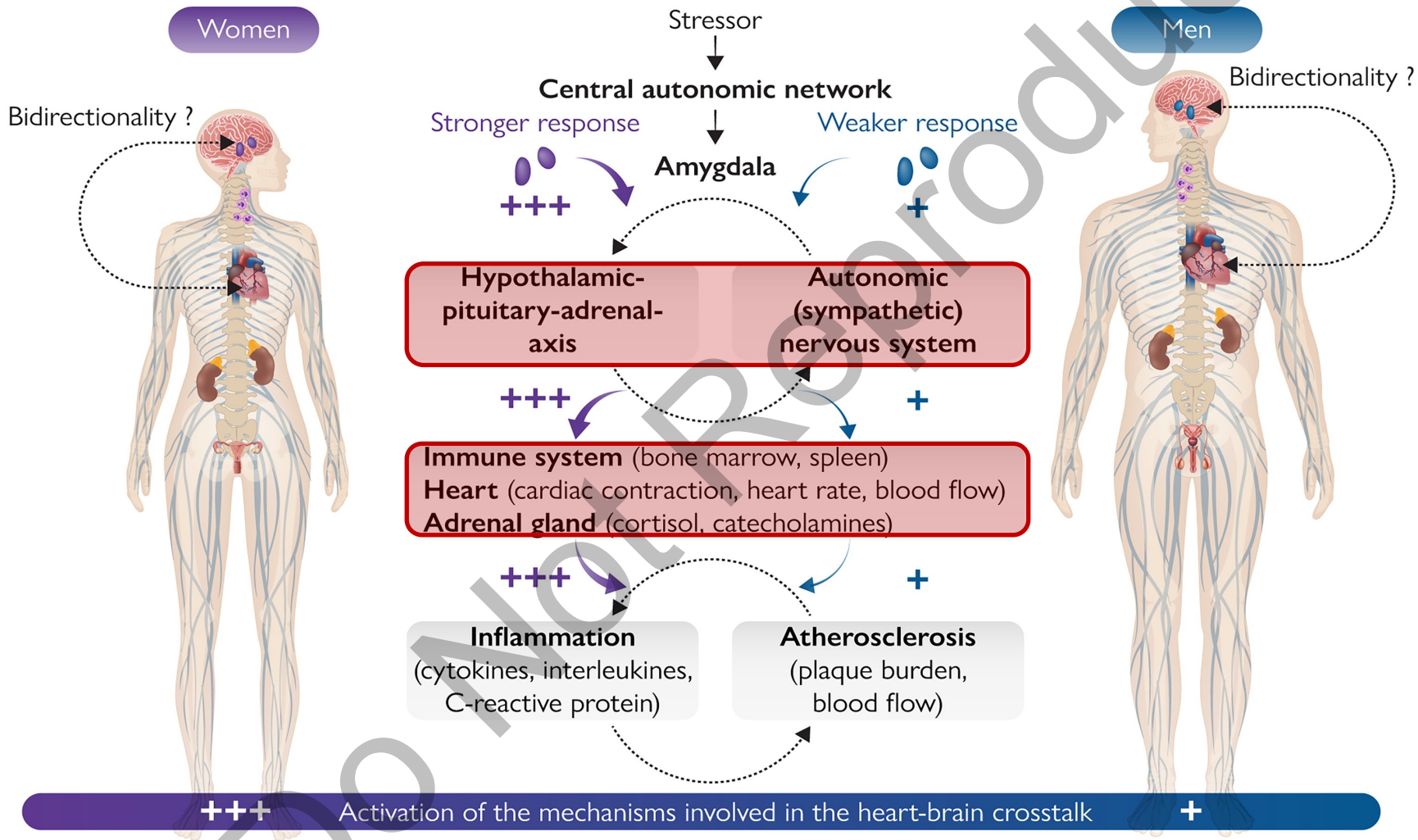
European Heart Journal - Cardiovascular Imaging (2019) **20**, 633–635
doi:10.1093/ehjci/jez086

EDITORIAL

Adverse cardiovascular outcomes in women: blame the amygdala?

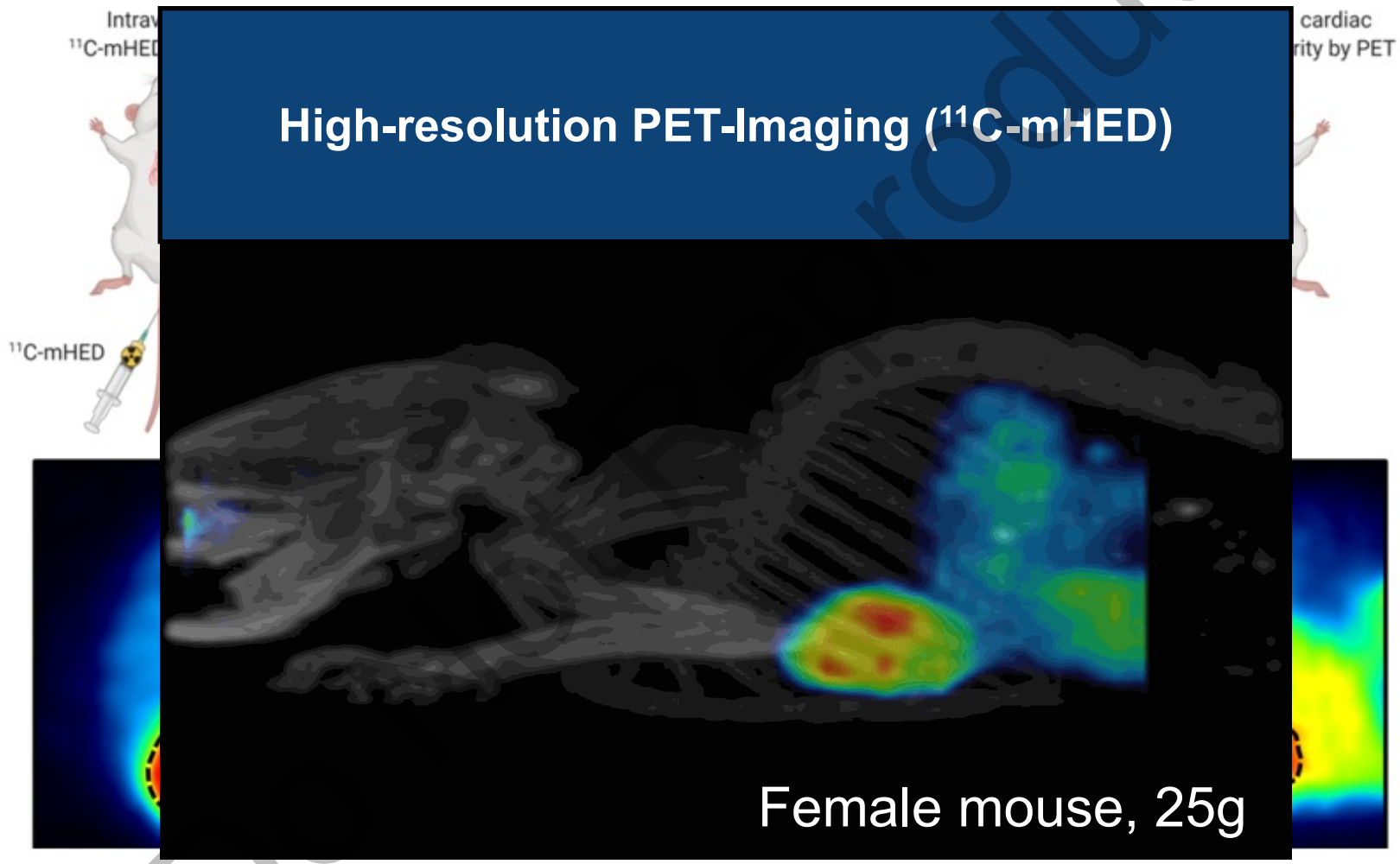
Puja K. Mehta [1,2]*, Bruno B. Lima[2,3], Michael D. Nelson[4], and C. Noel Bairey Merz[5]

(Patho)physiological Systems Regulating Heart–brain Interactions



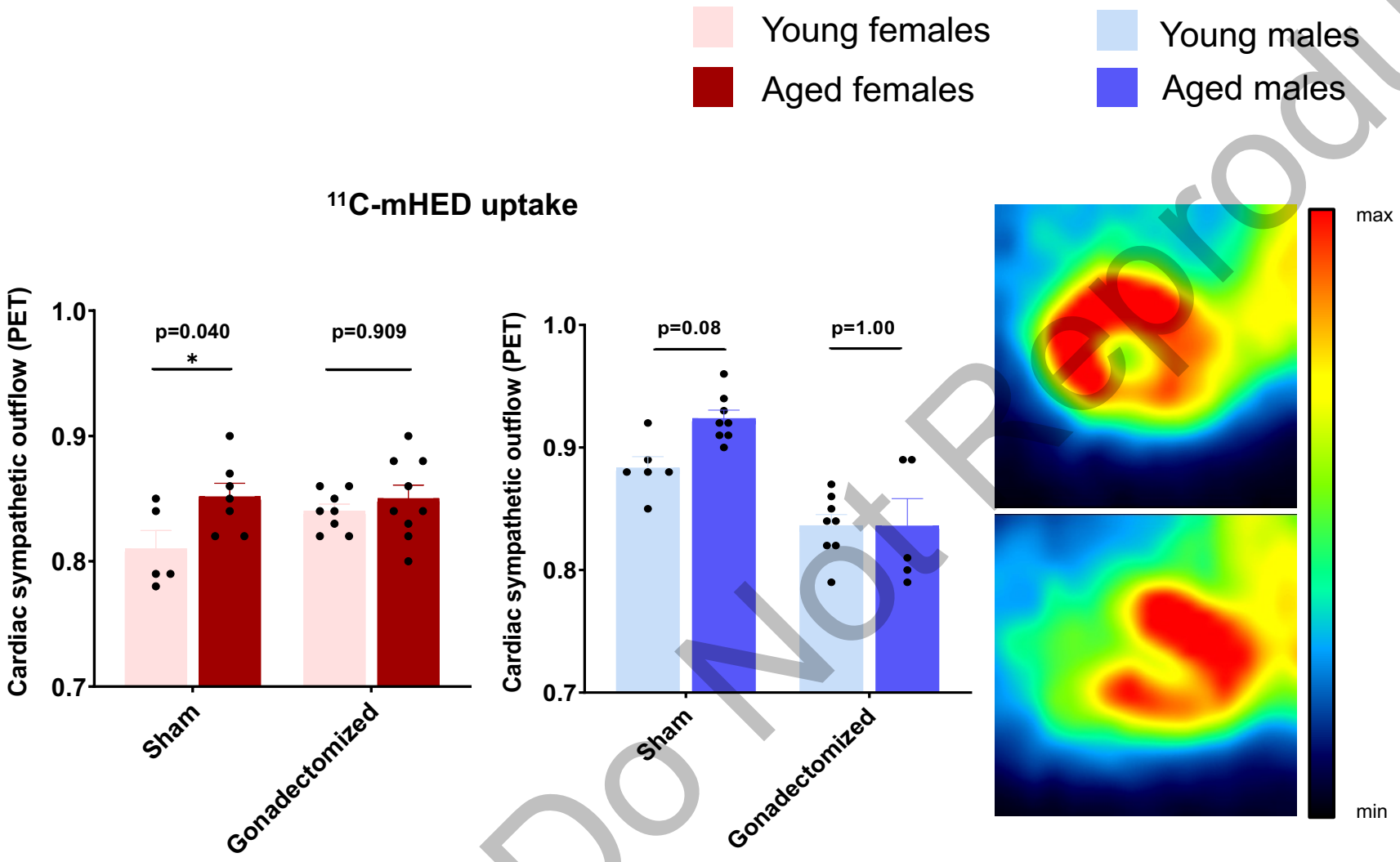
Rossi A […] Gebhard C. Eur Heart J. 2022

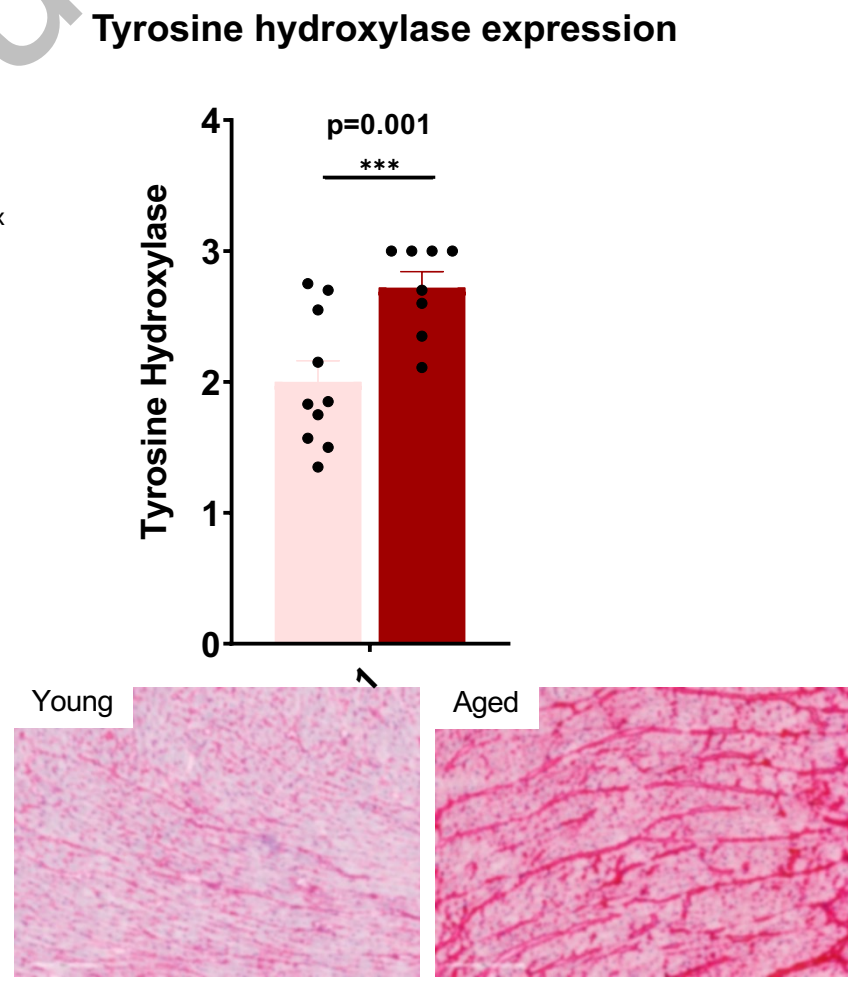
Measuring Cardiac Sympathetic Activity in Mice



Haider A [….] Gebhard C. 2023. Manuscript in preparation

Sex Hormones, Age, and Sympathetic Activity

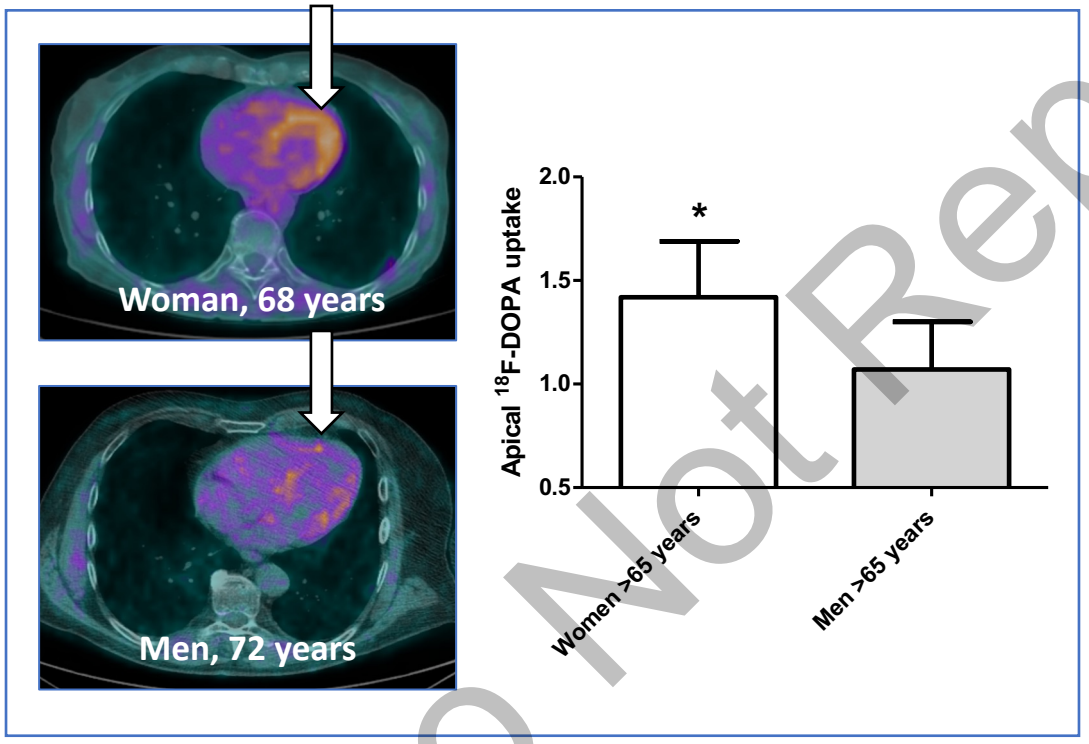


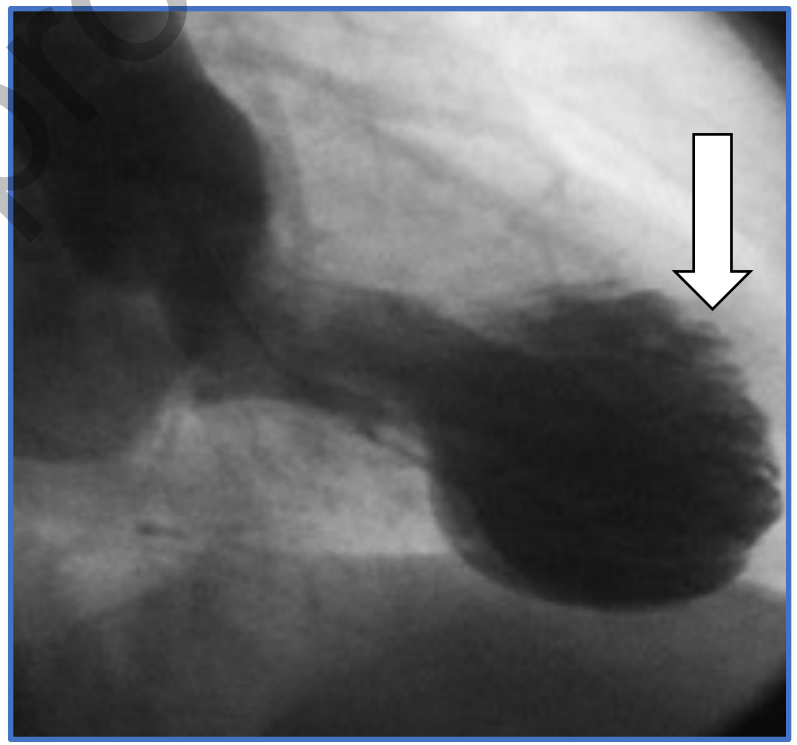


Haider A [….] Gebhard C. Manuscript in preparation

Sex, Age, and Sympathetic Activity

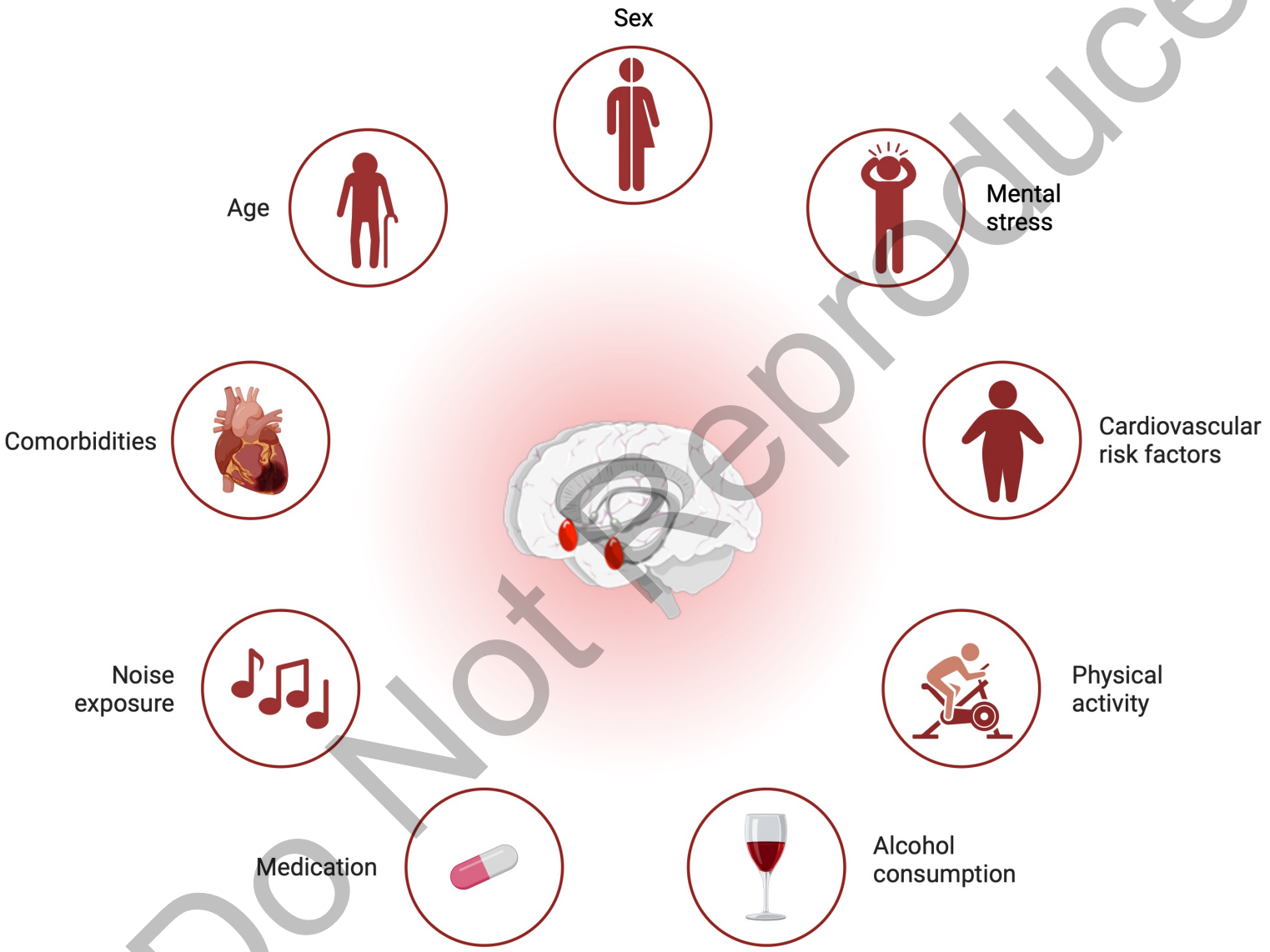
Enhanced cardiac sympathetic activity in healthy postmenopausal women





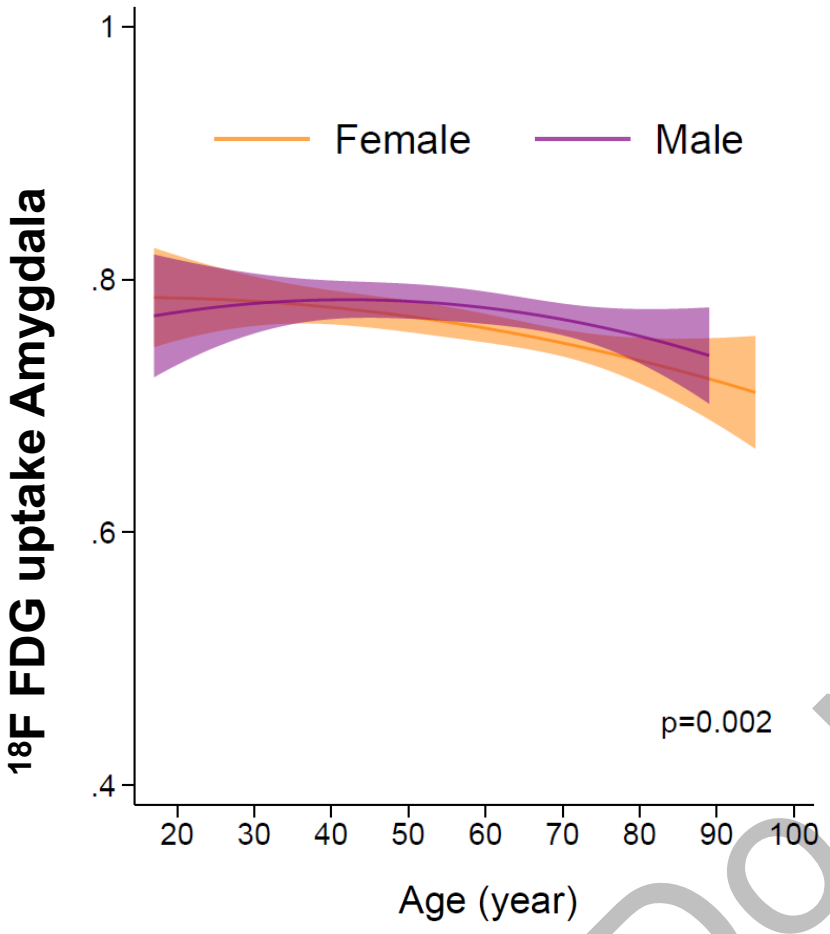
Burger I [….] Gebhard C. Plos One. 2018

Factors Influencing Amygdala Activity



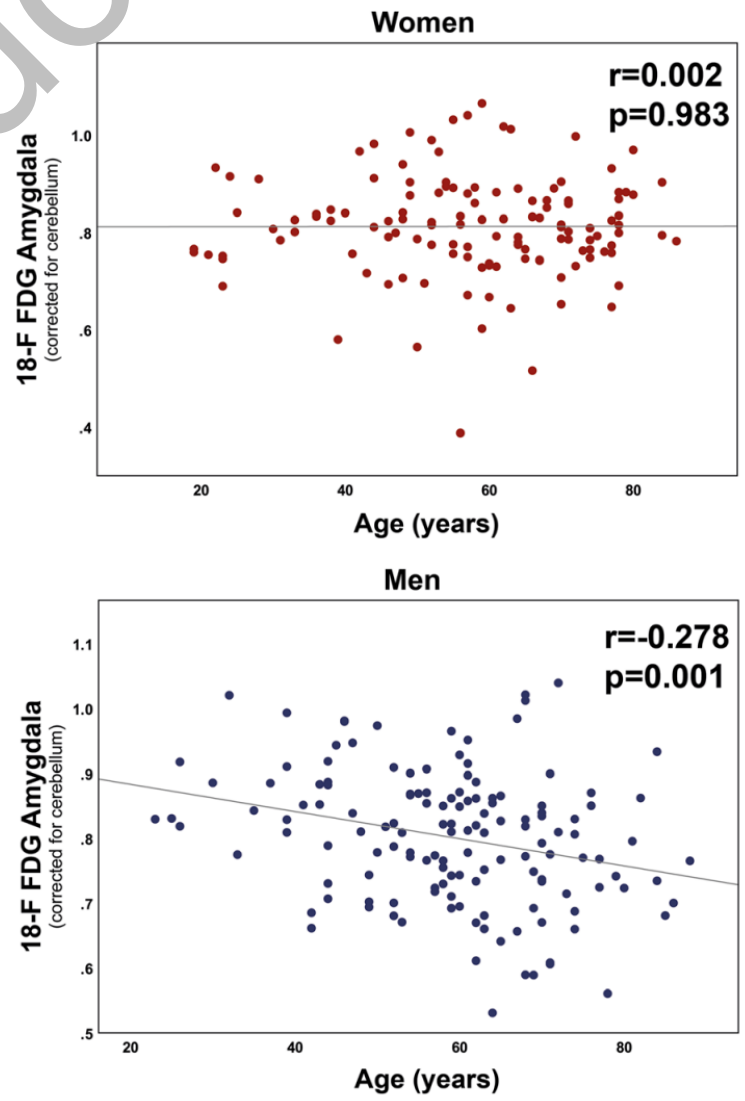
Factors Influencing Amygdala Activity: Age, Sex, Comorbidities

Comorbidities



- **Decrease in amygdala volume is seen after the sixth decade**
- **fMRI: Inverted-U-shape trend with age in functional connectivity of amygdalar subregions**

Healthy



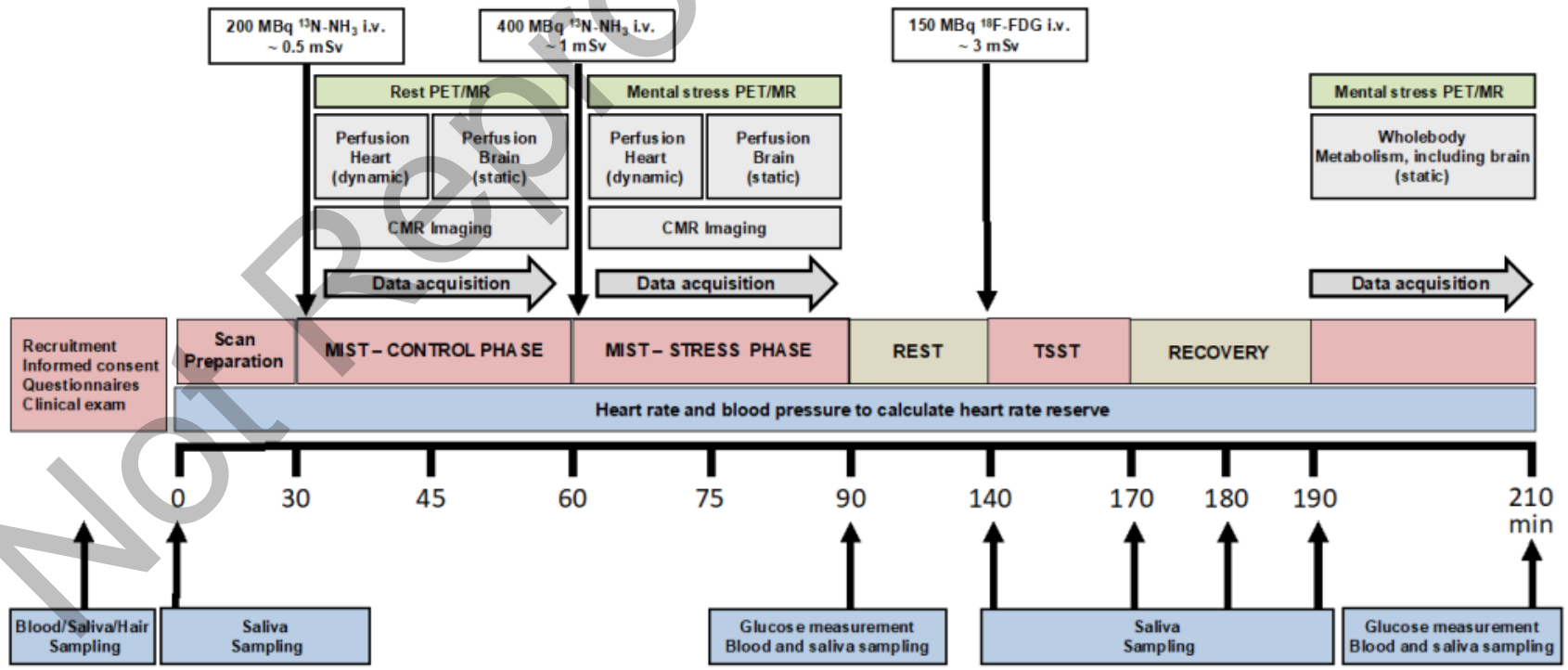
Mikail N [….] Gebhard C. Manuscript submitted; Dima D et al. Hum Brain Mapp. 2022; Jiang Y et al. Front Hum Neurosci. 2019

Simultaneous Heart-Brain Imaging in Healthy Individuals

Role of Sex Hormones, Inflammation, Sympathetic Pathways, and Psychosocial Complexity

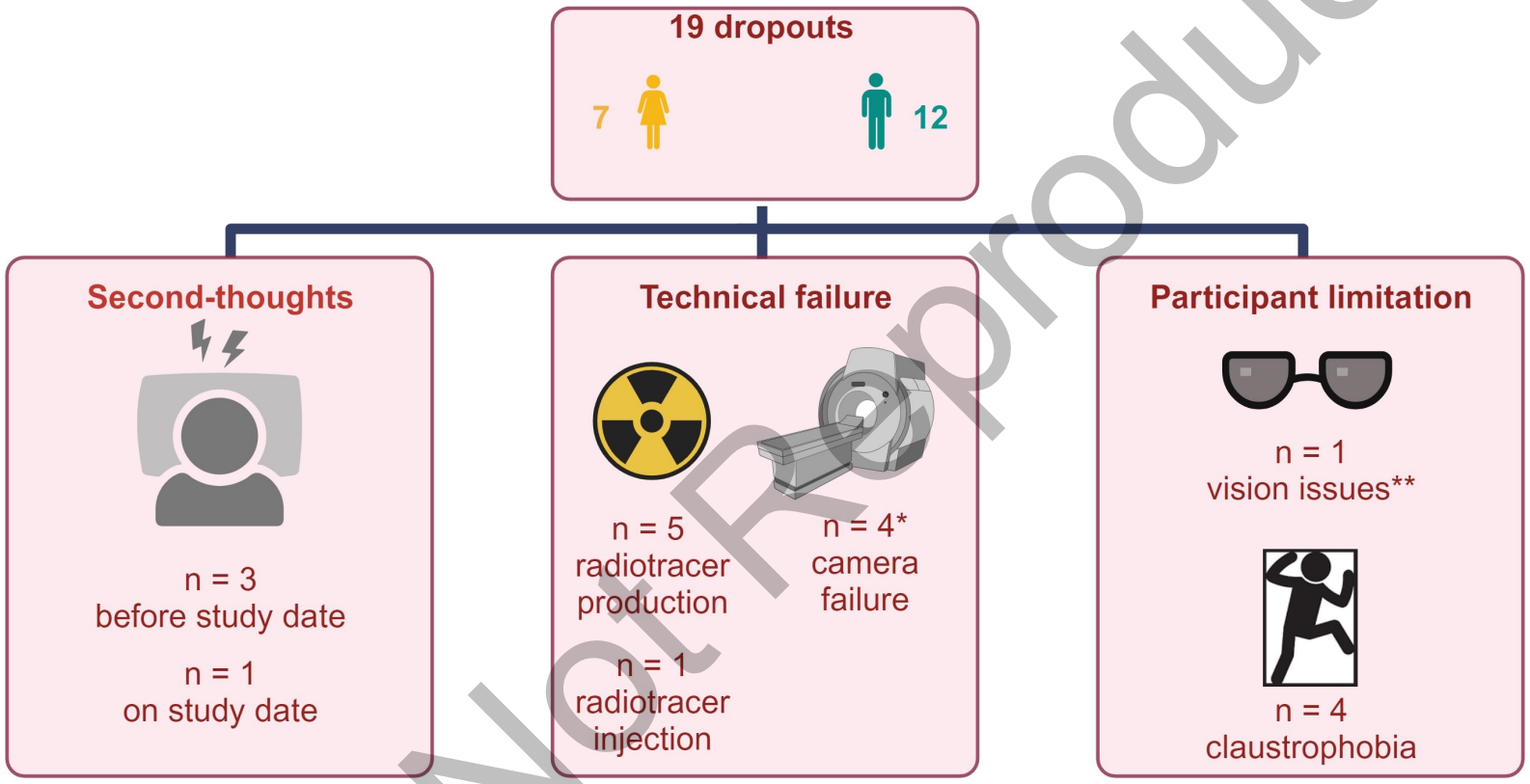
Sex and Gender in Medicine

SIGNA PET/MR Hybrid Scanner



Simultaneous Heart-Brain Imaging in Healthy Individuals: Challenges

Sex and Gender in Medicine

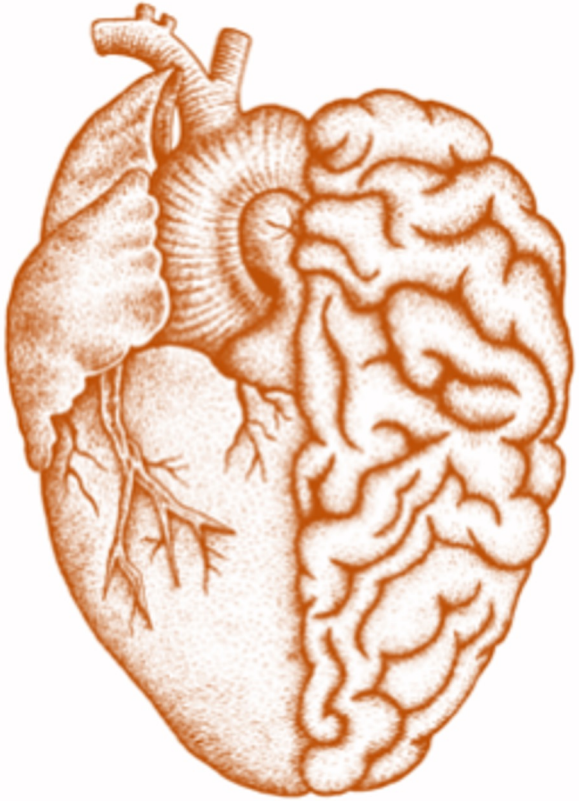


*Plus one camera failure, but reprogrammed and successfully scanned

**Plus one on study date (forgot lenses), but reprogrammed and successfully scanned

Summary

- It’s complex!
- Many confounders
- Sex (hormones) AND sociocultural Gender impact heart-brain interactions
- Lack of appropriate animal models
- Technical challenges of multi-organ/multi-system imaging



Thank you!

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Sex and Gender in Medicine

Simultaneous Heart-Brain Imaging in Healthy Individuals: Challenges

Sex and Gender in Medicine