ISCO2023
OIST/Okinawa

March 1, 2023

Toward seamless approach to build up fusion healthcare-medicare-solutions platform

Yasuyoshi Watanabe, MD, PhD
Team Leader, Laboratory for Pathophysiological & Health Science/RIKEN Center for Biosystems Dynamics Research
President, Japanese Society of Fatigue Science
President, Japan Recovery Association

Main contributers:

RIKEN:

Kei Mizuno, Kyosuke Watanabe, Satoshi Kume, Kei Taneishi, Hisashi Doi, Yasuhiro Wada, Kayo Onoe, Yosky Kataoka, Hiroshi Ohno, Toshimori Kitami, Yoshihide Hayashizaki, Emi Yamano, Kyoko Ebisu

Osaka Metropolitan University:

Hirohiko Kuratsune, Kouzi Yamaguti, Sanae Fukuda, Masaaki Tanaka, Akira Ishii, Yasuhito Nakatomi

MI Clinic:

Akira Kida, Yasuo Iwamoto, Mamoru Furuyashiki, Ami Igesaka

Precision Healthcare Research Organization:

Chiaki Urata, and all staffs

Extending healthy life expectancy through establishment of seamless social system from acquisition of precise health indices, prediction pathway analyses, personalized disease source imaging diagnosis, to maximize the effects of solutions for individual healthy life

User-friendly Health Measure

1. Positioning Map for Integrated Health Scores
2. Point of care
3. Street Medical City

Precise Medical Examination

1. Diseases & Their Predicting Biomarkers
2. Omics Analyses
3. Liquid Biopsy
4. Precise multi-stage functional analyses

AI

Fusion Imaging on Problemed Foci

1. Fusion Imaging among PET, MRI, fMRI, MEG, CT, Optical & Photoacoustic Imaging,
2. Multimodal & Multi-molecular Imaging

Development of Solutions & Therapeutics

1. Prediction of & Prevention from Vulnerability
2. Promotion of Upgrading Health State
3. Delay of Onset, Anti-fatigue & Anti-stress
4. Solutions from Synthetic Biology, Biofoundry
5. Theranostics
6. Regeneratiive Medicine, Cell therapy

Open Innovation!!

Seamless Approach with Precision Healthcare & Precision Medicine toward Maximization of Personalized Health Solution (SPHM)

"Fatigue Science for Human Health"

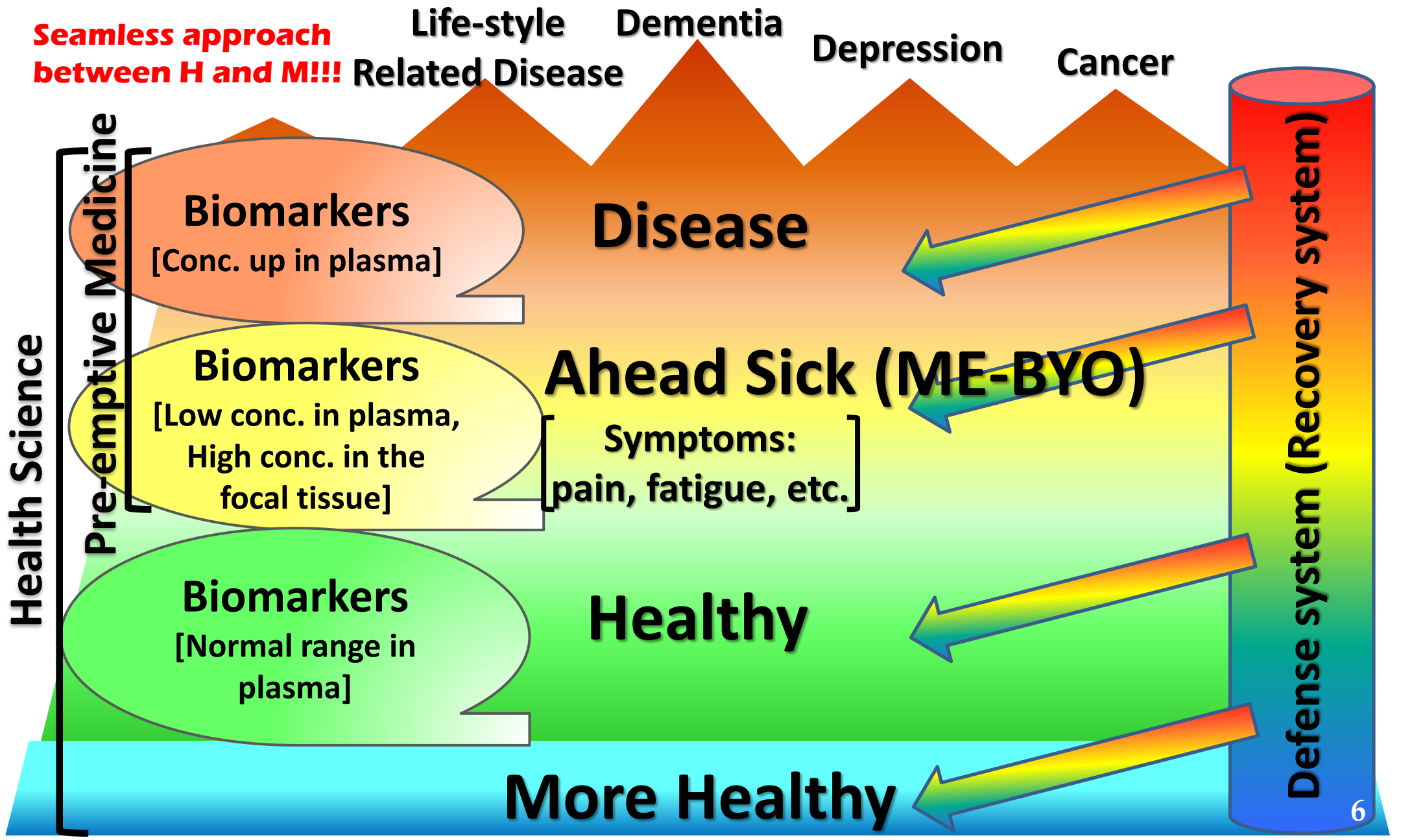
Watanbe, Y., Evengård, B., Natelson, B., Jason, L.D., Kuratsune, H., eds., Springer, 2008.

The molecular/neural mechanisms and the ways to overcome & prevent from "fatigue" are great hints for health promotion, prevention from onset of diseases, anti-ageing, and vitality/regeneration!!!

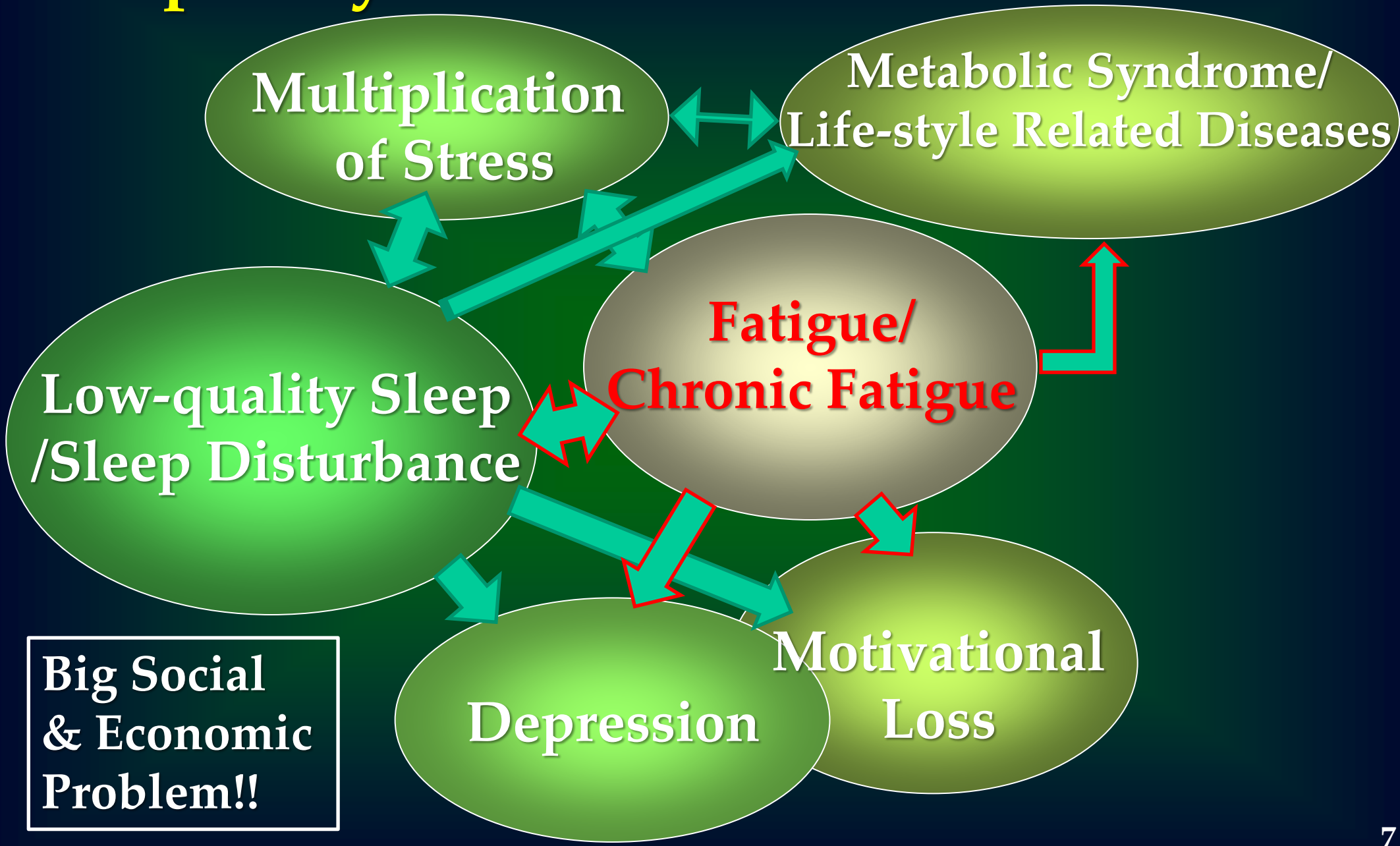
Symptomatology-driven Fatigue & Ahead Sick Science Toward Pre-emptive Medicine

疲労と未病の科学：有効な先制医療へ

Health Science and Pre-emptive Medicine



Reciprocity



Projects for Fatigue and Chronic Fatigue Syndrome

- Investigational group under MHW (1991-1999, T. Kitani)

  Chronic Fatigue Syndrome (CFS), Diagnostic criteria

- Special Coordination Funds from MEXT (1999-2005, Y. Watanabe)

  26 Universities & Institutes, Measures of Fatigue, Statistics, Animal models, Mechanisms of fatigue & chronic fatigue

- 21st Century COE Program "Base to Overcome Fatigue" from MEXT (2004-2009, Y. Watanabe)

  Osaka City Univ., Fatigue & CFS, Anti-fatigue projects

- Learning motivation and children's chronic fatigue from JST, RISTEX (2005-2009, Y. Watanabe)

  Motivational loss and fatigue, Childhood CFS

- Discordant twin ME/CFS PET study on serotonergic system and neuroinflammation by Special Grant from Tekeda Science Foundation (2010-2019, Y. Watanabe)
- Novel Biomarkers and Therapeutics for ME/CFS patients under AMED (2016-2019, Y. Watanabe)
- AMED GAPFREE2 project, Biomarkers and Therapeutics for ME/CFS (2016-2021, Y. Watanabe)

Statistics in Japan（2,742 answers）

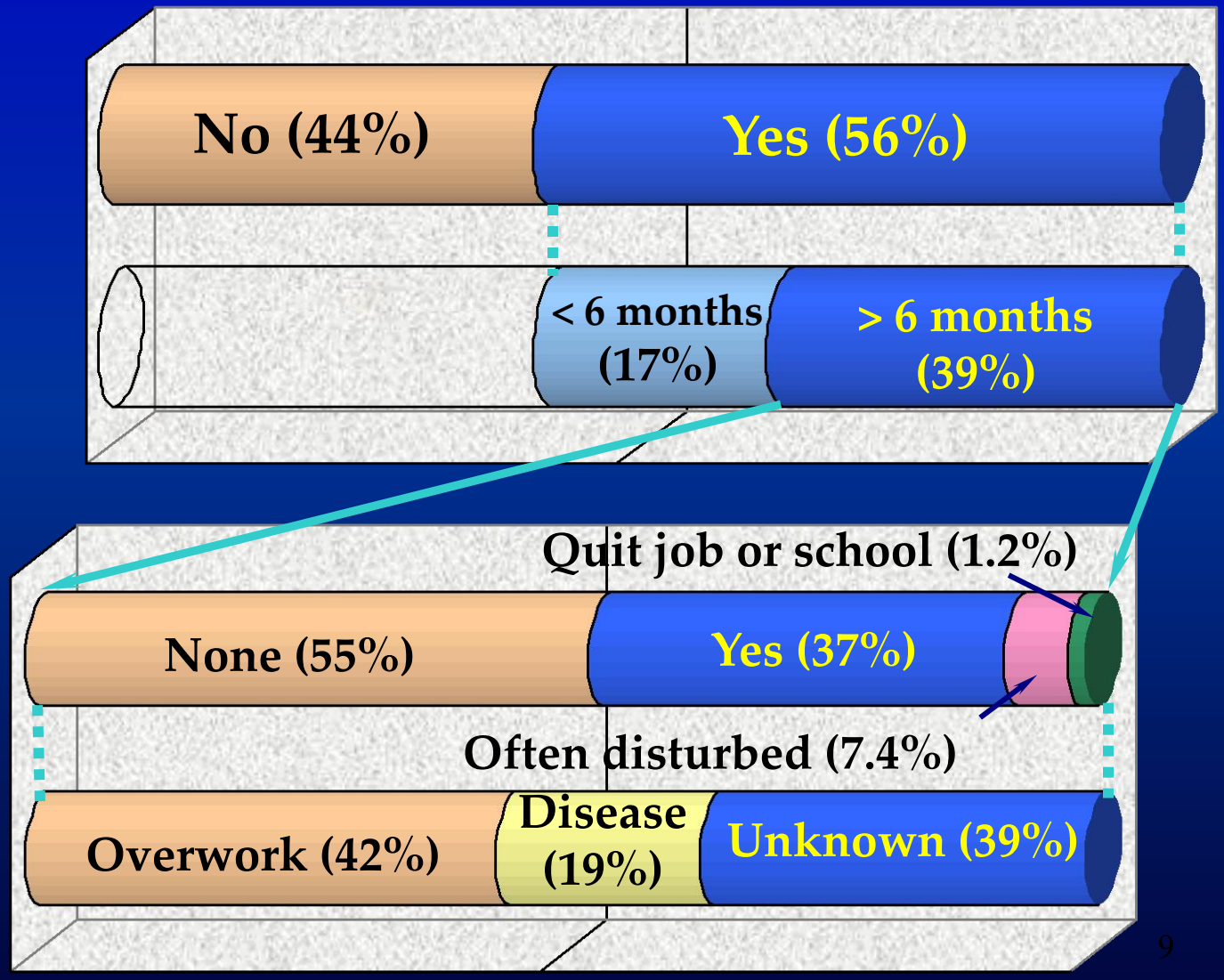
- 2004 Ministry of Education, Culture, Sports, Science & Technology -

Are you tired?

Period?

Disturbance in daily life

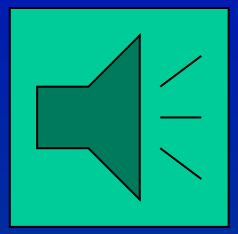
Cause of chronic fatigue



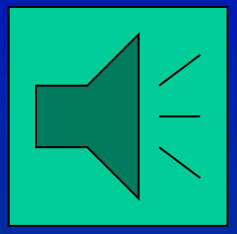
9

Three Major Bio-alarm Systems:

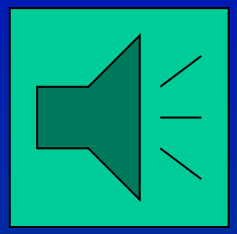
Sensing abnormality, alarming and controlling defense system



Pain



Fever



Fatigue

	Pain	Fever	Fatigue
Causative mechanisms	Bradykinin Prostaglandins Nociceptin Neurokinin	Endotoxin Interleukins Prostaglandin	Oxygen radicals Cytokines Low amino acids Low repair energy
Reset substance(s)	Serotonin Nocistatin	α-MSH	Anti-oxidants Repair energy

Subjective Fatigue Scale

1. Visual Analog Scale (VAS)
2. Face Scale
3. Chalder's Fatigue Score
4. Questionnaire on Fatigue
5. Questionnaire PC version

Objective Fatigue Scale

Objective quantitative scales are essential for:

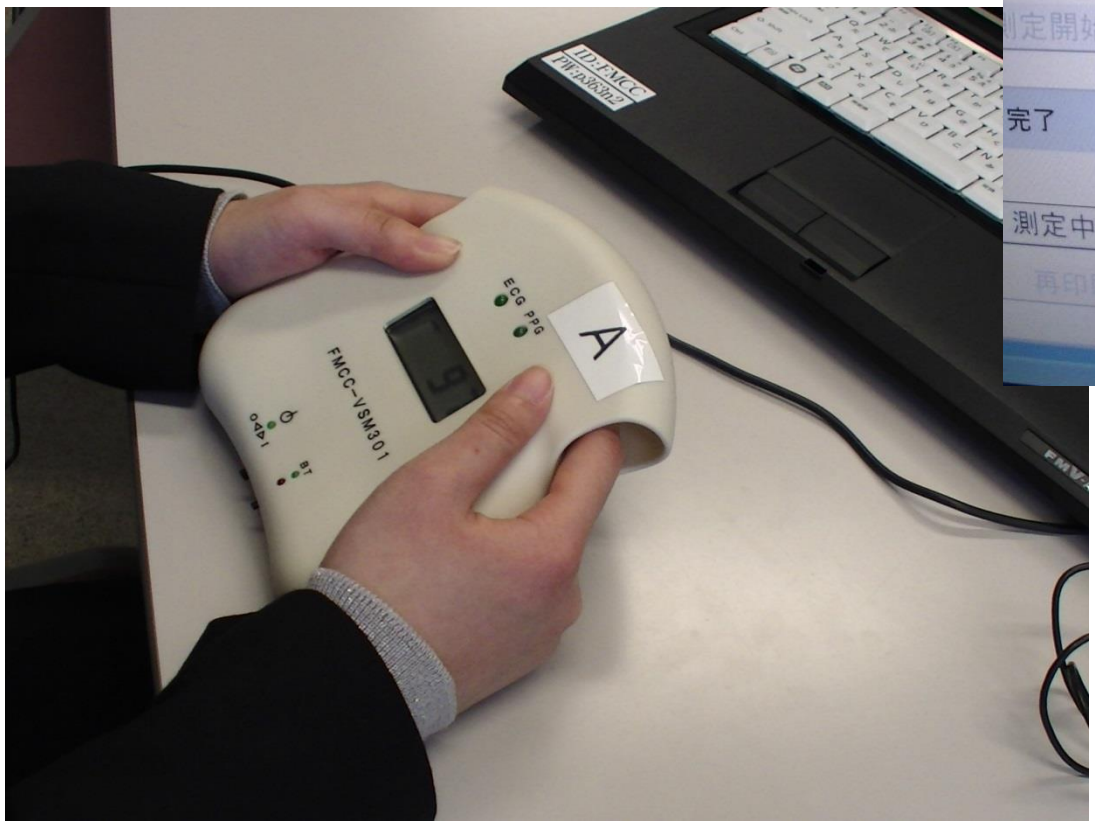
1. **Elucidation of molecular/neural mechanisms of fatigue, chronic fatigue (CF), and CFS**
2. **Development of therapeutics and preventive medicine for CF and CFS**
3. **Development of daily food and products for recovery and prevention from fatigue**

Development of Biomarkers for Quantification of Fatigue

- Cortical function: Attention, Concentration, & WM
  - Advanced Trail Making Test (ATMT)
  - Dual Task Test (DTT), n-back task, kana-picking up
- Evaluation by behavioral measures
  - Actigraph (Gyroscope-type)
  - Motion capture
- Autonomic nerve function
  - Acceleration plethysmography (APG), ECG
- Biochemical markers in the plasma and saliva
  - Immune & Endocrine biomarkers, Amino acids, Iron, Heme, Oxidative stress, Viruses, Auto-antibodies, and NIR- factors

Development of the System for Fatigue Measurement

FMCC-VSM301(then VSM500)
Fatigue/Stress detection system



Hitachi Systems, Ltd./muRata/Fatigue Science Lab. Inc./FMCC/our group

Guideline of Evaluation for Chronic Fatigue: Ministry of Health, Labor, and Welfare of Japanese Government (Proposal, 2009-2015) through our work

1. Autonomic nerve function; sympathetic/parasympathetic
2. Activity and Sleep problems
3. Oxidative stress
4. Metabolome, Proteome, & Transcriptome
5. Biological evaluation (virus, etc.)
6. Others (Auto-antibody, Serum amino acids, Endocrine & immunological abnormality, Near-infrared analysis, etc.)

Extension of Fatigue Research to Clinical Centers

Stress and Acute Fatigue

Chronic Fatigue

Chronic Fatigue Syndrome

Chronic Fatigue with Diseases

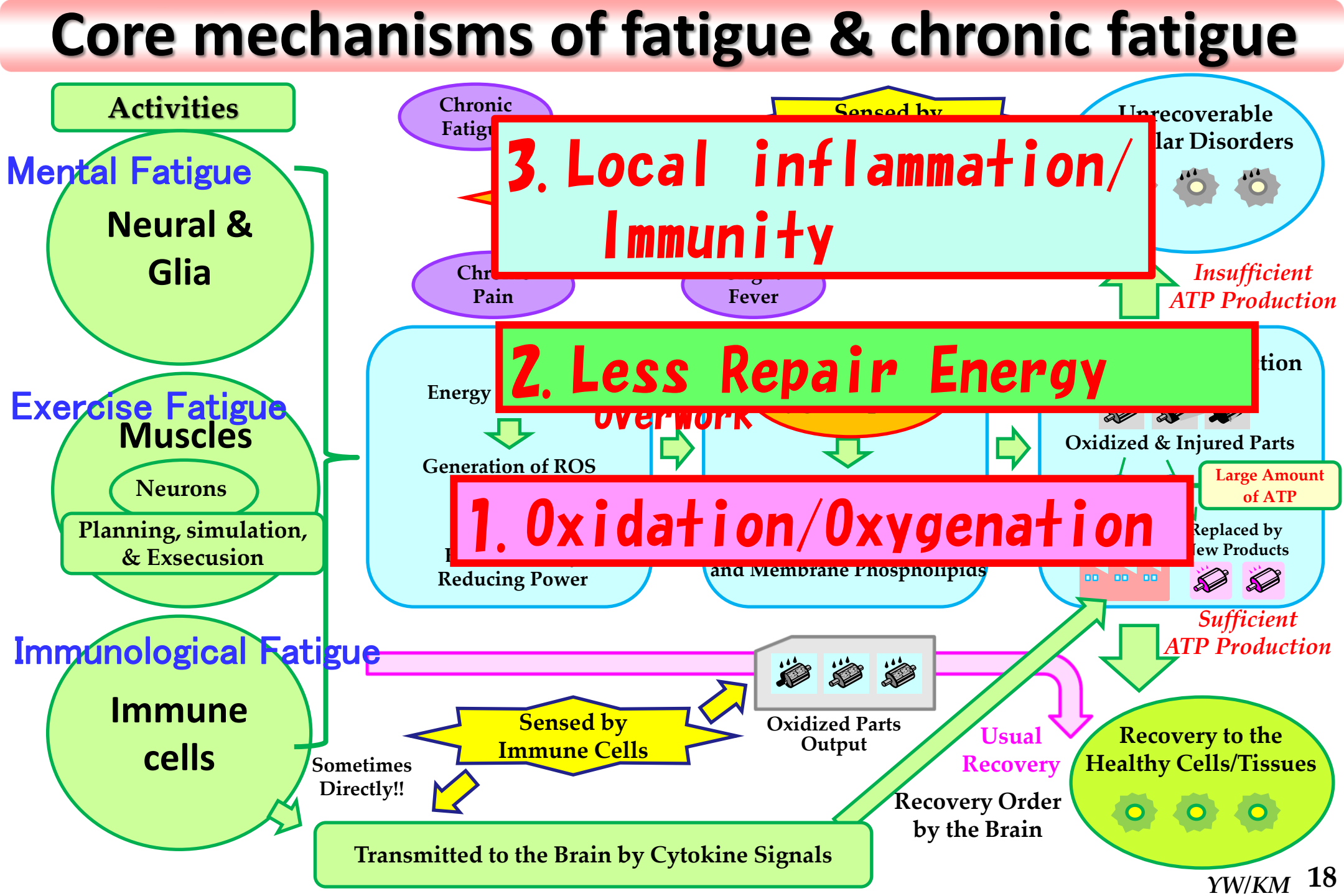
Renal Failure/Art. Dialysis
Lifestyle related diseases
Cancer-related
Hepatic Diseases
Allergic Disorders
Neuropsychiatric Disorders

Sergical Operation

Side effects of drugs

Complex Cause of Fatigue

Core mechanisms of fatigue & chronic fatigue



Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) 筋痛性脳脊髄炎/慢性疲労症候群

Diagnostic Criteria [CDC(USA), MHLW(JPN)]

Major criteria

1. Intolerable fatigue longer than 6 months
2. Exclusion of any other precedent diseases

Minor criteria

1. Symptomatic criteria 6/11 items (self-report)
2. Physical findings by medical doctors 2/3 items

Prevalence rate

0.26% in JAPAN

0.2-0.5% in the world

Biomarkers of ME/CFS

1. **Specific genetic background: Not yet found despite many challenges**
2. **Specific features of low energy production!!**

Fukuda, S. *et al.* Ubiquinol-10 supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome. *Biofactors* 42, 431-440 (2016)

Yamano, E. *et al.* Index markers of chronic fatigue syndrome with dysfunction of TCA and urea cycles. *Sci. Rep.* 6, 34990 (2016)

3. **Specific features of immune activation & dysfunction!!**

Klimas, N. G., Broderick, G. & Fletcher, M. A. Biomarkers for chronic fatigue. *Brain. Behav. Immun.* 26, 1202-1210 (2012)

Montoya, J. G. et al. Cytokine signature associated with disease severity in chronic fatigue syndrome patients. Proc. Natl. Acad. Sci. U. S. A. 114, E7150-E7158 (2017)

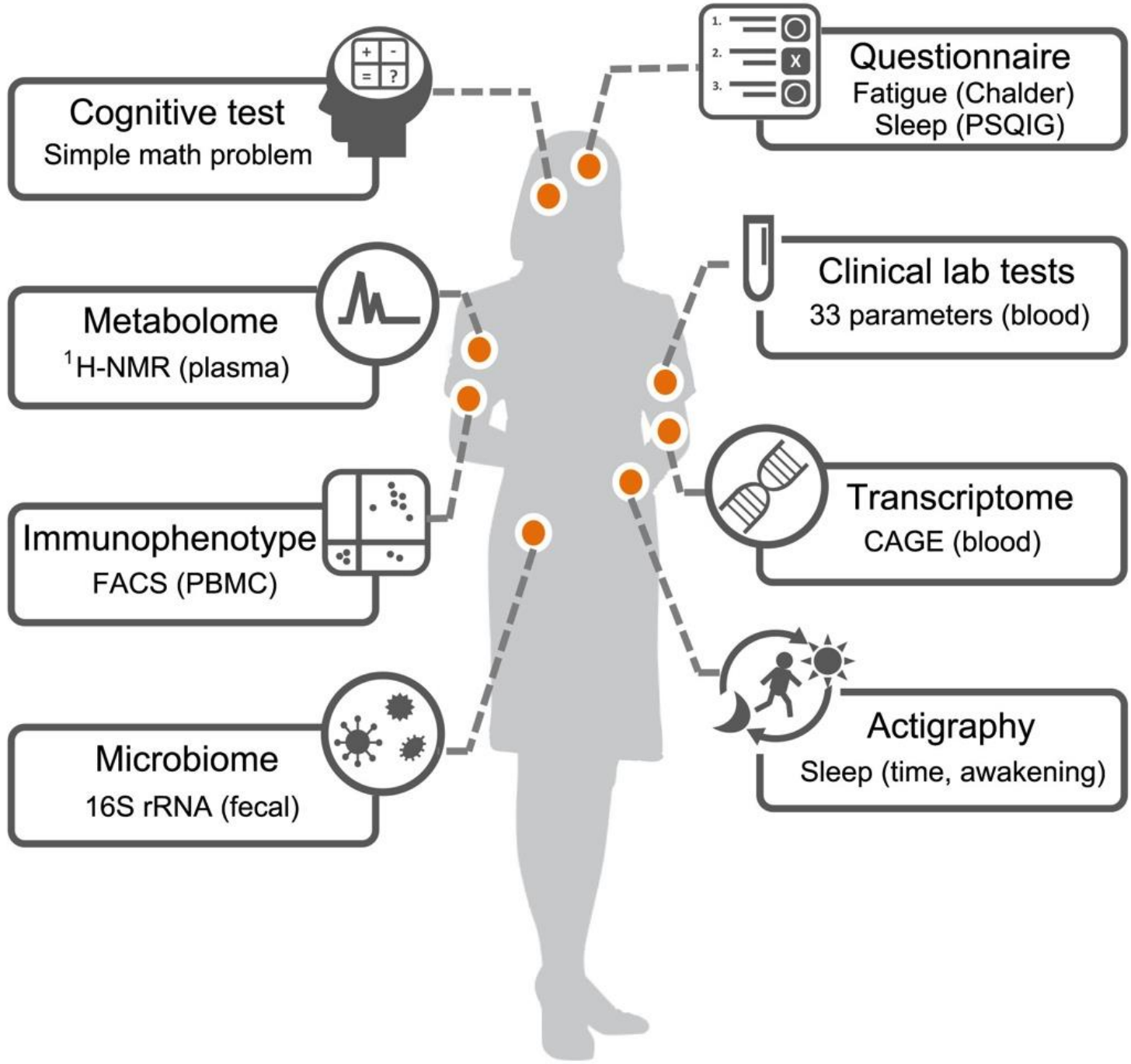
4. **Specific features of autonomic nerve dysfunction, HPA axis dysfunction, increased oxidative stress and less anti-oxidant potential!!**

Scientific Reports, 10: 19933, November 16, 2020

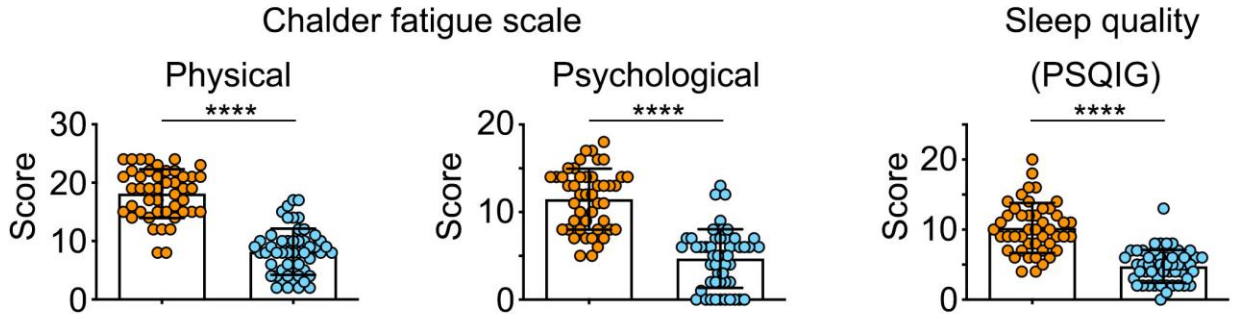
Deep Phenotyping of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome in Japanese Population

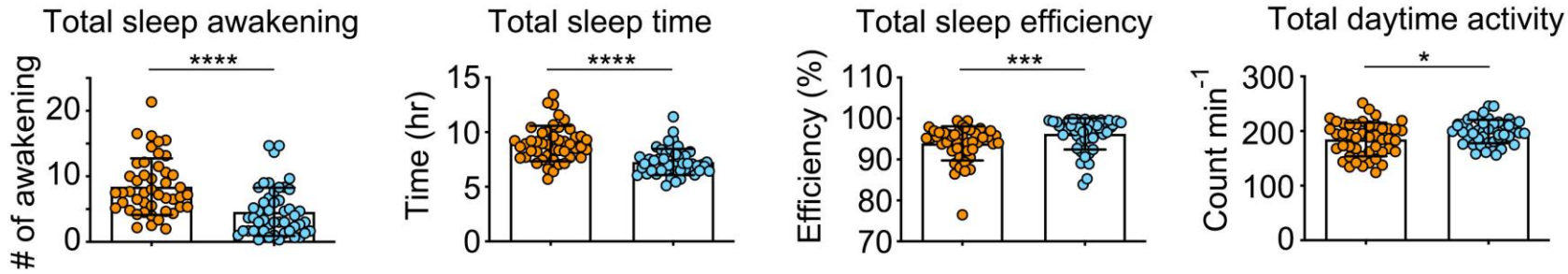
Toshimori Kitami[1]†*, Sanae Fukuda[2-4]†, Tamotsu Kato[1]†, Kouzi Yamaguti[2], Yasuhito Nakatomi[2,5], Emi Yamano[2,4,6], Yosky Kataoka[2,4,6-7], Kei Mizuno[2,4,6], Yuuri Tsuboi[8],Yasushi Kogo[9], Harukazu Suzuki[1], Masayoshi Itoh[9], Masaki Suimye Morioka[1], Hideya Kawaji[1,9], Haruhiko Koseki[1], Jun Kikuchi[8,10-11], Yoshihide Hayashizaki[9], Hiroshi Ohno[1,11], Hirohiko Kuratsune[2-6], **Yasuyoshi Watanabe[2,4,6]***

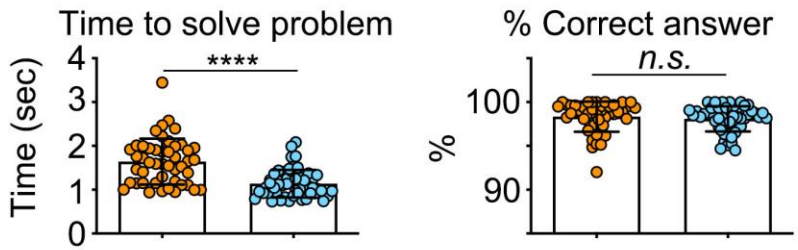
[1]RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan.
[2]Osaka City University Graduate School of Medicine, Osaka, Japan.
[3]Kansai University of Welfare Sciences, Osaka, Japan.
[4]RIKEN Center for Biosystems Dynamics Research, Hyogo, Japan.
[5]Nakatomi Fatigue Care Clinic, Osaka, Japan.
[6]RIKEN Compass to Healthy Life Research Complex Program, Hyogo, Japan.
[7]RIKEN Baton Zone Project, RIKEN-JEOL Collaboration Center, Hyogo, Japan.
[8]RIKEN Center for Sustainable Resource Sciences, Kanagawa, Japan.
[9]RIKEN Preventive Medicine and Diagnosis Innovation Program, Saitama, Japan.
[10]Graduate School of Bioagricultural Sciences, Nagoya University, Aichi, Japan.
[11]Graduate School of Medical and Life Sciences, Yokohama City University, Kanagawa, Japan.


Cognitive test
Simple math problem
Questionnaire
Fatigue (Chalder)
Sleep (PSQIG)
Metabolome
1H-NMR (plasma)
Clinical lab tests
33 parameters (blood)
Immunophenotype
FACS (PBMC)
Transcriptome
CAGE (blood)
Microbiome
16S rRNA (fecal)
Actigraphy
Sleep (time, awakening)

Non-molecular measures of fatigue



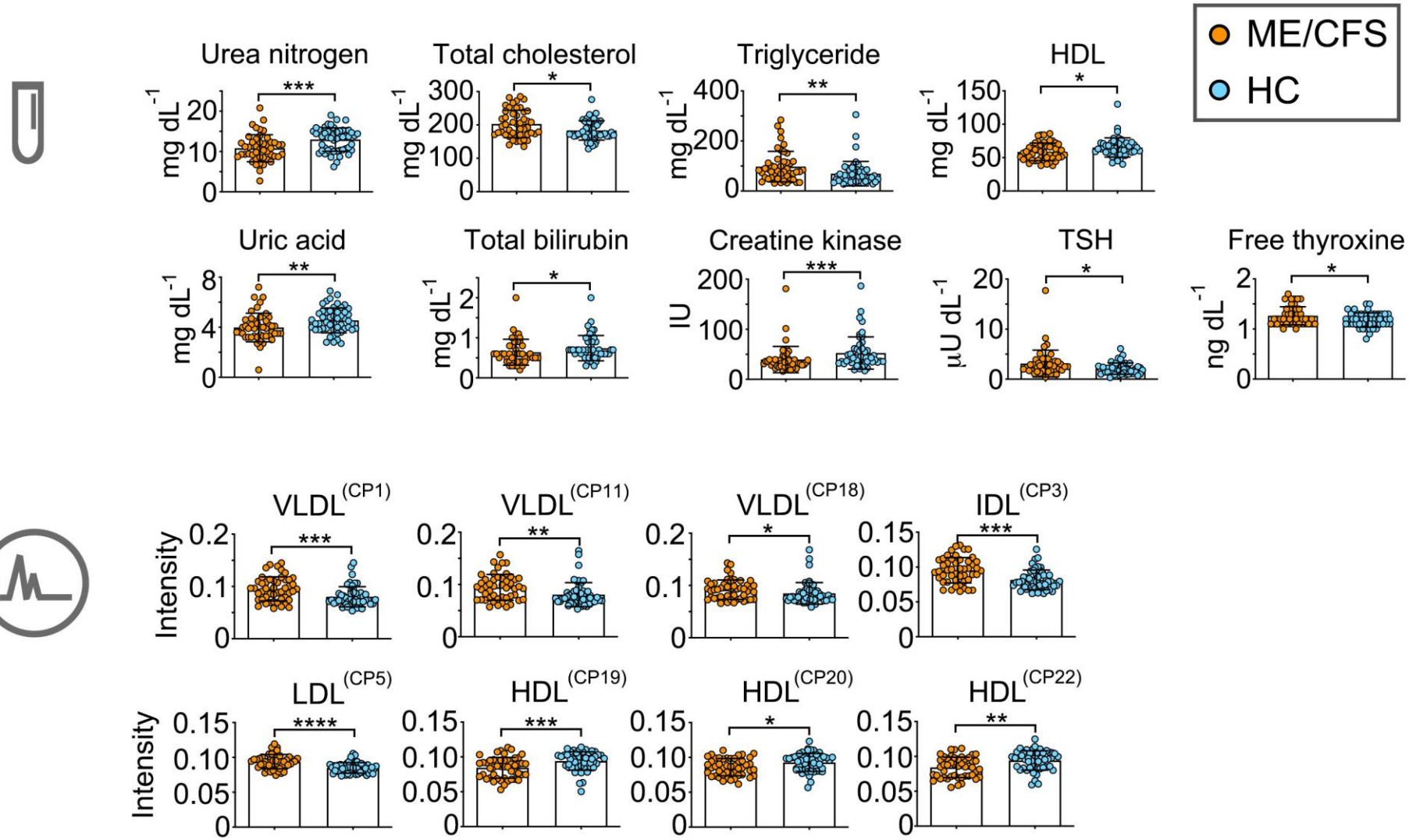




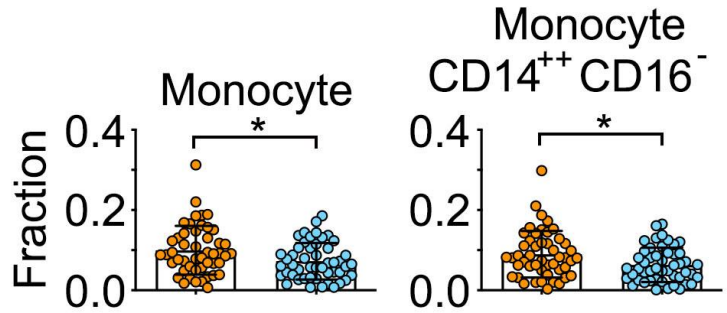
Sleep and activity pattern within an average 24 hour period were measured using actigraphy. Cognitive performance was assessed by administration of simple mathematical problems.

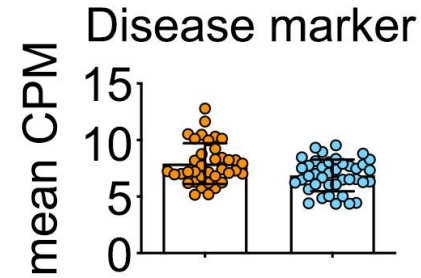
P values were determined by two-tailed Mann-Whitney U-test with Benjamini-Hochberg correction, adjusted for false discovery rate (FDR) of less than 0.20. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, or not significant (n.s.).

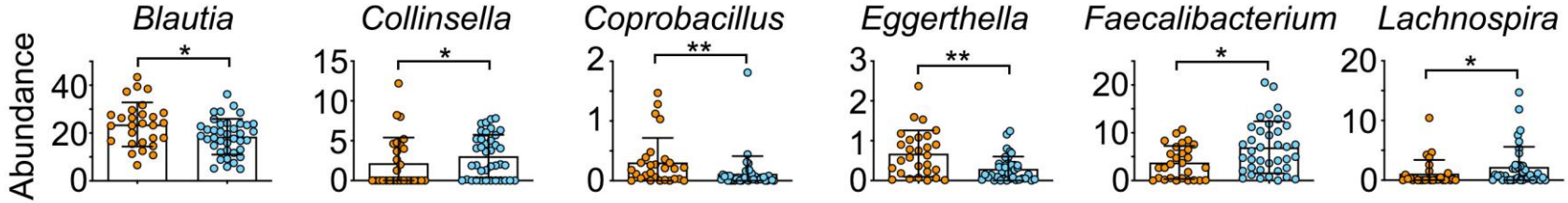
Summary results of the molecular platform-1



Summary results of the molecular platform-2

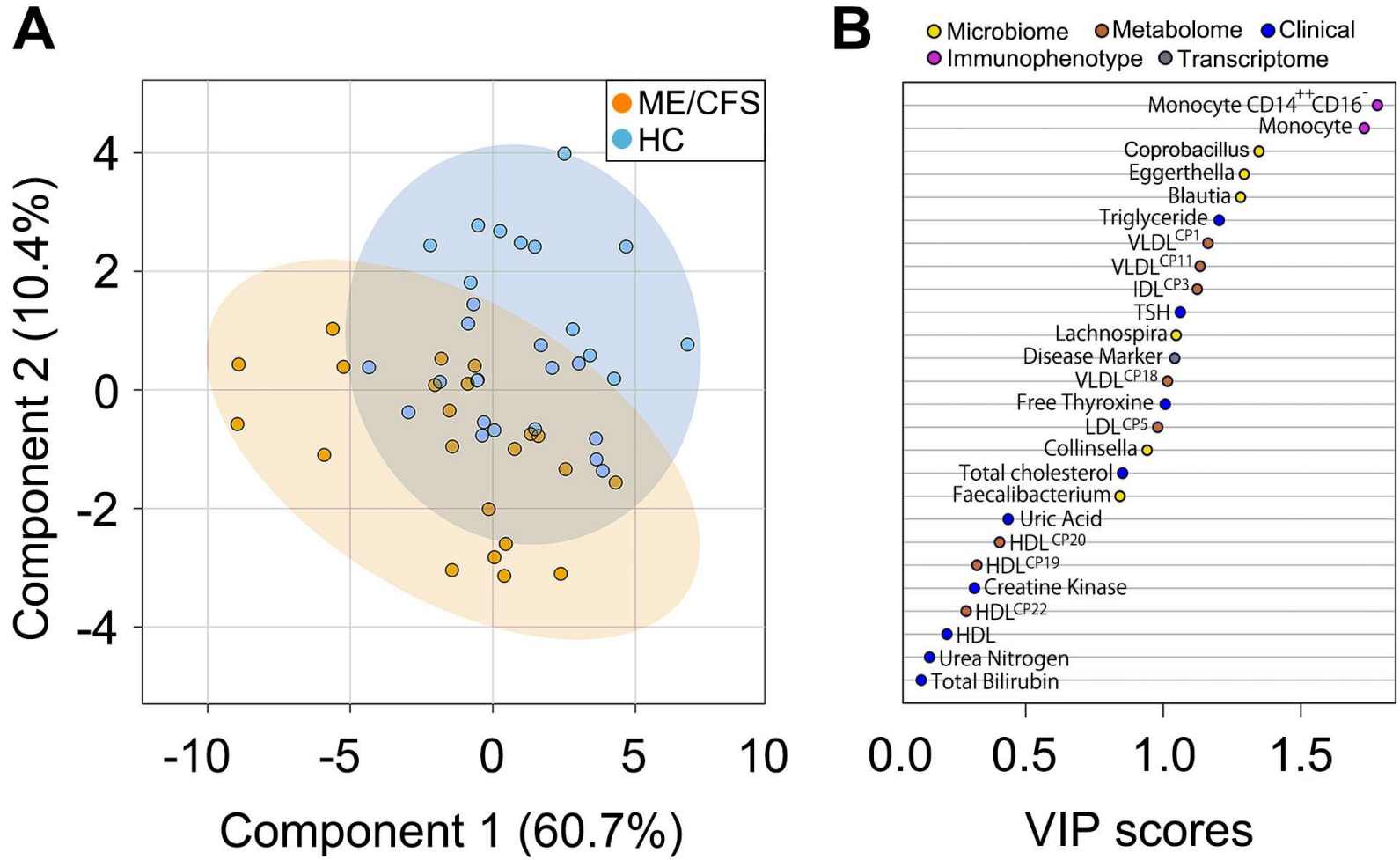






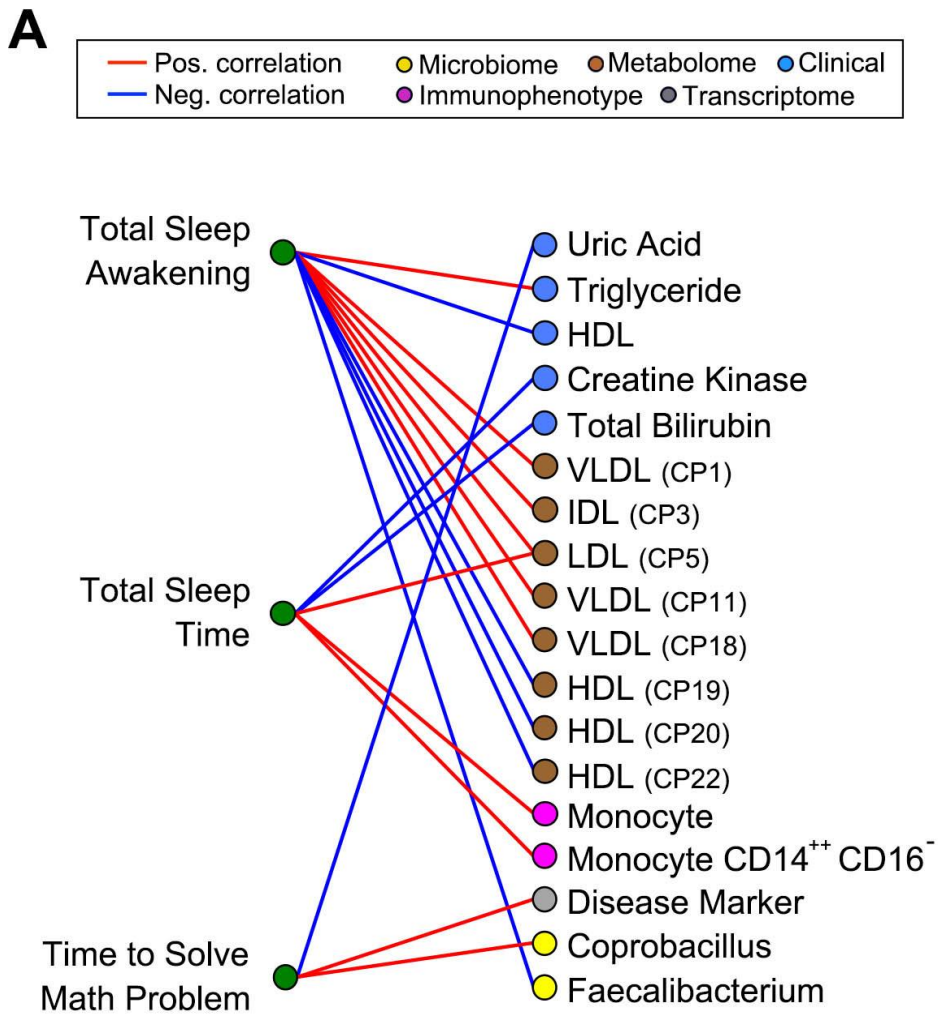
Combinatorial analysis of molecular markers

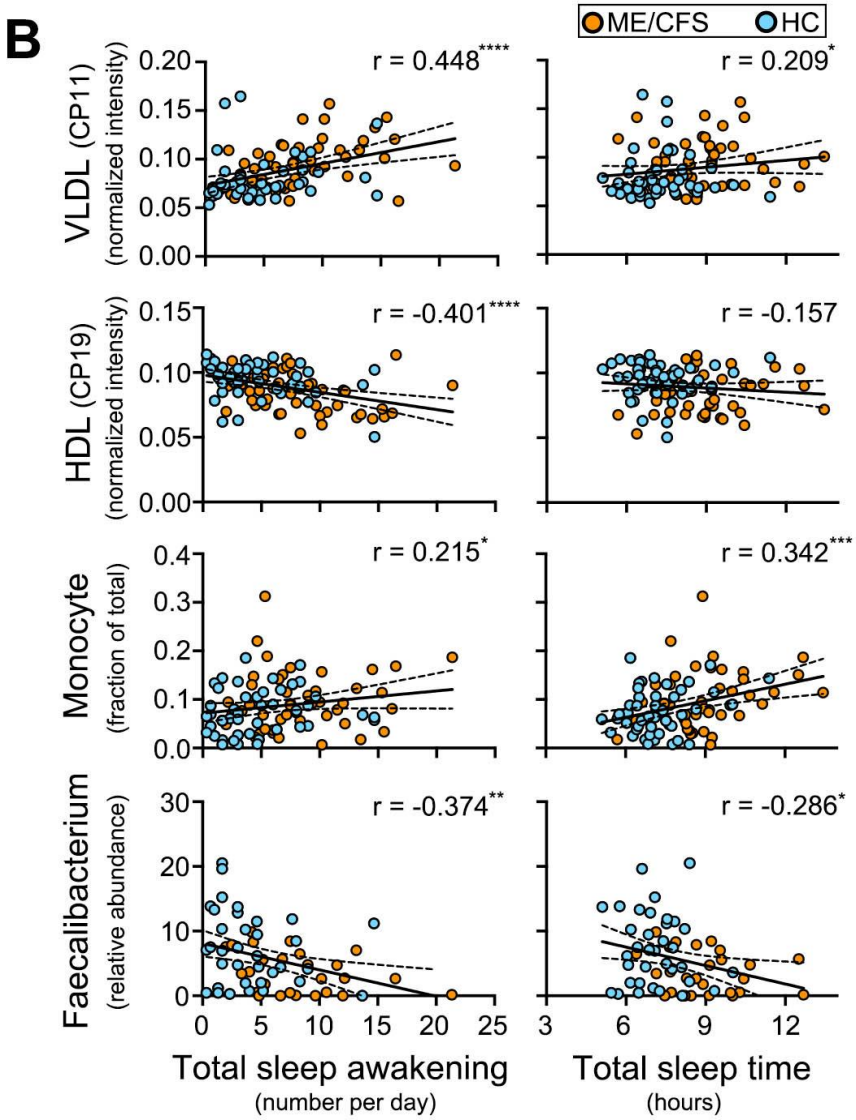
Combination of top 26 molecular markers for distinguishing ME/CFS patients from healthy controls (HC). (**A**) Partial least squares discriminant analysis (PLS-DA) of top 26 molecular markers. (**B**) Variable importance of projection (VIP) scores for distinguishing ME/CFS patients from HC based on component 1.



ME/CFS patients (n=22) and HC (n=29) with complete molecular profiling across five platforms (clinical lab tests, metabolome, immunophenotype, transcriptome, microbiome) were used.

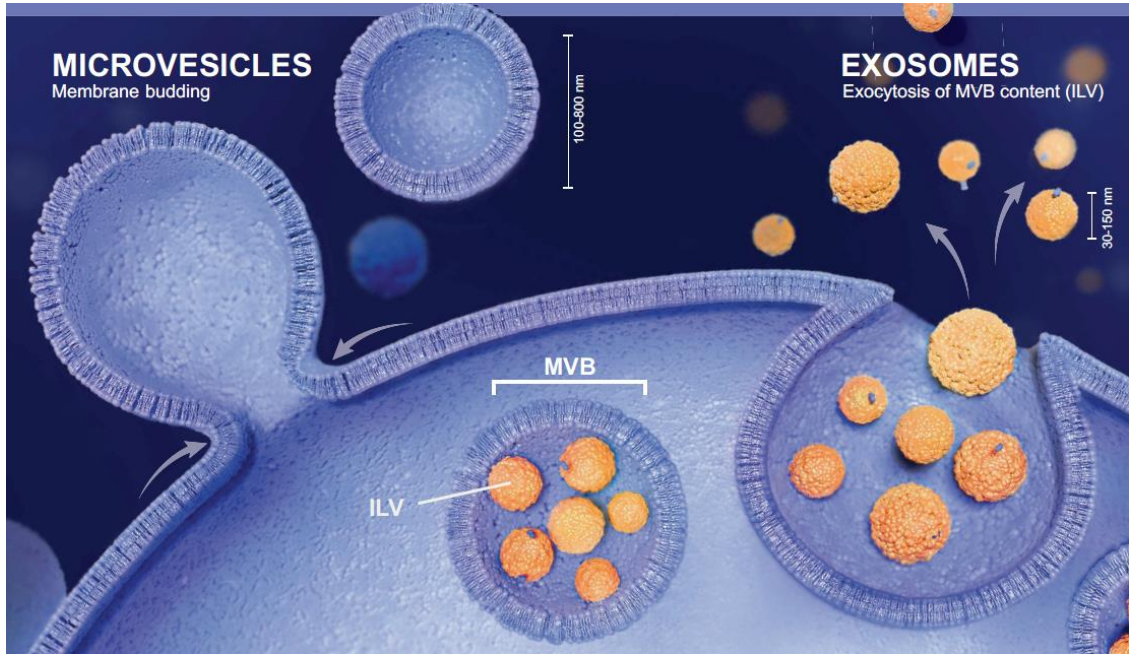
Correlation between measured phenotypes and molecular markers of ME/CFS
(**A**) Spearman rank correlation between three measures related to fatigue (total sleep awakening, total sleep time, time to solve math problem) and molecular markers. Spearman rank correlation with $P < 0.05$ are indicated with red (positive correlation) or blue line (negative correlation).

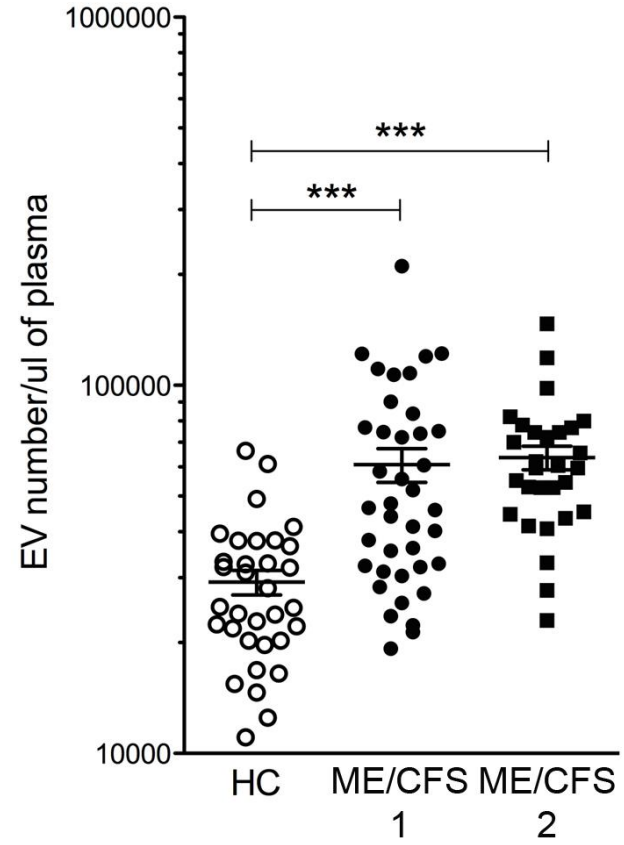




Novel Biomarkers of ME/CFS

1. **Eguchi, A., Fukuda, S. *et al.* Identification of actin network proteins, talin-1 and filamin-A, in circulating extracellular vesicles as blood biomarkers for human myalgic encephalomyelitis/chronic fatigue syndrome. *Brain. Behav. Immun.* 84, 106-114 (2020).**

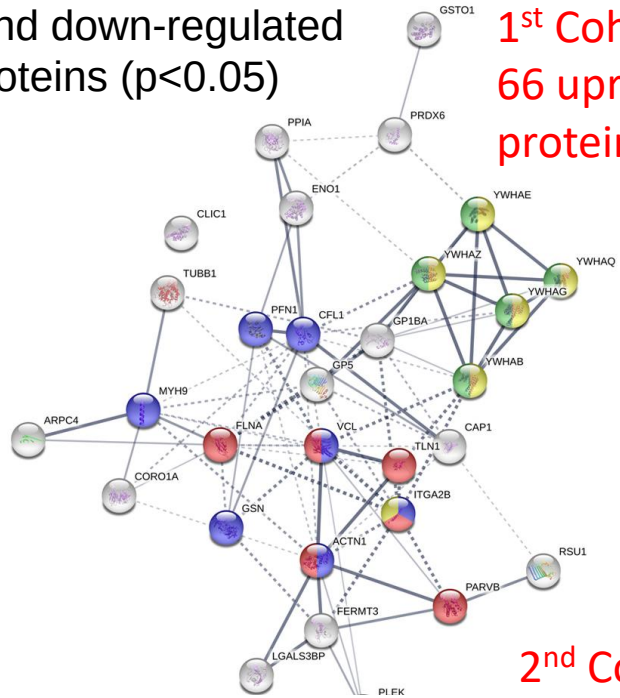




Specific features of microbiome, exosome size, exosomal proteins, exosomal microRNAs!!

Statistically significant increase of EV proteins in ME/CFS

Up- and down-regulated EV proteins (p<0.05)

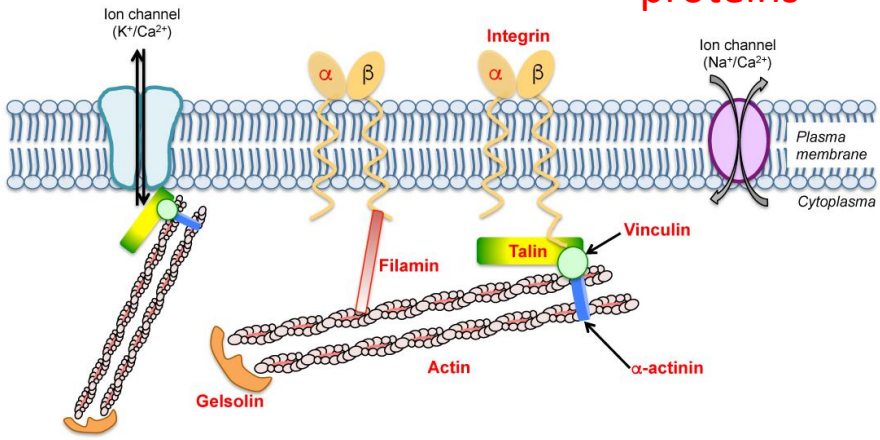


1st Cohort
66 upregulated proteins

Top12 EV protein abundance in 69 ME/CS compared to 35 HC

Identified proteins	average normalized total spectra
Talin-1	37
Filamin-A	26
Actin	18
Alpha-actinin-1	14
14-3-3 protein zeta/delta	10
Vinculin	9
Myosin-9	9
Gelsolin	8
Integrin alpha-IIb	8
14-3-3 protein gamma	6
14-3-3 protein theta	6
14-3-3 protein beta/alpha	6

Actin network



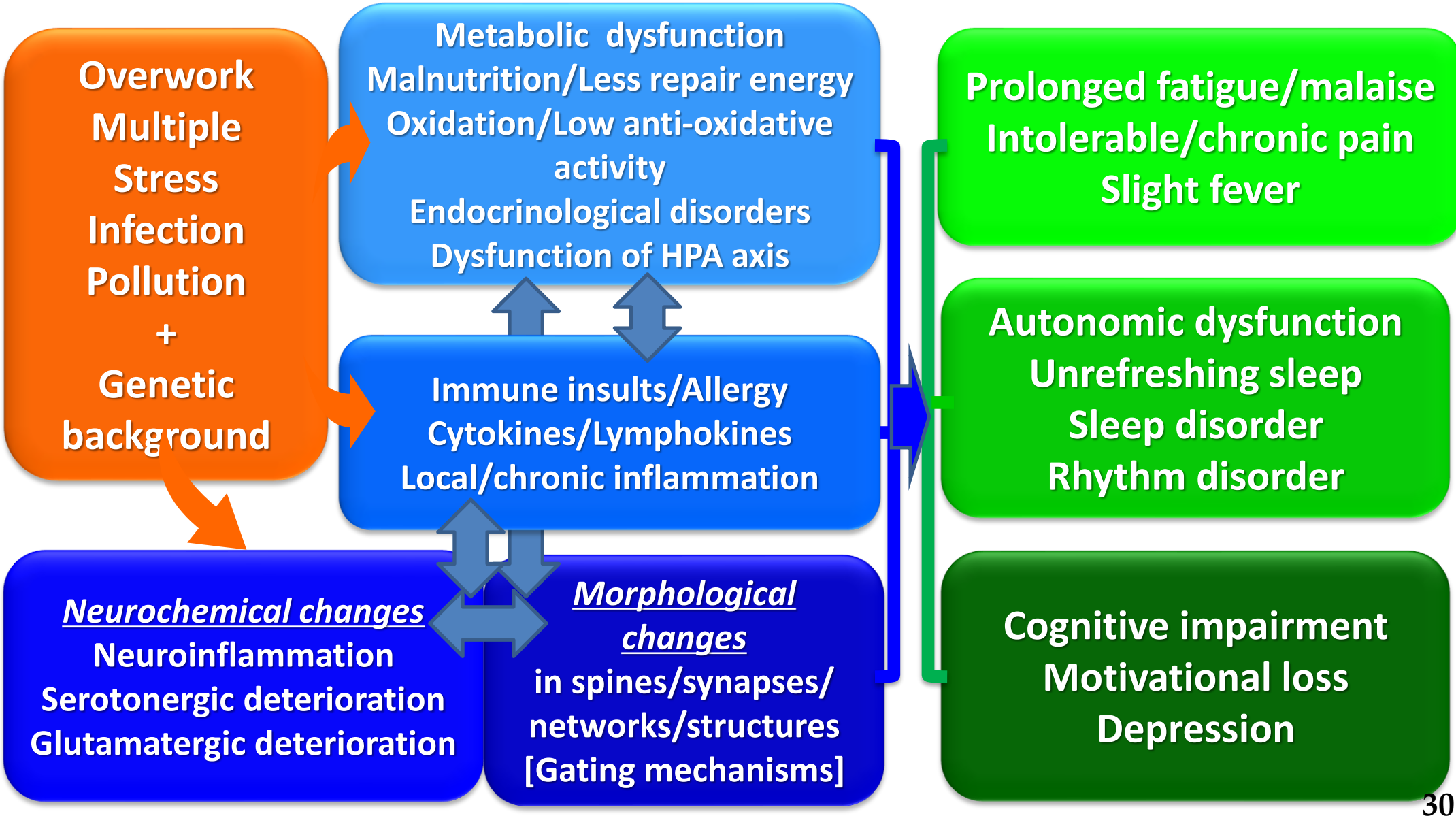
2nd Cohort
111 upregulated proteins

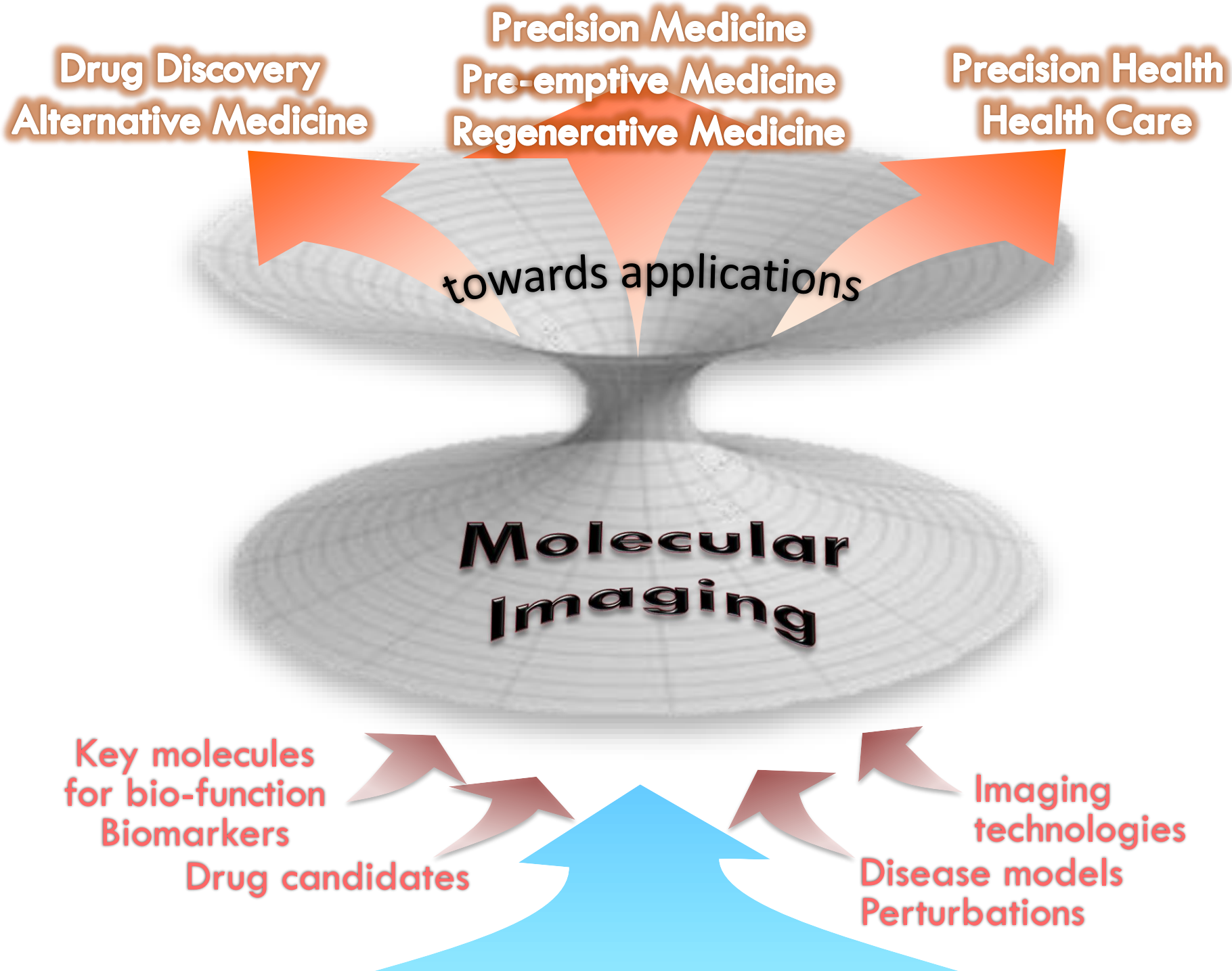
Top12 EV protein abundance in 32 ME/CS compared to 8 depression and 6 ICF

Identified proteins	average normalized total spectra
Talin-1	103
Filamin-A	87
Actin	59
Vinculin	55
Myosin-9	44
Integrin alpha-IIb	42
14-3-3 protein zeta/delta	21
Fermitin family homolog 3	20
Tubulin beta-1 chain	13
Gelsolin	12
Alpha-actinin-1	12
Profilin-1	11

Eguchi et al. Brain Behavior and Immunity 2020

Pleusible mechanistic structure from ME/CFS studies on a variety of biomarkers integrated with PET/MRI/fMRI/MEG



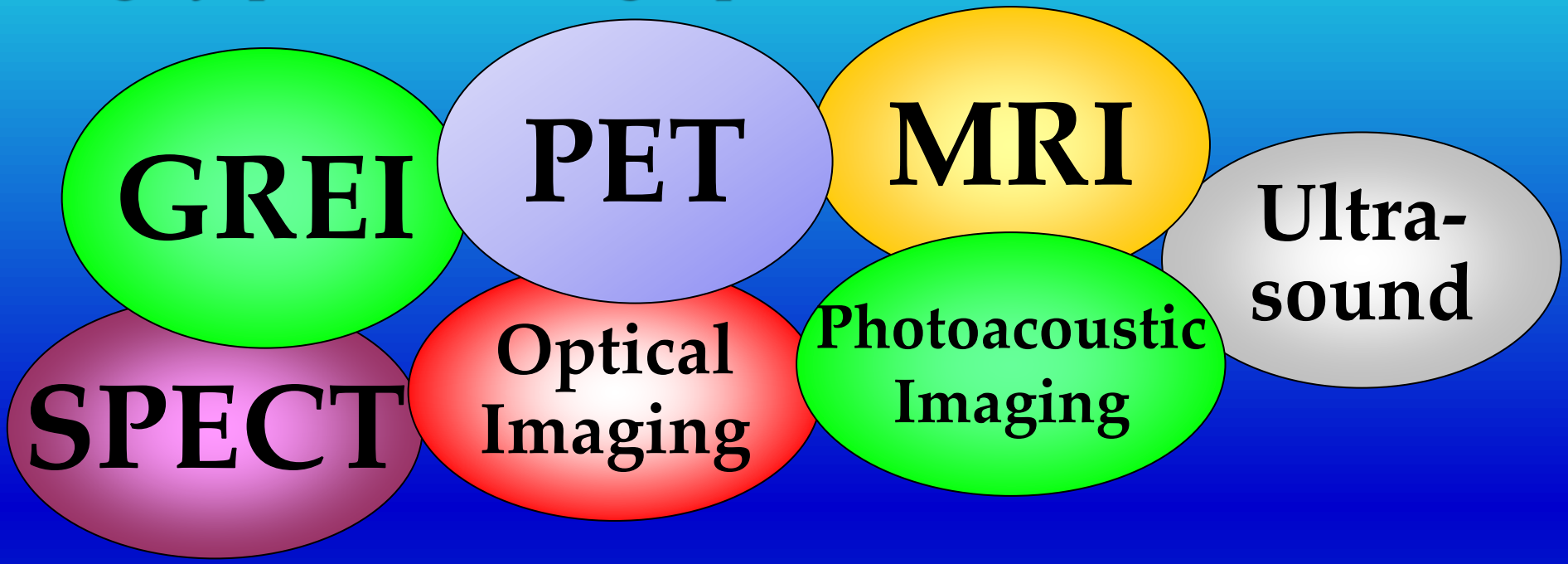

Drug Discovery
Alternative Medicine
Precision Medicine
Pre-emptive Medicine
Regenerative Medicine
Precision Health
Health Care
towards applications
Molecular Imaging
Key molecules
for bio-function
Biomarkers
Drug candidates
Imaging technologies
Disease models
Perturbations

RIKEN Multi-Modal Molecular Imaging

Why is PET central?

For application to human and functioning animals

Ultra-high sensitivity, Broad spectrum of target molecules,
Highly quantitative, High spatial resolution (close to 1 mm)



To extend PET molecular probes to other modalities
To develop multi-modal (fusion) molecular imaging
To develop simultaneous multi-molecular imaging tool

PET

Why is PET central for application to human and functioning animals?

1. **Ultra-high sensitivity (thus microdose)**

   ultra-high specific radioactivity (short half-life):

   i.e., injection mass = 0.1-10 nmol (30-3,000 ng, if MW=300)

1′. **Little perturbation to intrinsic system**

2. **Broad spectrum of target molecules**

   A variety of positron emitters for the radiolabel

   ^{11}C, ^{18}F, ^{13}N, ^{15}O; *"Physiological!"*, ^{64}Cu, ^{68}Ga, ^{76}Br, ^{89}Zr, ^{124}I

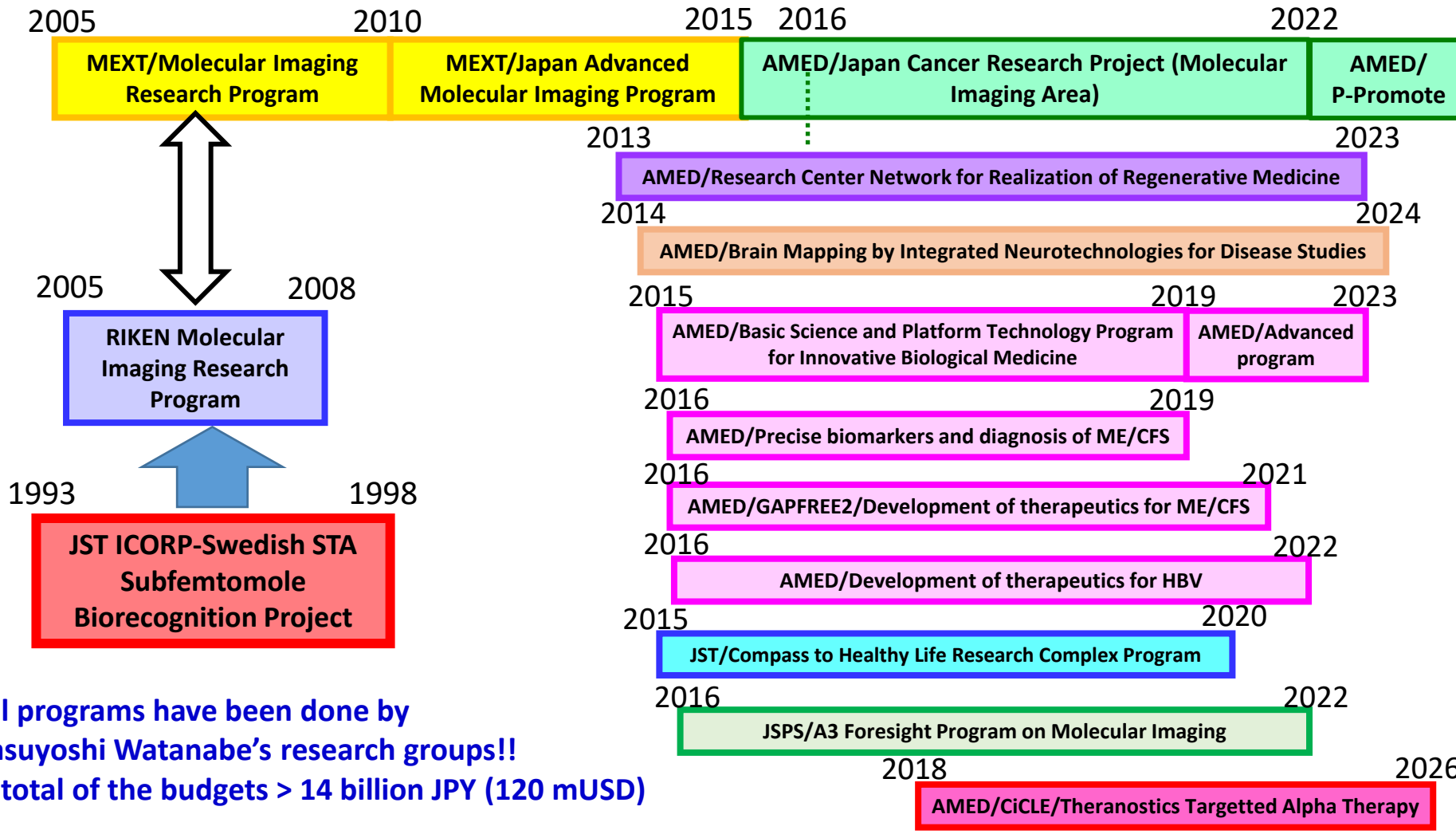
   principally, any organic compounds can be introduced

3. **Highly quantitative even in depth of the body**

   coincidence detection of annihilation photons

   accurate attenuation correction

National Grants and RIKEN Biomedical Imaging Researches

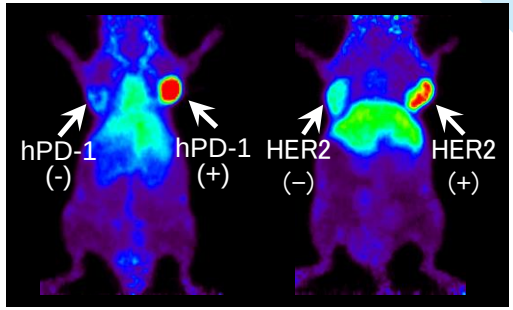


All programs have been done by Yasuyoshi Watanabe's research groups!!
A total of the budgets > 14 billion JPY (120 mUSD)

Governmental organizations: ***MEXT****, Ministry of Education, Culture, Sports, Science and Technology Japan;* ***AMED****, Japan Agency for Medical Research and Development;* ***JST****, Japan Science & Technology Agency*

Fundamental Research

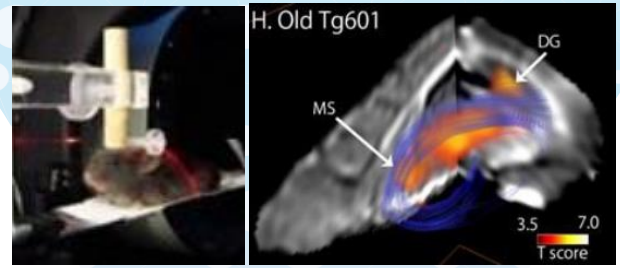
Development of antibody-based PET probes



^{64}Cu-DOTA-Nivolumab

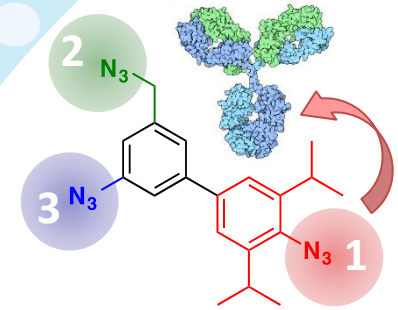
^{64}Cu-DOTA-IGBP-Trastuzumab

Small animal neuroimaging study with PET and MRI



Imaging using head holder under consciousness (w/o anesthesia)

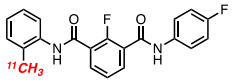
Development of novel technologies for multi-modal imaging



Therapy + Delivery + Imaging, etc…

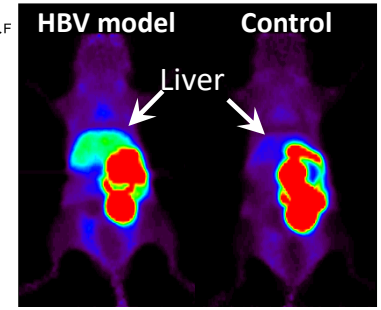
Multi-click platform molecule

Development of imaging probe for HBV diagnosis



[^{11}C]CBT-078

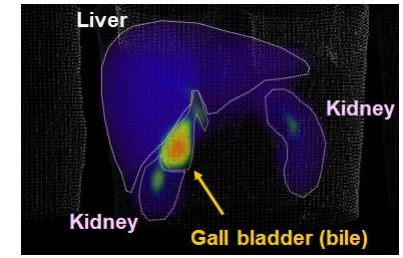
Novel probe targeting HBV-capsid

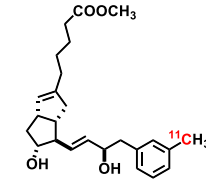


Pathophysiology & Health Science

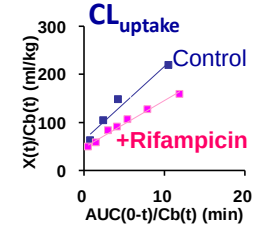
Yasuyoshi Watanabe, M.D., Ph.D.

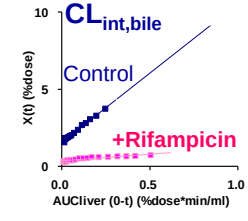
PET study platform for PK/PD



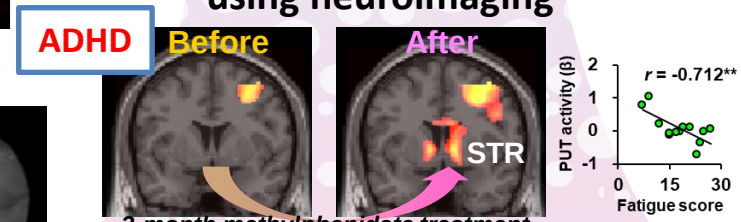


15*R*-[^{11}C]TIC-Me

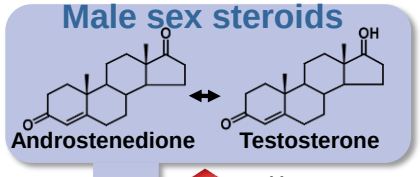


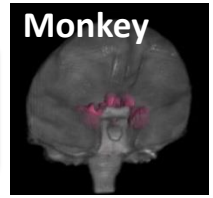


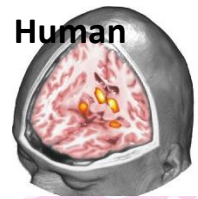
Pathophysiological science using neuroimaging



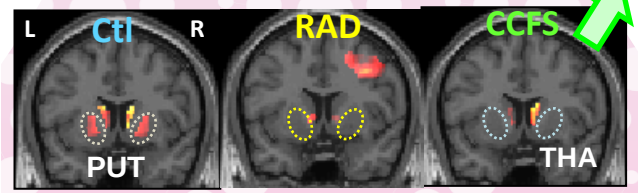
Imaging of human emotion



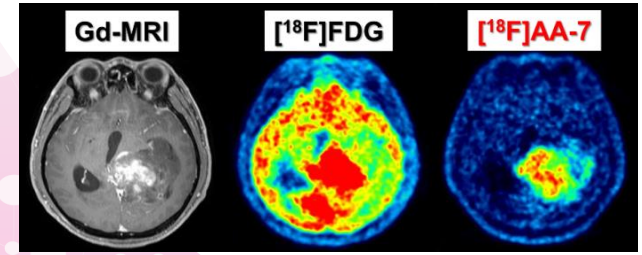




[^{11}C]Cetrozole



Novel tumor probe for L-type Amino Acid Transporter



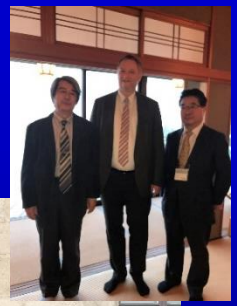
First-in-human study of [^{18}F]AA-7

Clinical Research

International Collaboration

Asia 3: Japan, China, & Korea

KI, Uppsala U., SciLifeLab, Sweden



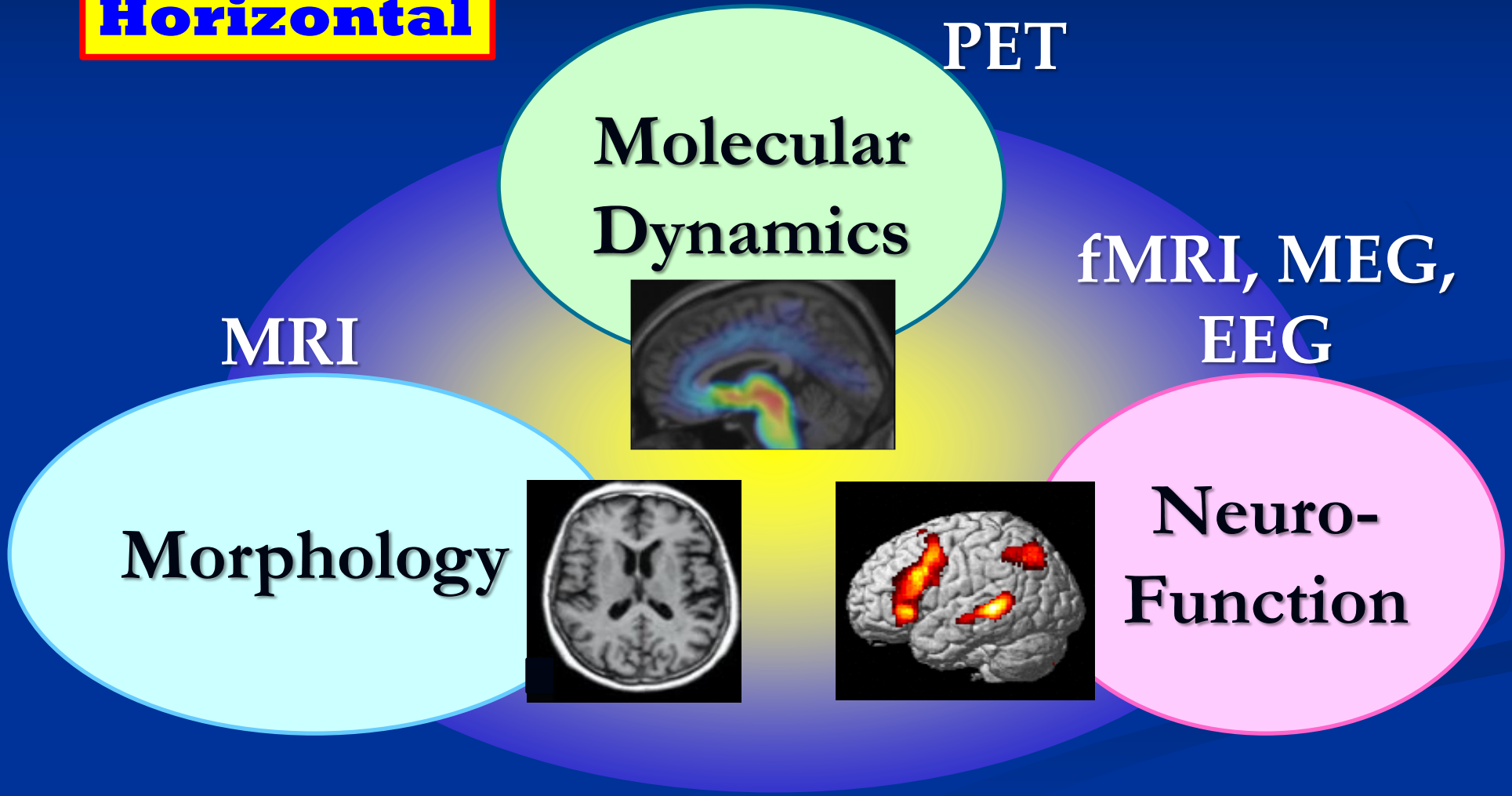
Tubingen Univ.

Singapore, RIKEN-NTU-KI

UCL

4D Super Multi-modal Imaging Project-1 by integrated approaches of PET/MRI/MEG

Horizontal



Brain region(s) and neural pathway responsible for fatigue sensation and chronic fatigue

1. PET/fMRI/MEG studies
   in normal human volunteers
   in patients with chronic fatigue
2. microPET, IEG expression studies
   in primate fatigue models
   in different animal models

Outcome from Magnetoencephalogram (MEG) studies

39

Mechanisms to cause chronic fatigue (Hypothesis)

Overwork
Stress

Fatigue

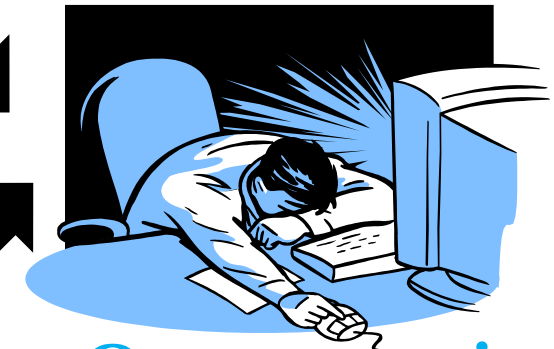
Fatigue
sensation

The posterior cingulate cortex
The insular cortex

Overactivation

Protection

Chronic fatigue



Overprotection

Conditioning

The posterior cingulate cortex
The insular cortex

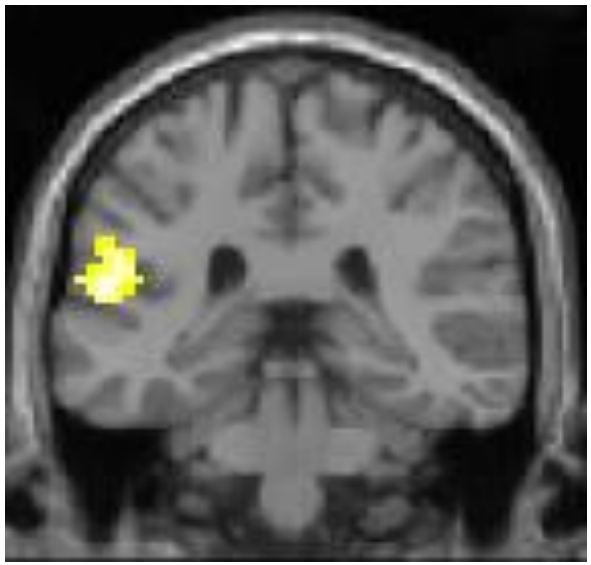
Outcome from fMRI and morphometry studies

New concept of *fatigability* in ME/CFS patients

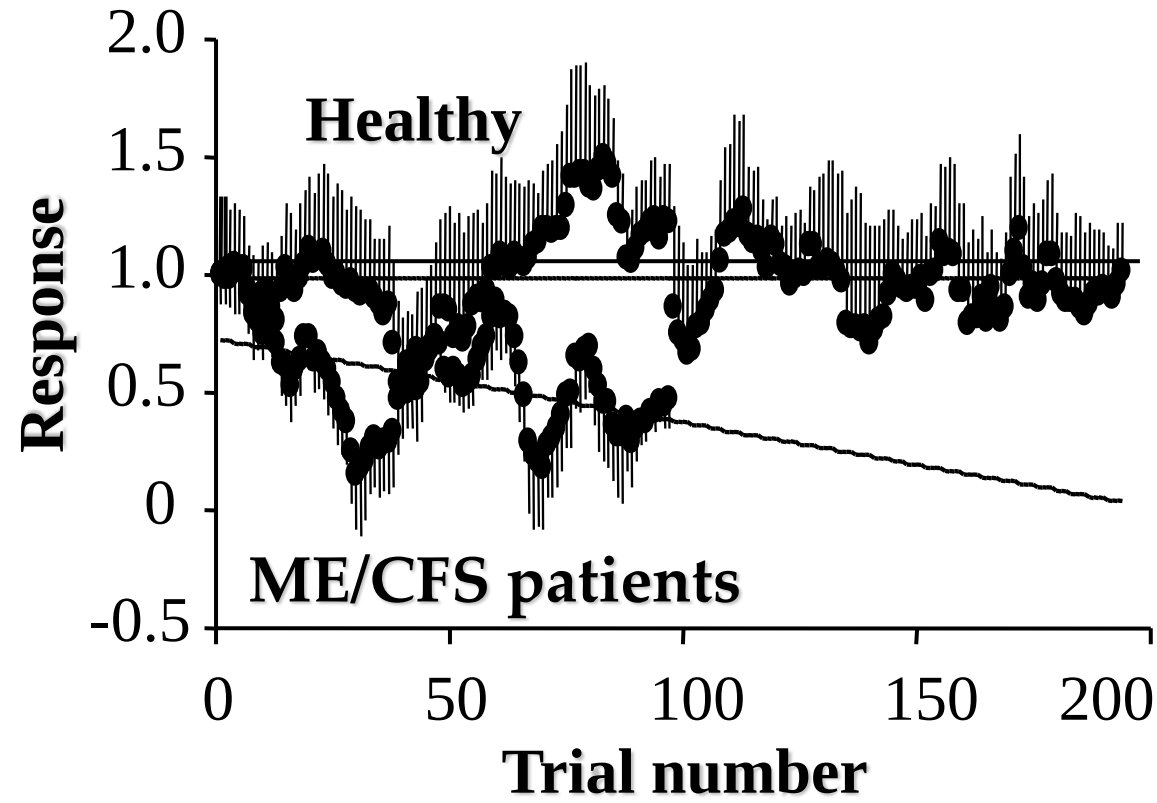
(Tanaka et al., BMC Neurology, 2006)

Functional MRI study during visual task: revealed vulnerability of task-unrelated brain regions.

Self-defense mechanism!!



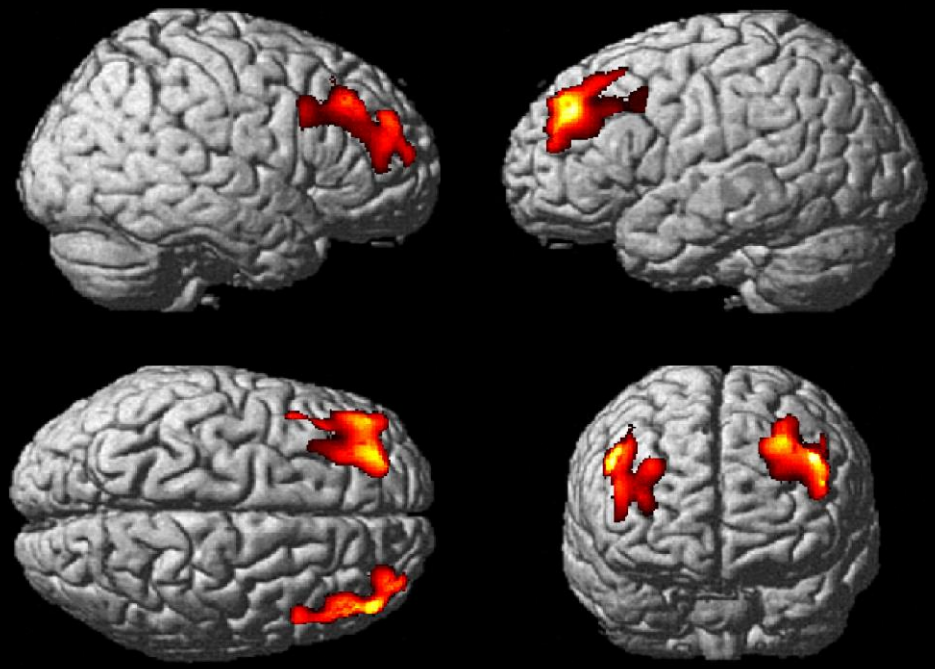
Left temporal auditory cortex



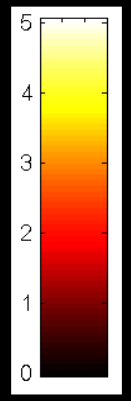
The activity decreased during visual task

MRI Morphometry in patients with ME/CFS

Volume reduction in prefrontal cortices

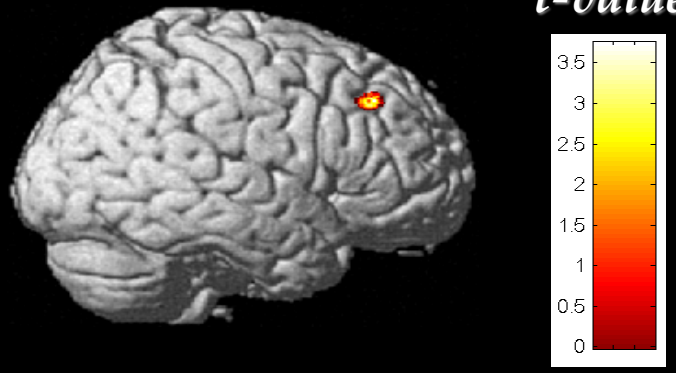


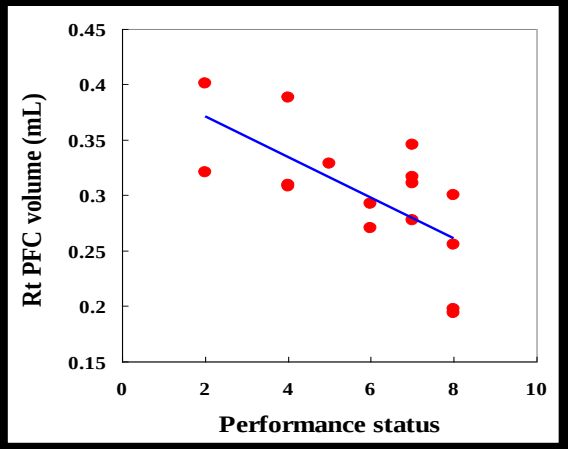
t-value



Especially that in right prefrontal cortex focus well correlates with the extent of their functional loss

t-value





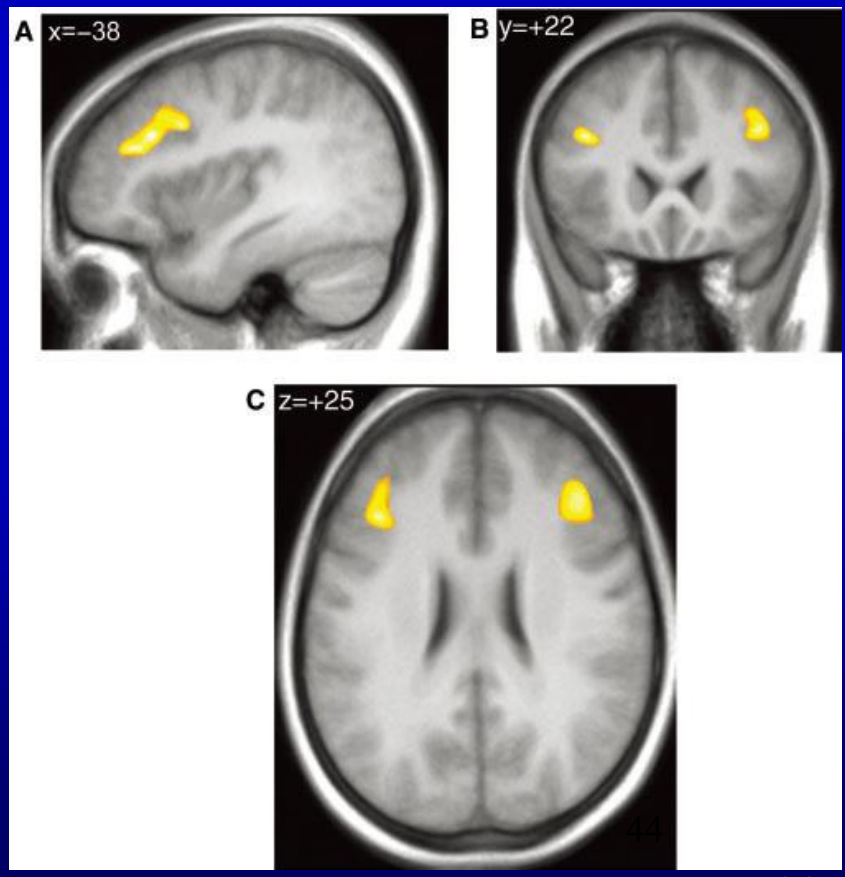
Okada, T. et al., BMC Neurol., 2004

"Cortical Plasticity" *Brain*, 2008

Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with ME/CFS

Floris P. de Lange,1 Anda Koers,1 Joke S. Kalkman,2 Gijs Bleijenberg,2 Peter Hagoort,1,3 Jos W. M. van de Meer4 and IvanToni1,3

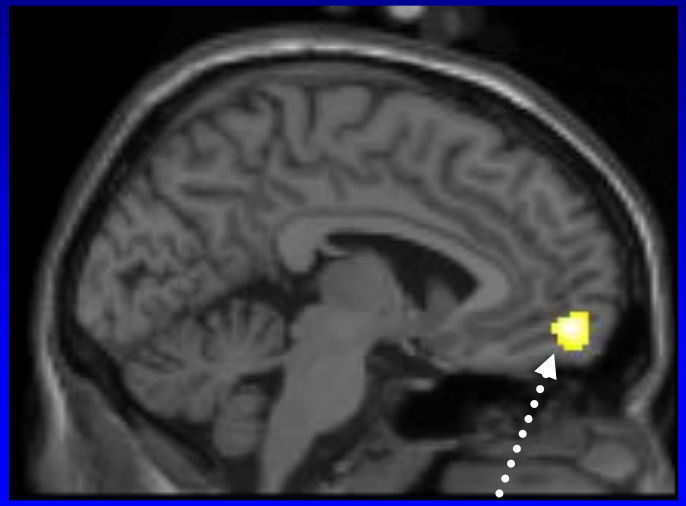
1F.C. Donders Centre for Cognitive Neuroimaging, Radboud University Nijmegen,
2Expert Center Chronic Fatigue, Radboud University Nijmegen Medical Center,
3Nijmegen Institute for Cognition and Information, Radboud University Nijmegen and
4Department of General Internal Medicine, Radboud University Nijmegen Medical Center, Netherlands



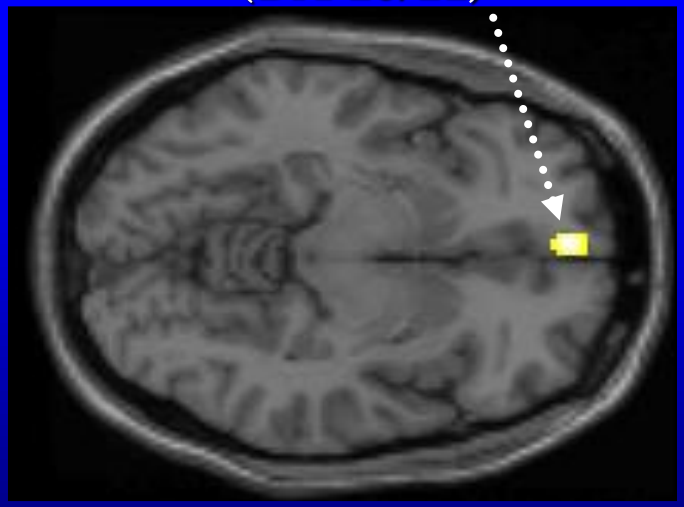
Outcome from Positron Emission Tomography (PET) studies

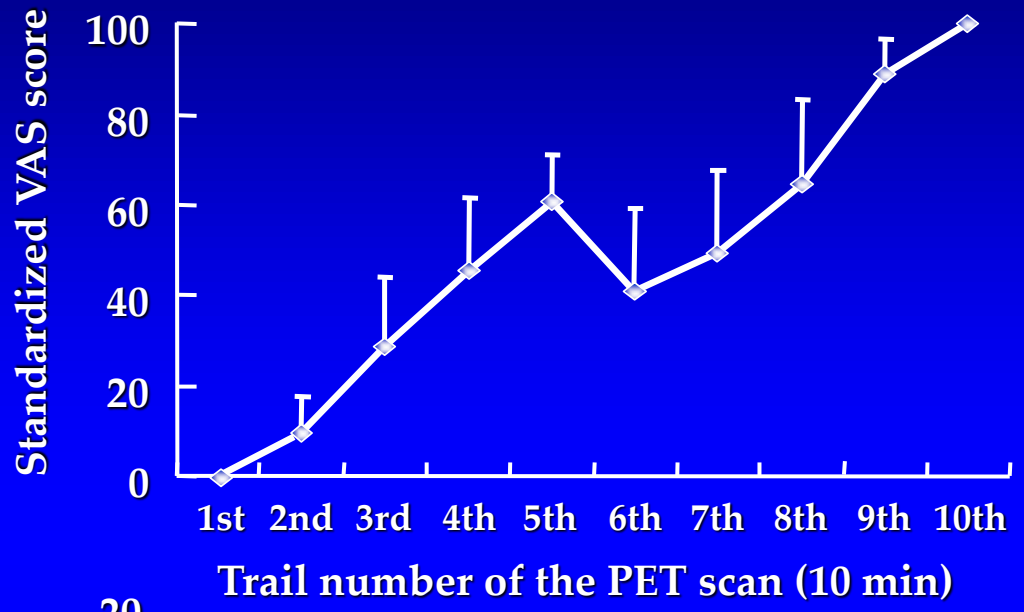
45

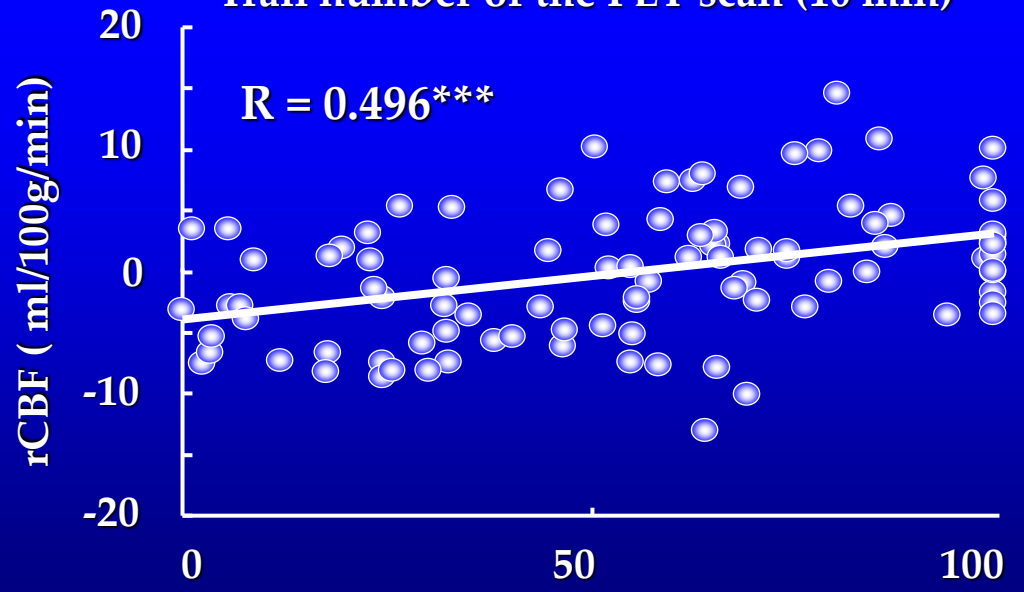
Brain region associated with fatigue sensation



Orbitofrontal cortex
(BA 10/11)

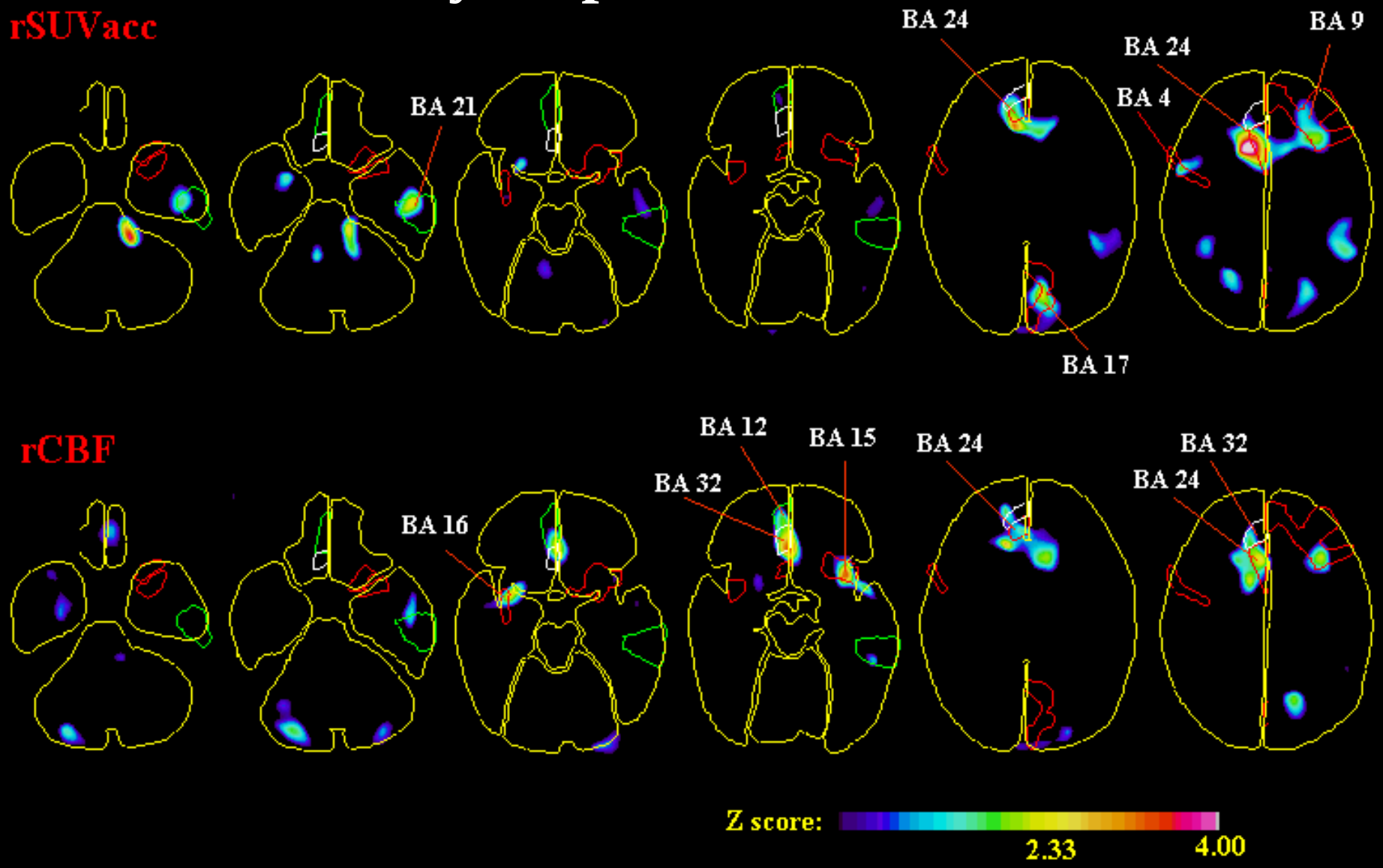






Tajima, S. *et al.*

PET study in patients with ME/CFS



Kuratsune, H. et al., NeuroImage, 2002

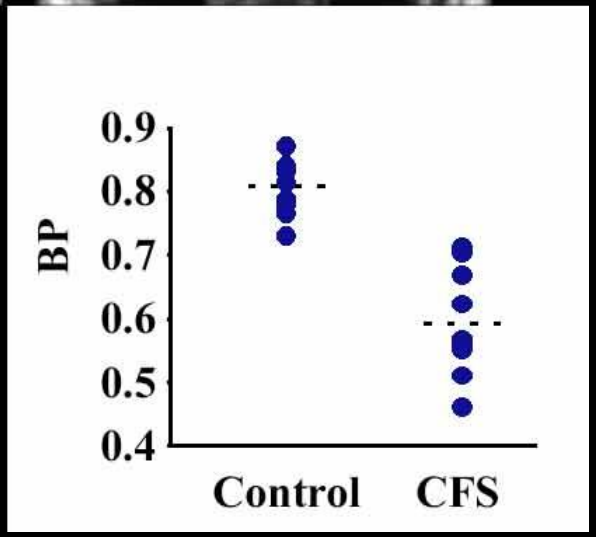
Serotonergic system

1. Indication of endocrine abnormality induced by dysfunction of 5-HT system in ME/CFS
   (Bakheit et al., 1992; Cleare et al., 1995)
2. 5-HT transporter gene polymorphism in ME/CFS patients
   (Narita M. et al., 2003)
3. Dysfunction in 5-HT system in the animal models
   (Katafuchi T. et al., 2004)
4. One third of the ME/CFS patients responded to SSRI
   (Kuratsune H. et al., in Japan)

---> PET study with 5-HT transporter ligand

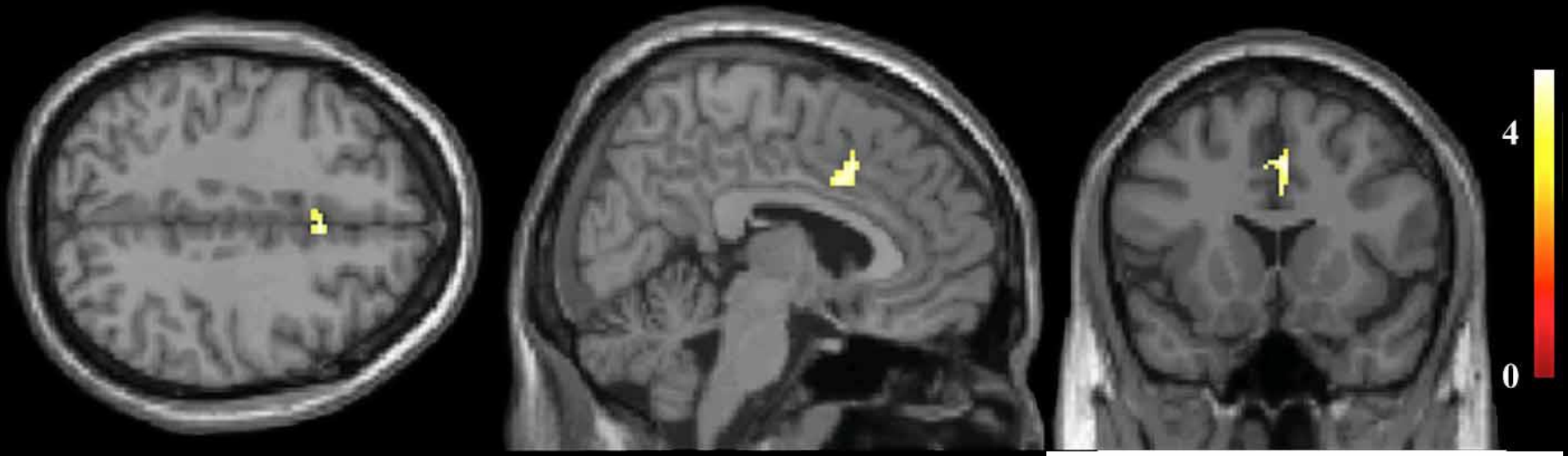
Reduced binding potential of 5-HTT in ME/CFS

Binding potential (BP) of the rostral subdivision of anterior cingulate cortex (Brodmann's area 24/32) was significantly reduced (corrected, p=0.008, Z=4.95) in CFS patients.

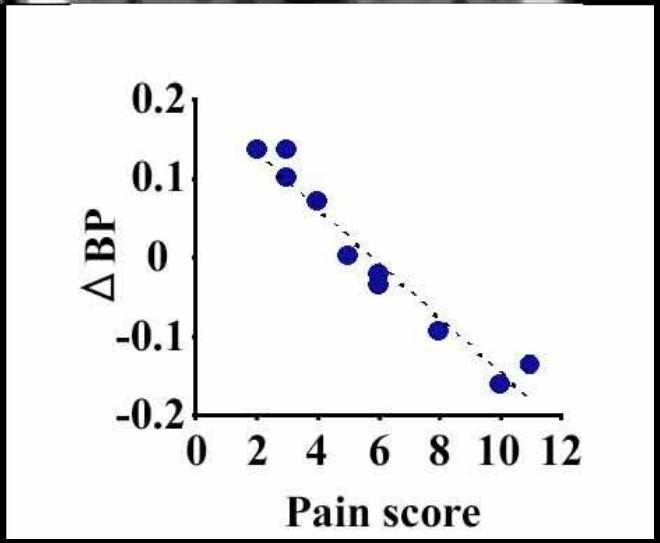


Yamamoto, S. *et al.*, NeuroReport, 2004

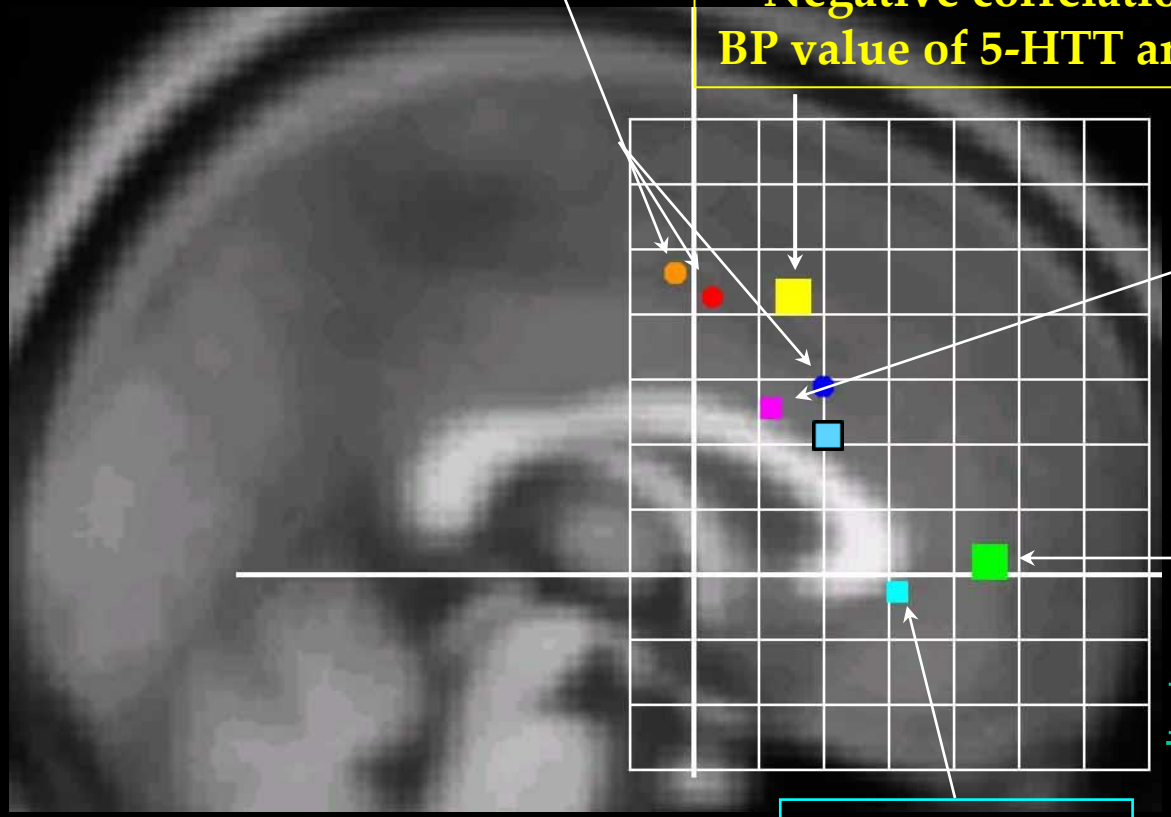
Correlation between BP of 5-HTT and pain score in ME/CFS patients



BP in the dorsal subdivision of anterior cingulate cortex (Brodmann's area 24) was negatively correlated (uncorrected, $p<0.00001$, $Z=4.71$) with the pain score.



Summary of PET studies with ME/CFS patients: Sectors in the Anterior Cingulate



Pain center

Negative correlation between BP value of 5-HTT and pain score

Attention center

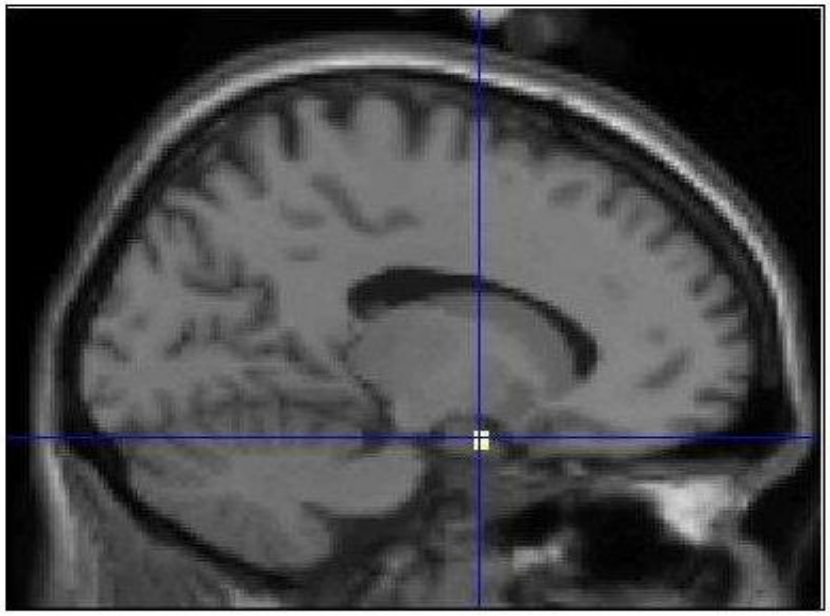
Decreased acetyl-L-carnitine uptake

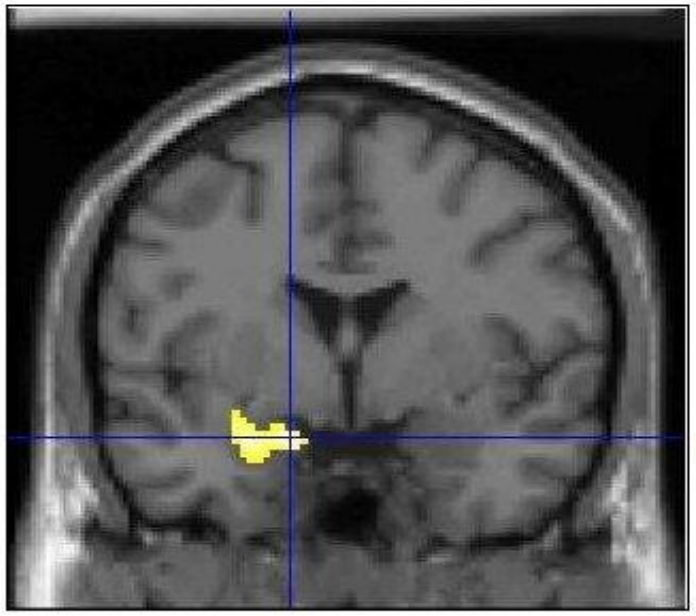
Decrease in BP of 5-HTT

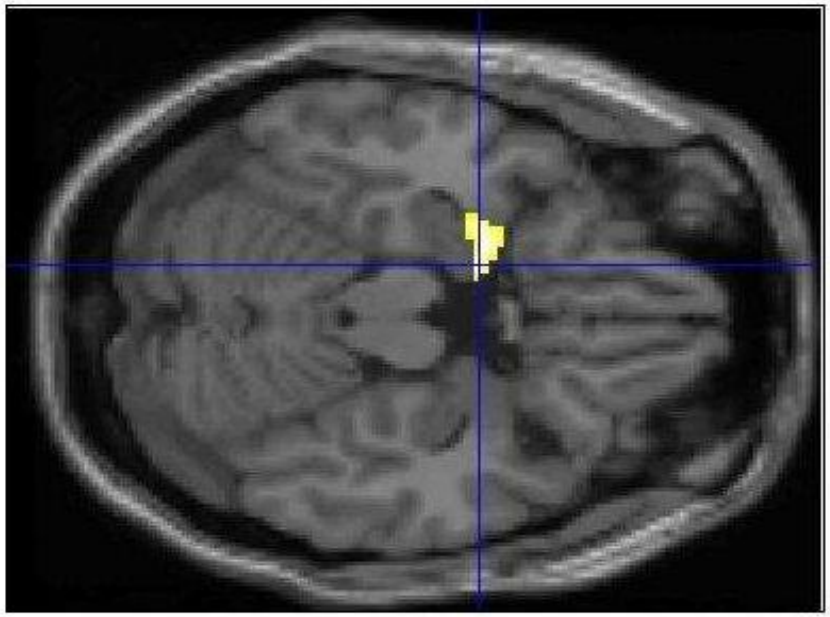
Fatigue center

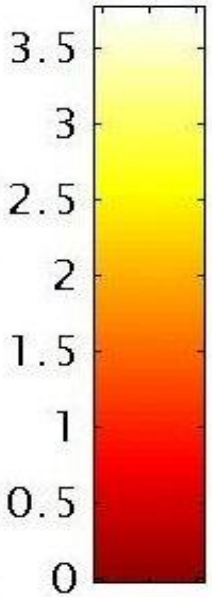
rCBF decrease

Higher uptake of L-[^{11}C]DOPA in the amygdala of ME/CFS patients







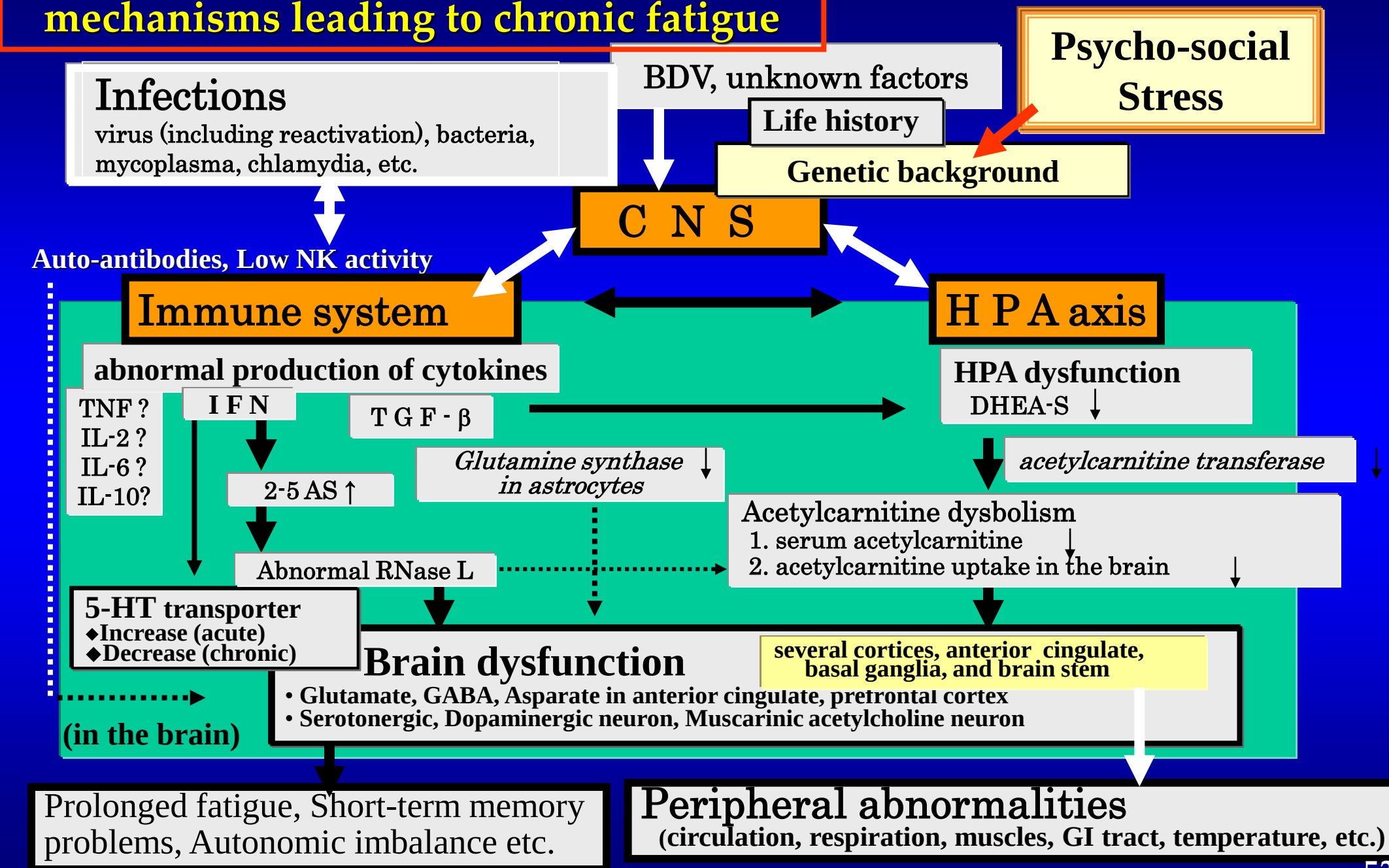


8 ME/CFS patients
49.3 ± 4.5 years old

8 healthy controls
49.5 ± 4.2 years old

uncorrected
P = 0.001

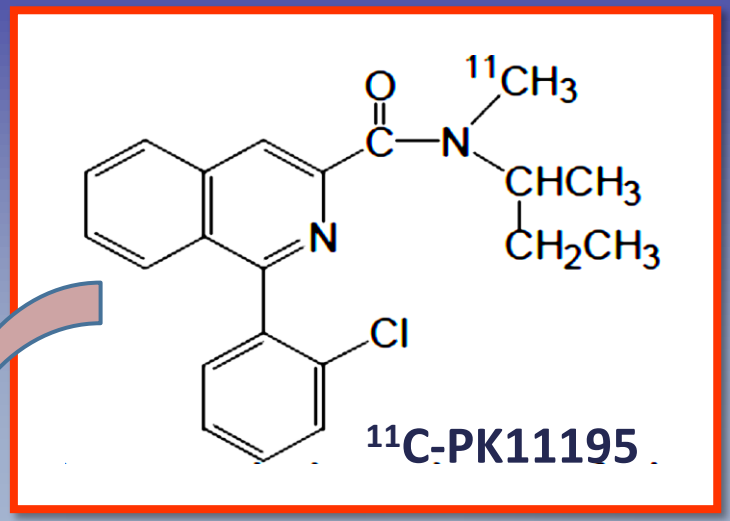
Hypothesis: Neural and molecular mechanisms leading to chronic fatigue

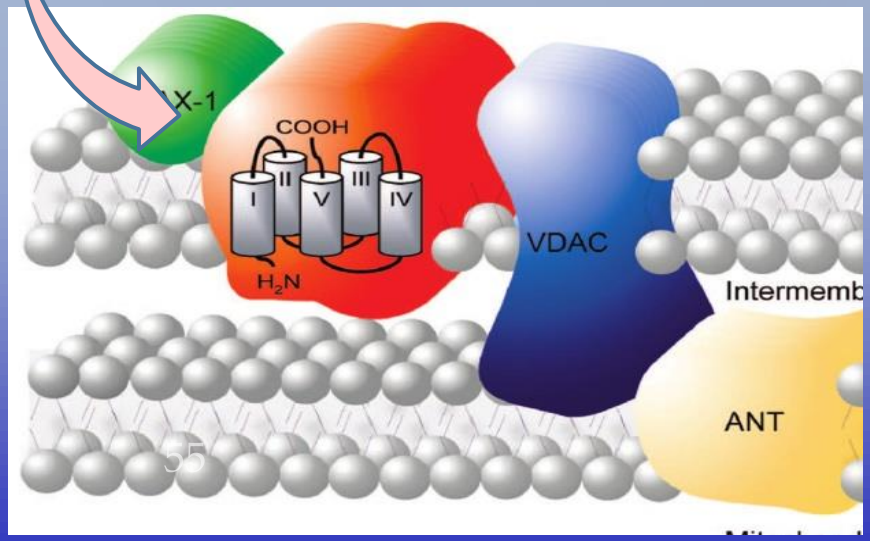


PET study on Neuroinflammation in ME/CFS patients

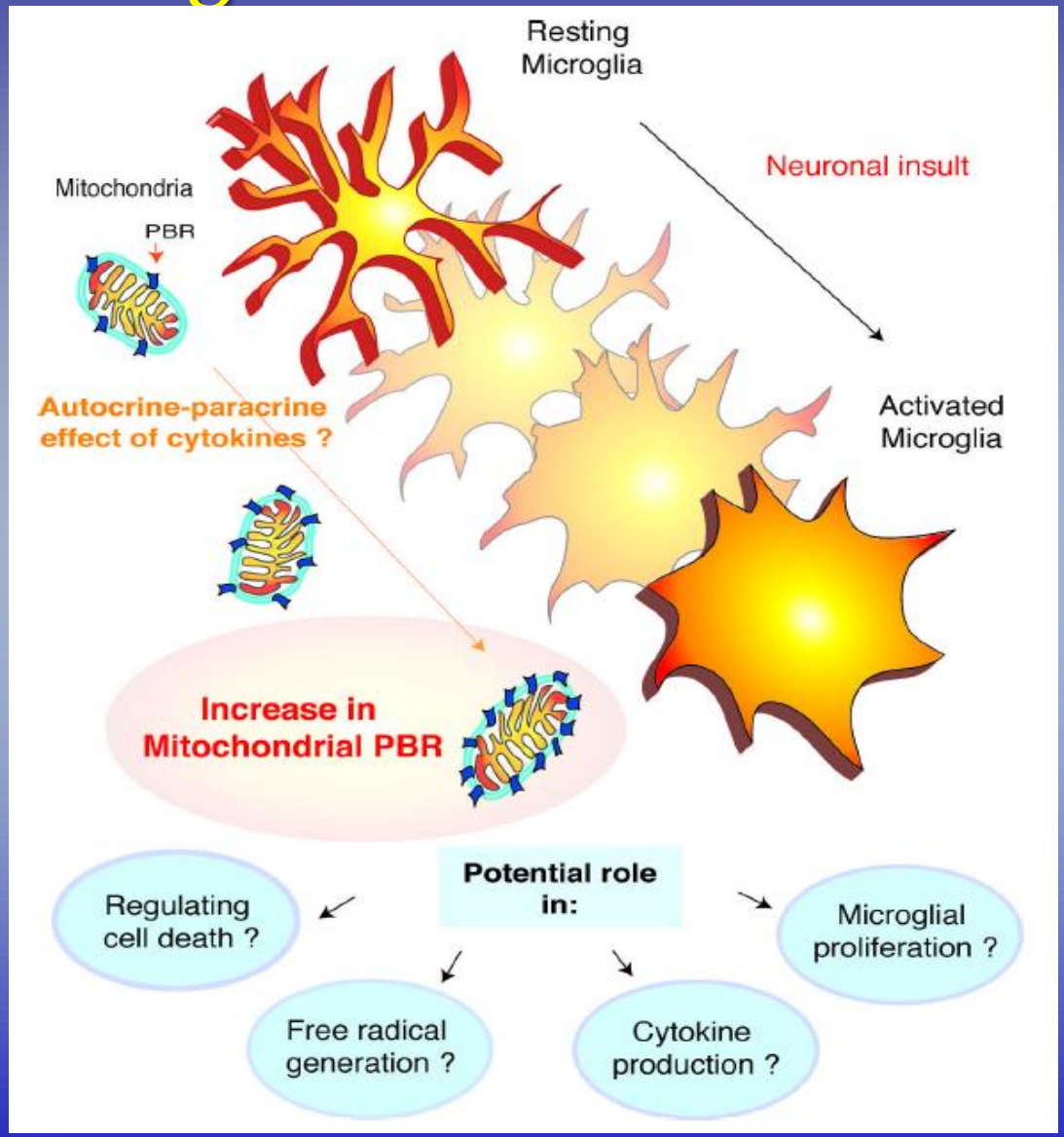
Elevation of cytokine levels in the plasma of the ME/CFS patients: LTα, IL-6, IL-1α, IL-1β, IL-2, IL-4

^{11}C-PK11195 binds to the translocator protein (PBR), the index of Activated Microglia



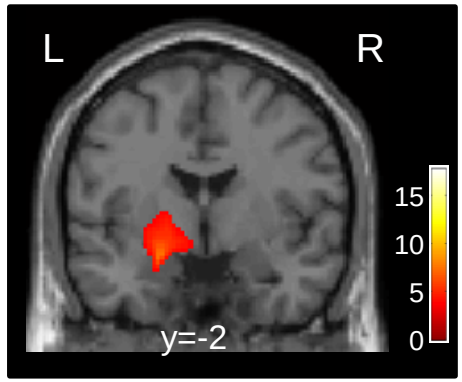


Scarf, et al., *J. Med. Chem.*, 2009.

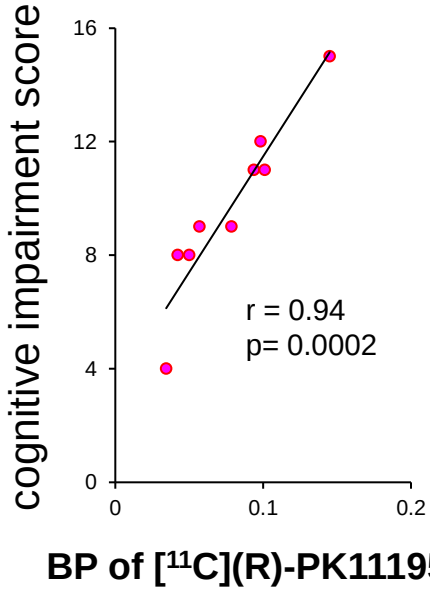


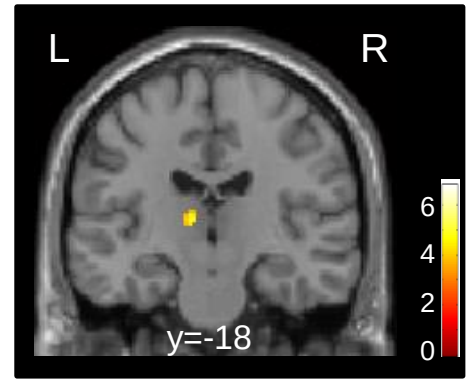
Venneti, et al., *Prog. Neurobiol.*, 2006.

Correlation: Neuroinflammation and deterioration

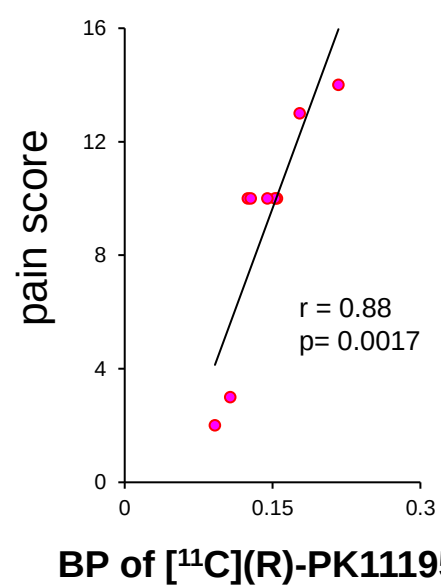


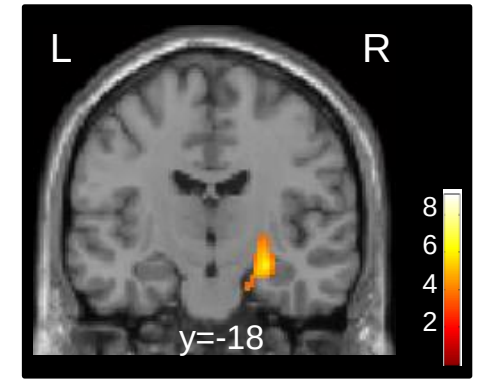
Amygdala



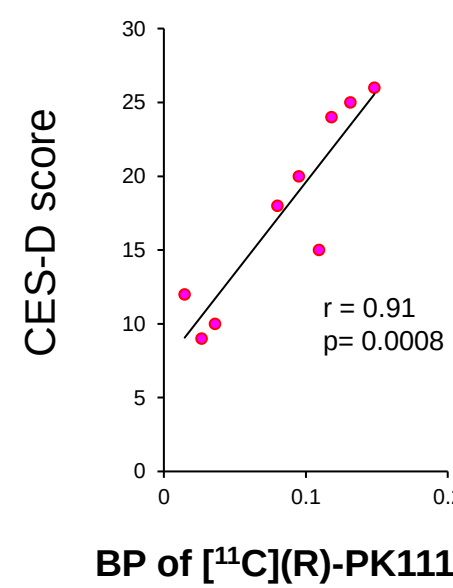


Thalamus





Hippocampus



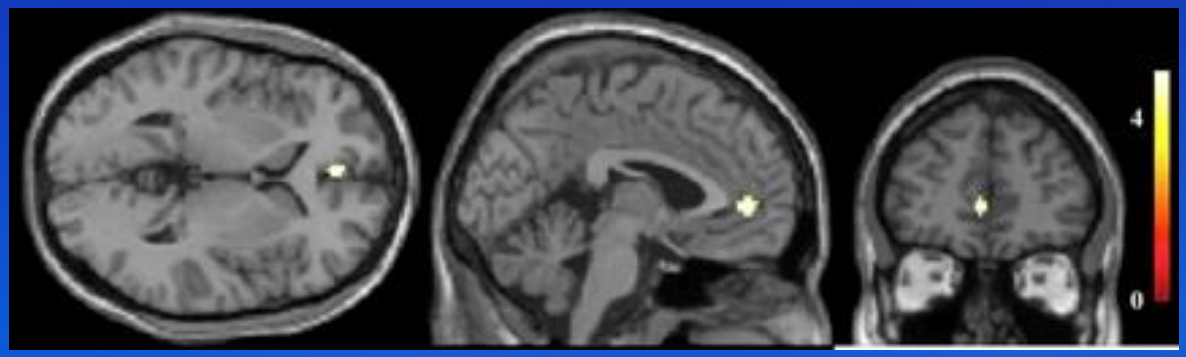
Latest PET study

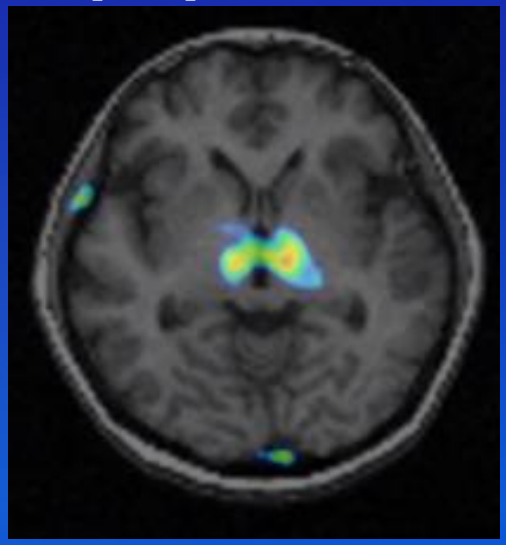
Serotonergic dysfunction
[^{11}C]DASB

Correlation?

Neuroinflammation
[^{11}C]PK11195

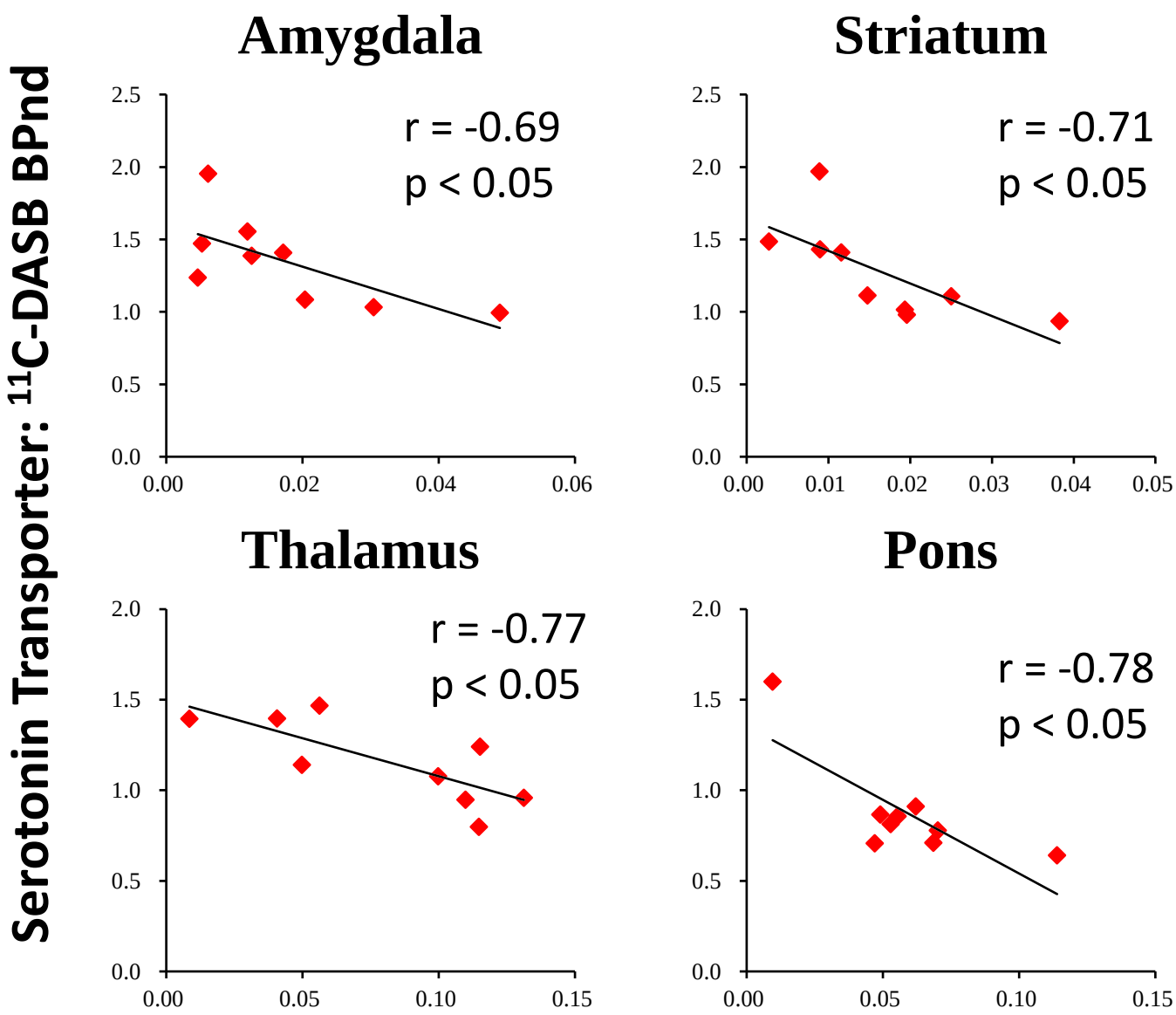
ME/CFS *vs.* HV



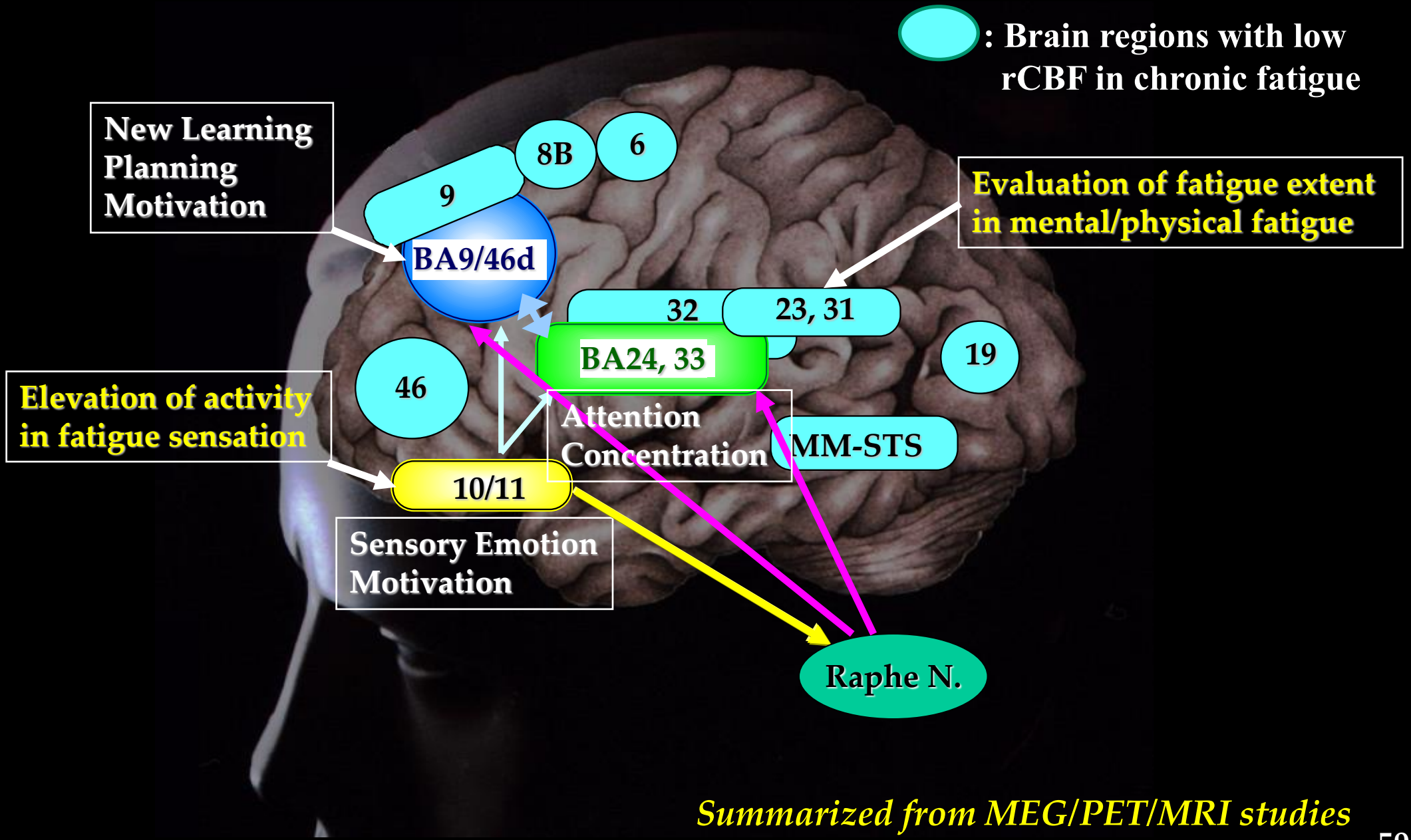


questionnaire: Chalder, VAS, CES-D, BDI, STAI, FP
autonomic function: APG, active tracer
sleep quality: actigraph, EEG
blood sample: proinflammatory cytokines
oxidative stress
metabolome, transcriptome, chemokine
SNPs
brain MRI

Correlation between Neuroinflammation and Serotonin dysfunction



Neural correlates of fatigue: from acute to chronic phase

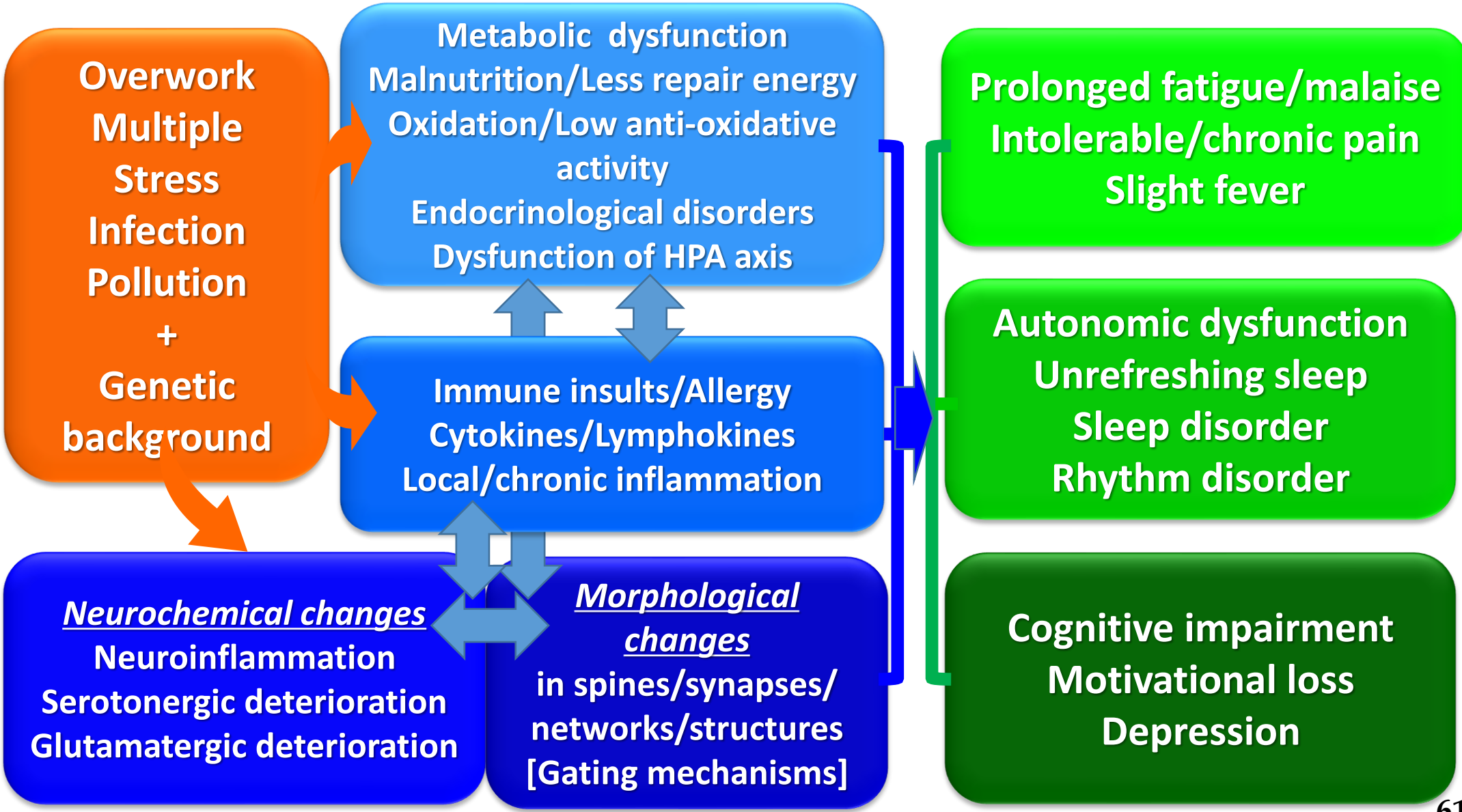


Summarized from MEG/PET/MRI studies

REVIEWS from our research group

1. Tanaka M & Watanabe Y: A new hypothesis of chronic fatigue syndrome: co-conditioning theory. *Med. Hypotheses*, 75: 244-249, 2010.
2. Tanaka M & Watanabe Y: Supraspinal regulation of physical fatigue. *Neurosci. Biobehav. Rev.*, 36:727-734, 2012.
3. Tanaka M, Ishii A, Watanabe Y: Neural mechanisms underlying chronic fatigue. *Rev. Neurosci.*, 24:617-624, 2013.
4. Ishii A, Tanaka M, Watanabe Y: Neural mechanisms of mental fatigue. *Rev. Neurosci.*, 25:469-479, 2014.
5. Tanaka M et al.: Frontier studies on fatigue, autonomic nerve dysfunction, and sleep-rhythm disorder. *J. Physiol. Sci.*, 65:483-498, 2015.
6. Watanabe Y: PET/SPECT/MRI/fMRI Studies in the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *In: PET and SPECT in Psychiatry (Dierckx RAJO, Otte A, de Vries EFJ, wan Waarde A, Sommer IE, eds.), pp.* Springer, 2021.

Pleusible mechanistic structure from ME/CFS studies on a variety of biomarkers integrated with PET/MRI/fMRI/MEG



How to acquire much more health and vitality [Regeneration]?

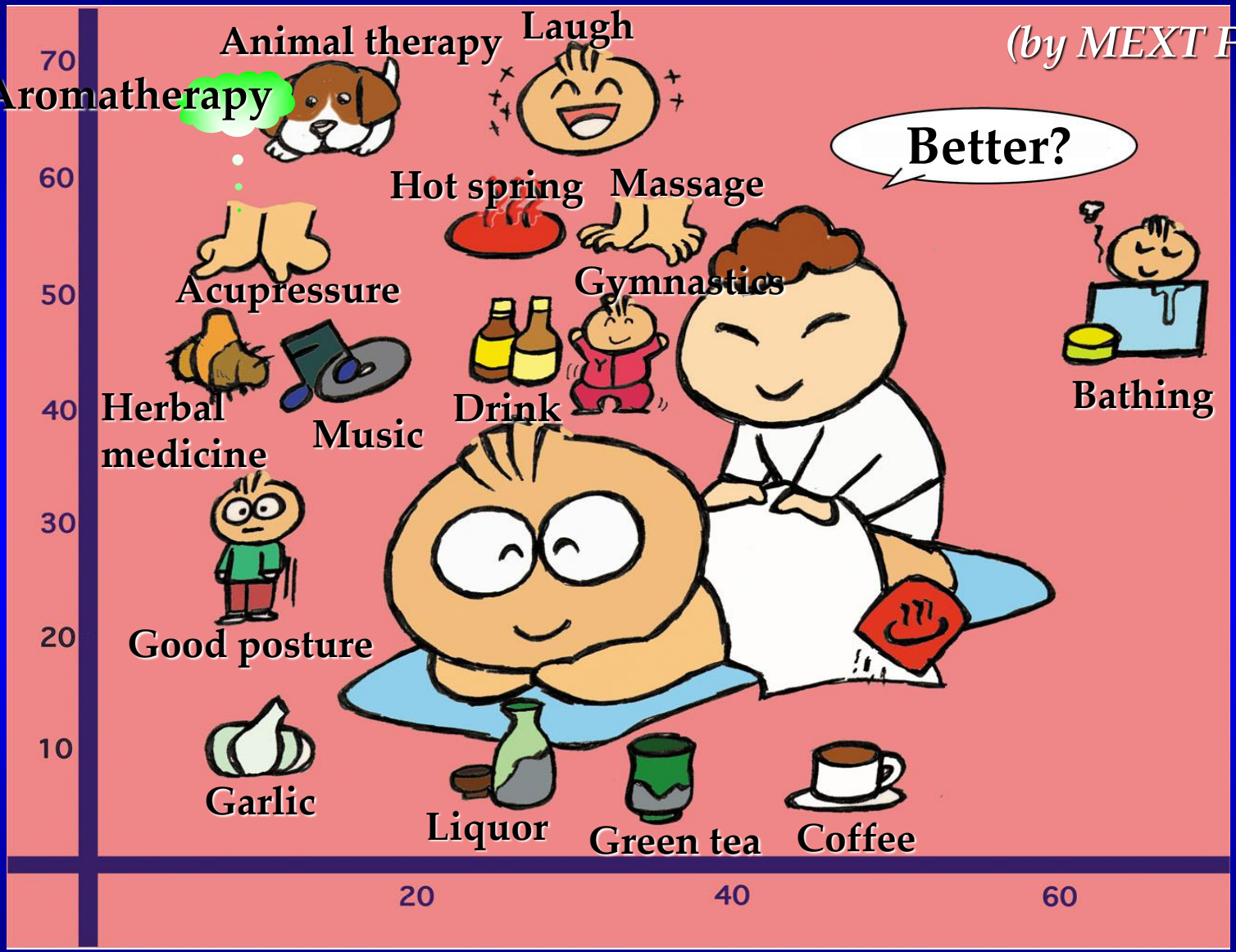
How to personalize??

For the development of solution, we should have multi-angle indices of individual health!!

Invention of "Personalized Health-state Positioning Map"


Intervention:
Anti-fatigue Products
Toward Pre-emptive Medicine
抗疲労・癒しの科学:有効な先制医療へ

Methods for Recovery from Fatigue: 1,300 Japanese



(by MEXT Fatigue Res. 2001)

Anti-fatigue food and medicine develop. project

Physiological Test

BT BP
Actigraph
Muscle stiffness
Advanced TMT

APG

Relaxed

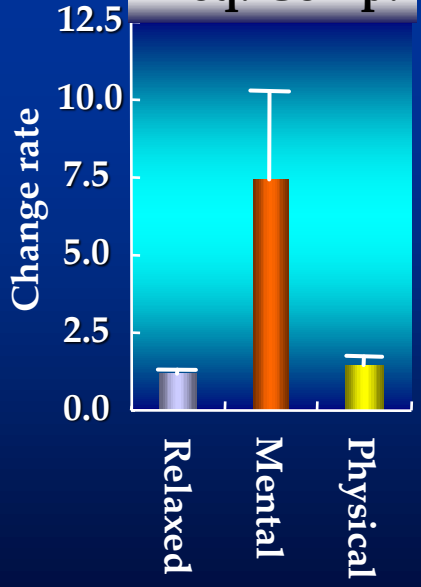
Biochemical Test

General biochemical
Endocrine
Vitamines, Ions
Cytokines

Amino acids

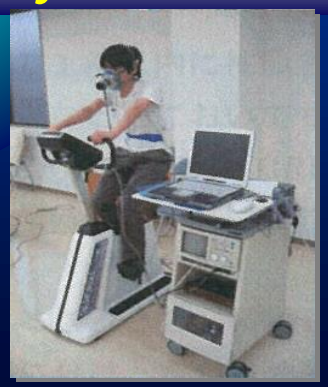
96 Healthy Volunteers
Cross-over design
4-hr session at 4 w intervals

Freq. Comp.

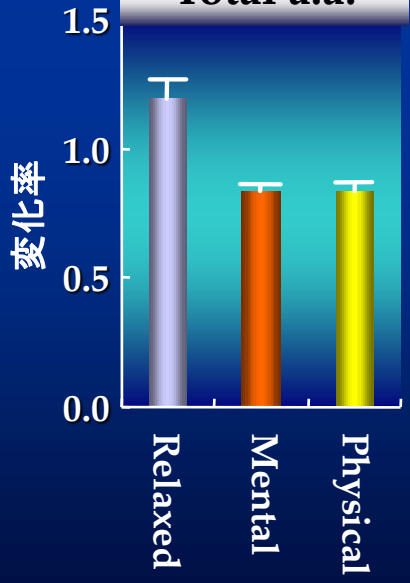


Mental tasks

Physical tasks



Total a.a.

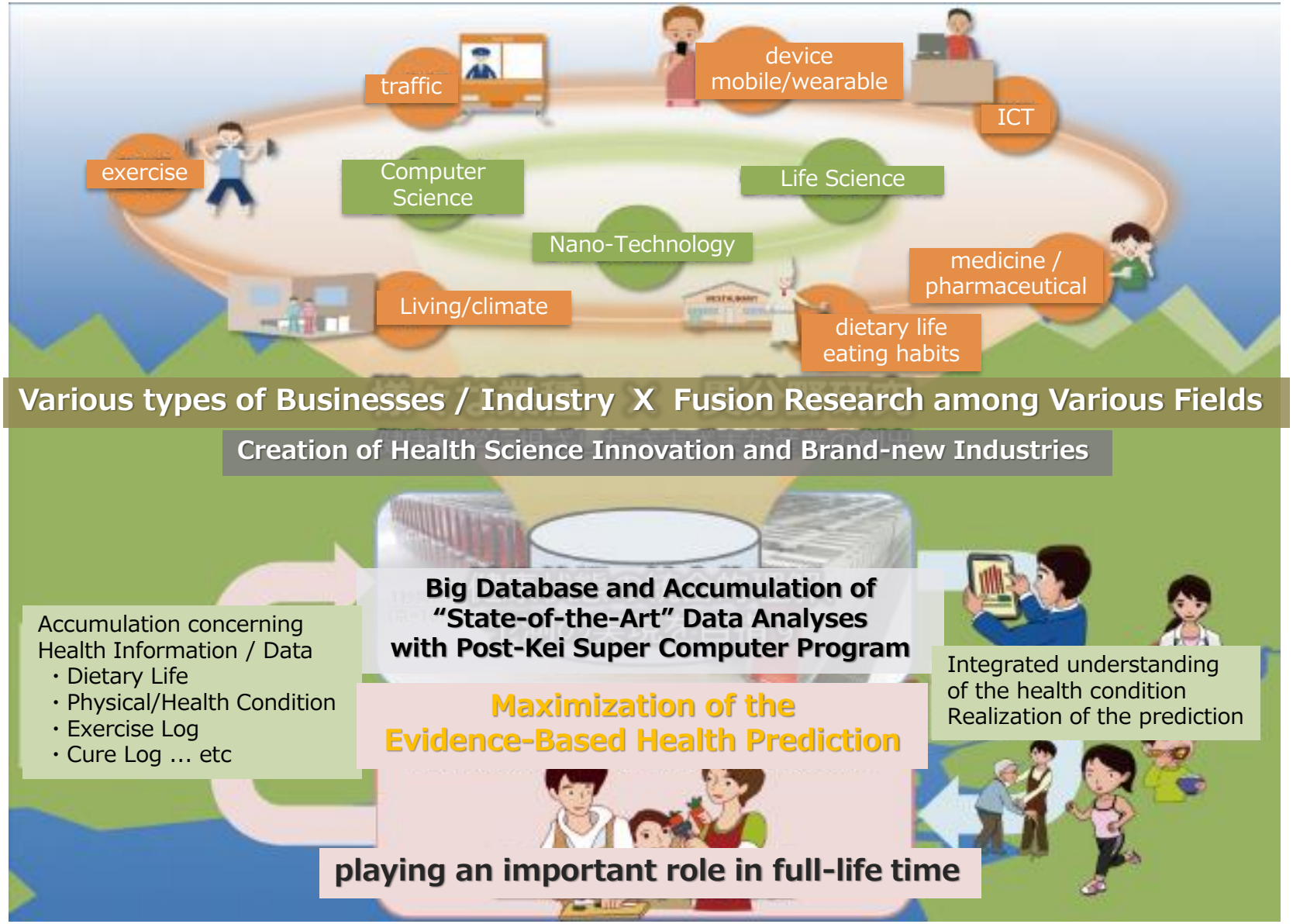


Health evaluation parameters
[indices for prediction and prevention]

- Basic data：BW/BL（BMI）, comp. analysis, bone density, blood pressure, etc.
- Standardized questionnaires [daily life habit, stress, sleep, fatigue, motivation, mood/depression, etc.]
- Various VAS（Visual Analogue Scale）
- Autonomic nerve function [sympathetic, parasympathetic; power and balance]
- Vascular function, Vascular pattern, Blood flow, Cutaneous & Sub-cutaneous function
- Muscle volume, Muscle power, Activity [Locomotor & Psychomotor]
- Sleep [Time & Quality], Fatigue
- Biological oxidation [dROMs, etc.] & Anti-oxidation activity {BAP, etc.]
- Metabolome analysis -→ Core metabolite analysis [4-6 components]
- Microbiome analysis
- General biochemical and blood cells biomarkers
- Inflammatory and immune biomarkers
- Cognitive function & Communication function
- Morphometry, tractography, and resting state function by MRI

Symbolic collaborations with many industries

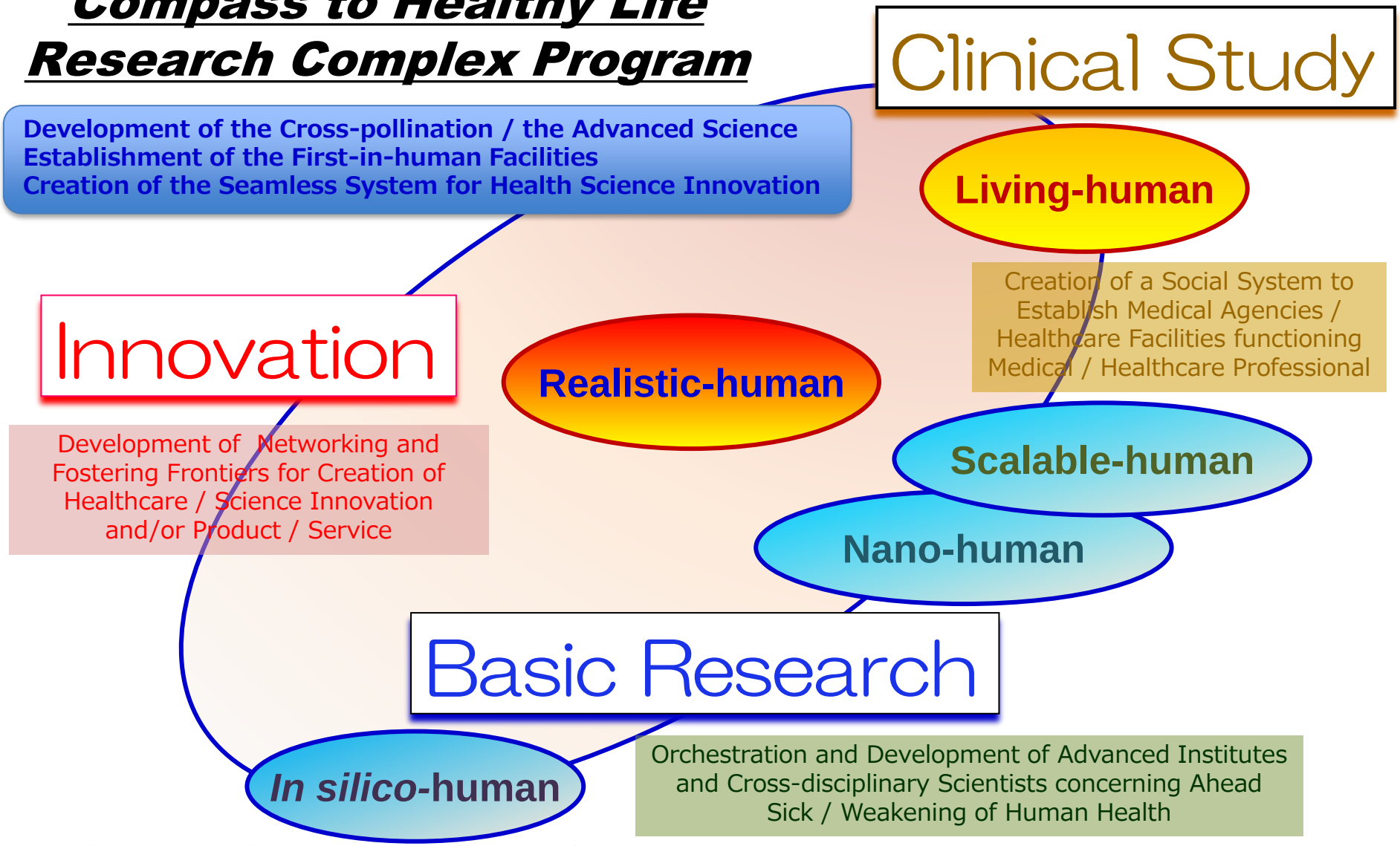
Compass to Healthy Life Research Complex Program (launched at Dec. 2015)



Development and Establishment of Cross-pollination Field

Compass to Healthy Life Research Complex Program

Development of the Cross-pollination / the Advanced Science
Establishment of the First-in-human Facilities
Creation of the Seamless System for Health Science Innovation



The “Compass to Healthy Life” Research Complex program

Organization and Participating Institutions

Core Institution : **RIKEN (Kobe)**

Prefectures and Ordinance-Designated Cities : **Hyogo Prefecture** & **Kobe City**

Total 157

Participating Institutions :

25 universities and research institutes, 125 companies and organizations, and 3 observer-participant institute

(listed in alphabetical order, as of December 01, 2019)

Universities, etc.

25

Foundation for Biomedical Research and Innovation at Kobe., Gunma University, Hyogo College of Medicine, Kagawa University, Kansai University, Kansai University of Welfare Sciences, Keio Research Institute at SFC, **Kobe University**, Kobe Yamate University, Konan University, Kumamoto University, Kwansei Gakuin University, **Kyoto University**, Nara Institute of Science and Technology, Niigata University, Osaka City University, Osaka Prefecture University, Osaka Shoin Woman's University, Osaka University, The University of Shiga Prefecture, Tokushima University, Tokyo Institute of Technology, **University of Hyogo**, University of Tokyo, Yamaguchi University

Companies

126

ACOS Co.,LTD., Aflac Life Insurance Japan Ltd., Ancient Tree, Asahi Soft Drinks Co.,Ltd., ASICS Corporation, Atonarp Inc., Atto Co.,Ltd., AXION RESARCH Inc., Bayer Yakuhin, Ltd., Biogrid Center Kansai, CMIC HOLDINGS Co.,Ltd., communitylink.npo, Consumers Co-Operative KOBE, COPEL consulting Co.,Ltd, CORONA CORPORATION, COSMO HEALTH Co., Ltd., Cykinso, Inc., Dai Nippon Printing Co.,Ltd., Dai-ichi Life Holdings, Inc., Daikin Industries Ltd., Dentsu ScienceJam inc., EcoNaviSta Co.,Ltd., ExaWizards Inc., Ezaki Glico Co.,Ltd., Familiar Ltd., Fatigue Science Laboratory Inc., FUJICCO Co., Ltd., Fujitsu Network Solutions Ltd., Fuji Xerox Co., Ltd., GUNZE LIMITED, **Hankyu Hanshin Holdings Inc.**, HA-PPY Co., Ltd, Hitachi Systems, Ltd., Icomes Lab Co.,Ltd., INTAGE Healthcare Inc., ITOCHU Corporation, iuto, J. Morita MFG. Corp., Japan Blood Products Organization, Japan Preventive Medicine Inc., KAN Research Institute Inc., Kaneka Corporation, Kaneka Techno Research Corporation, KANSAI Association of Health and Welfare, Kenlab, Kitahama Global Management Corporation, KNC Laboratories Co.,Ltd., Kochi Health Check-ups Clinic, Kokorotics Inc., KOKUYO Co.,Ltd., Kyocera Corporation, LaSuite Co.,Ltd., Lion Corporation, Loarant Corporatopn, Maruyanagi Foods Inc., Maxell, Ltd., Mediplus Research Institute, Inc., MediThink Inc., MEETSHOP INC., Merodian Co.,Ltd., MetLife Insurance K.K., Mikasa Shoji Co.,Ltd., Mitsubishi Tanabe Pharma Corporation, Mitsui Knowledge Industry Co.,Ltd., MIZUTA Seisakusho, Inc., MS&AD Insurance Group Holdings, Inc., Murata Manufacturing Co., Ltd., Nagase & Co., Ltd., **NEC Corporation**, Nihon Trim Co.,Ltd., Nippon Life Insurance Company, Nishikawa Co., Ltd., Noritz Corporation, OBAYASHI CORPORATION, Odakyu Electric Railway Co., Ltd., OKEIOS Co., Ltd., OM Kobe KK, OMRON HEALTHCARE Co., Ltd., ORIX Life Insurance Corporation, Osaka Gas Co.,Ltd., Otsuka Holdings Co.,Ltd., Otsuka Pharmaceutical Co.,Ltd., PAL Corp., P&G Innovation, Platinum data science Co.,Ltd, RE-Engineering Partners, Resona Bank, Ltd., Ricoh Company Ltd., Rohto Pharmaceutical Co.,Ltd., Sekisui House, Ltd., Sharp Corporation, **Shionogi & Co.,Ltd**, Shiseido Company, Limited, Soiken, Sompo Japan Nipponkoa Himawari Life Insurance, Inc., Splink, Inc., Sumita Optical Glass Co.,Ltd., **Sumitomo Mitsui Banking Corporation**, Suntory Wellness Ltd., **Sysmex Corporation**, Taisho Pharmaceutical Co., Ltd., Takeda Consumer Healthcare Co.,Ltd., TechnoPro, Inc., The Asahi Culture Center（Inc.）, The Incorporated Association of Future Design for Healthy Life and Health-Care Living, The Kobe Chamber of Commerce and Industry, The Minato Bank Ltd., The Osaka Chamber of Commerce and Industry, The Senshu Ikeda Bank, Ltd., The Tokio Marine Life Insurance Co., Ltd., TOA Corporation, Tokio Marine & Nichido Fire Insurance Co., Ltd., Total Brain Care Co.,Ltd., Toyobo Co.,Ltd., Triple W Japan Inc., Urban Innovation Institute, UT-Heart Inc., VENEX Corporation, Wellness Supply Co.,Ltd., Yamadenki Co.,Ltd., YAMATO LOGISTICS CO., LTD., YCH Medical & Healthcare Community Co., Ltd., and three other companies

Other

3

Health Science Innovation Steering Committee（HSIsc）, Life Intelligence Consortium（LINC）, Organization of Health Science Business Innovation（OHSbi）

（※ Core Eleven Organization and Institutions）

Procedure for Maximization of Individual Health

Step 1. Acquisition of health position in the map

Step 2. Prediction of future health condition

Step 3. Recommendation of personal menu to promote a better health position

Step 4. Verification of such personal menu

Step 5. Realization of the social system
Realization of "Personal Precision Health"

Why we selected the following core items for health positioning map?

Resulting from over 30 years research on the mechanisms of fatigue/chronic fatigue and vulnerability of health, there are "Common mechanisms" among fatigue/chronic fatigue, vulnerability of health, ageing, and disease onset.

1. Progression of biological oxidation and reduced anti-oxidative capacity → "Rust"
2. Reduced repair energy → Delayed repair from "Rust"
3. Immune response to damaged (rusted) cells → "Local inflammation"
4. Dysfunction of autonomic nervous system to detect and regulate these vulnerable changes

Measurements (242 items)

RIKEN BDR RIKEN Center for Biosystems Dynamics Research

1. Basics : Body Mass Index, Body components, Bone density, Blood pressure
2. Questionnaires (Personal history, Life habit, Sleep, Fatigue, Mood, Motivation, Depression, Stress, & other claims)
3. Various VAS's (Visual Analogue Scale)
4. Autonomic nerve function (Sympathetic/Parasympathetic, Power & Balance)
5. Vascular age, Vascular function, Blood flow, Skin & Sub-cutaneous function)
6. Mass of muscles, Muscle powers, Locomotive activities, Sleep time & quality)
7. Cognitive function
8. Respiratory gas & Skin gas analyses

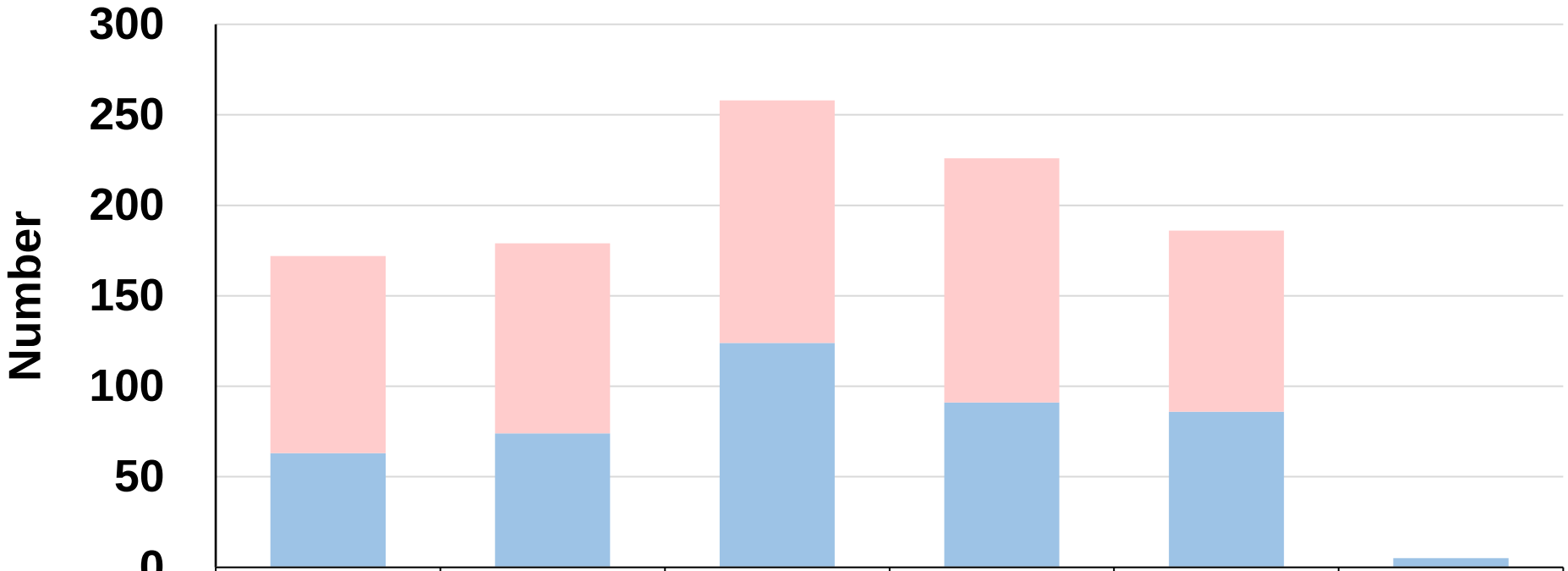
---

9. Serum oxidation (dROMs), Anti-oxidative ability (BAP)
10. Energy metabolism (iso-citrate, ornithine, citrulline, etc.)
11. Plasma CoQ10 (reduced & oxidized forms), Vitamins, Minerals
12. Routine plasma biochemistry, Blood cell counts
13. Plasma inflammation biomarkers (hs-CRP, IL-1β, IL-6, etc.)
14. Morphometry, Anisotropy, & resting-state fMRI by MRI (BHQ)

＊Items with blue letters are not routinely measured in routine HE.

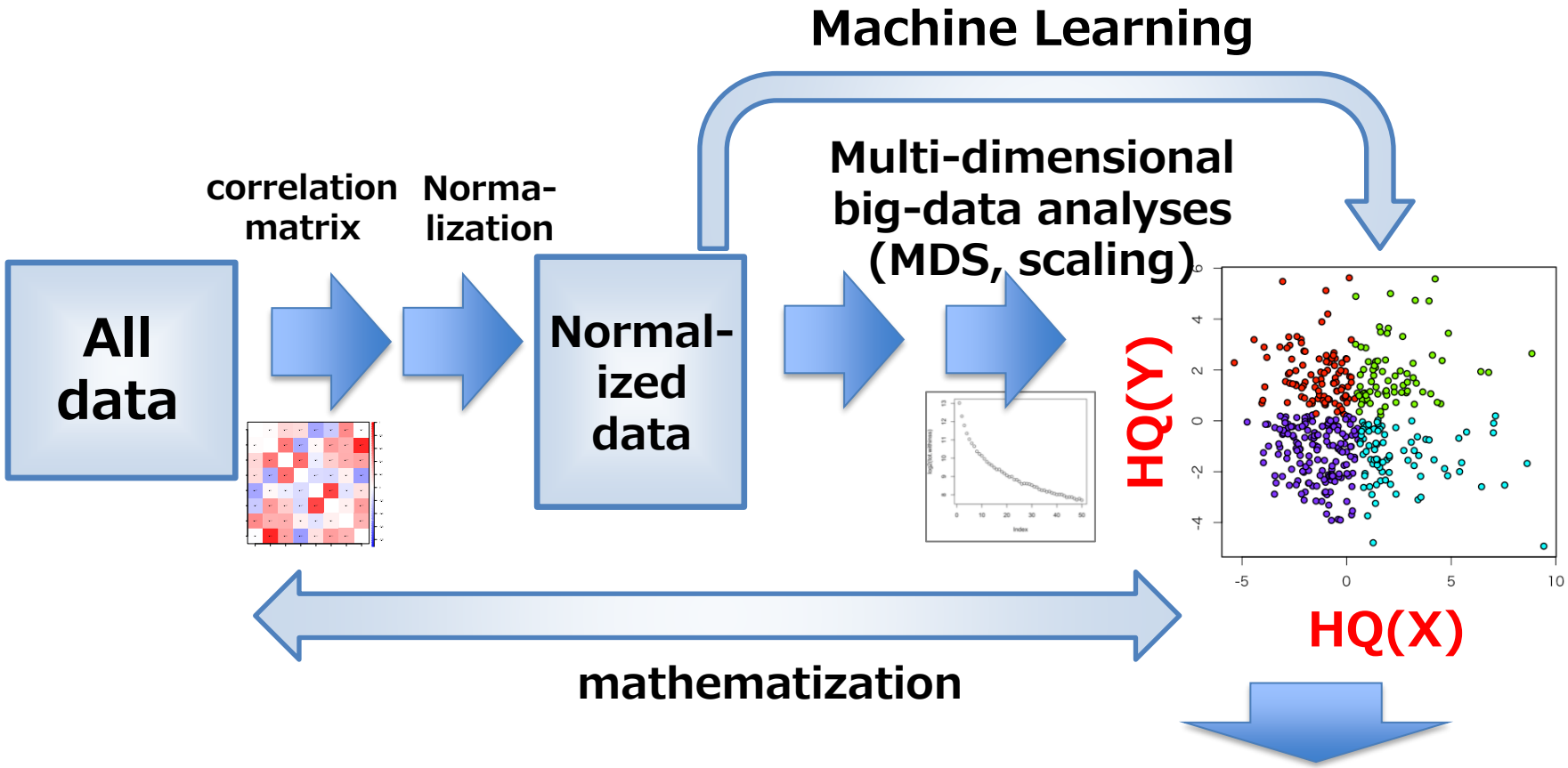
Healthy Participants

1,026（Female = 583; Male = 443）



	10-20s	30s	40s	50s	60s	70s
Female	109	105	134	135	100	0
Male	63	74	124	91	86	5

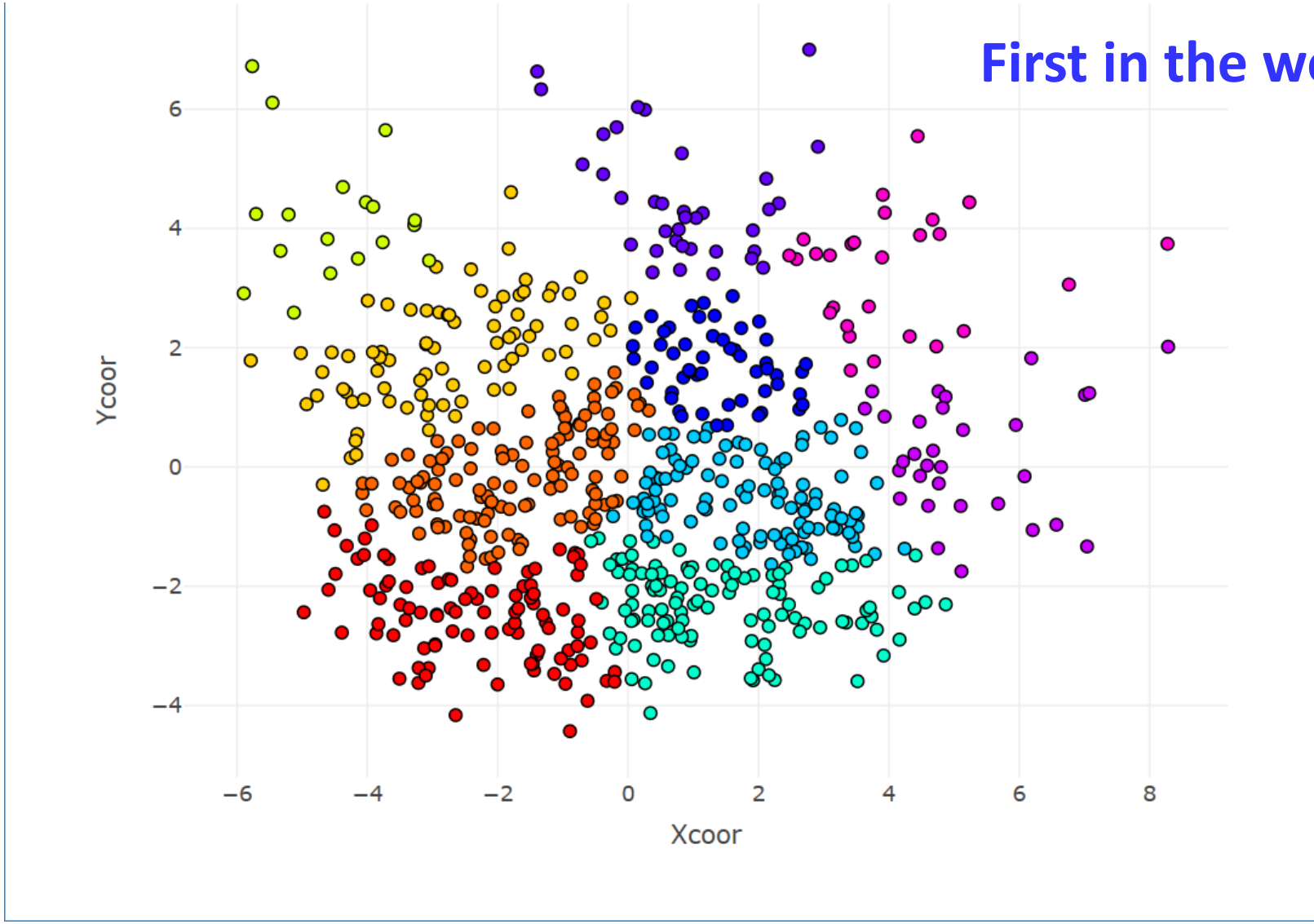
Protocol for Data Analyses



Interpretation & characterization of pre-disease states

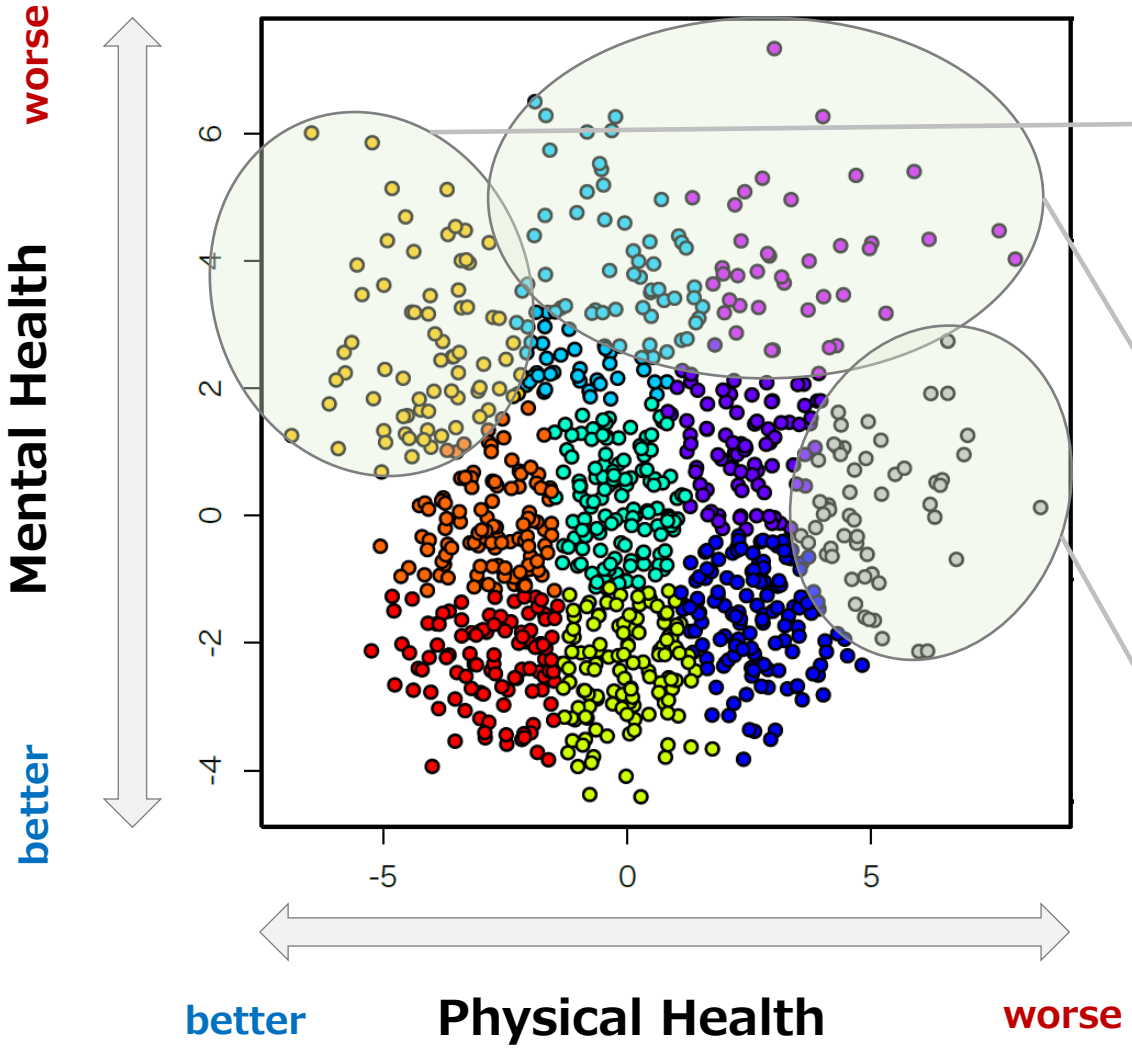
Simulation for Intervention

Individual health degree positioning map



file:///C:/Users/keimi/MotigueKM2018/Motigue/CMIS-CLST/150406_神戸市リサーチコンプレックス/00_RCH-Study/01_RCH-Res/RCH-ResKume/MDS_plot.html

Novel Health-Degree-Positioning Map



High-risk group of *Mental Health Disorders* in young adults 7.6%

High-risk group of *Life-style related Disease* in middle and old age 13.7%

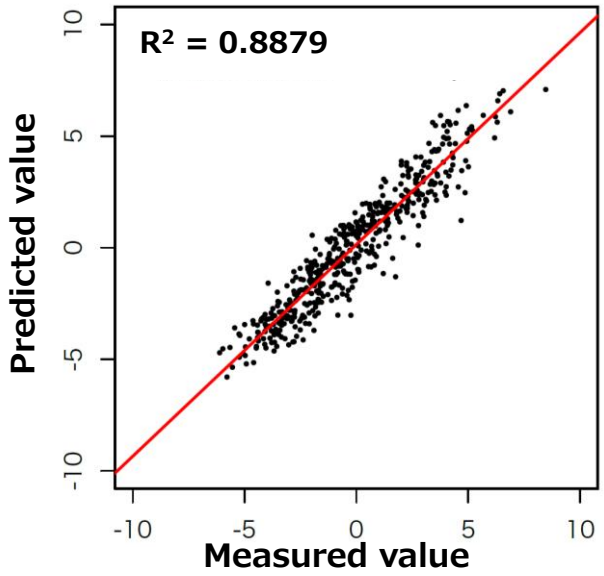
High-risk group of *Diabetes* in old age 5.7%

Health Quotients for Health Prediction

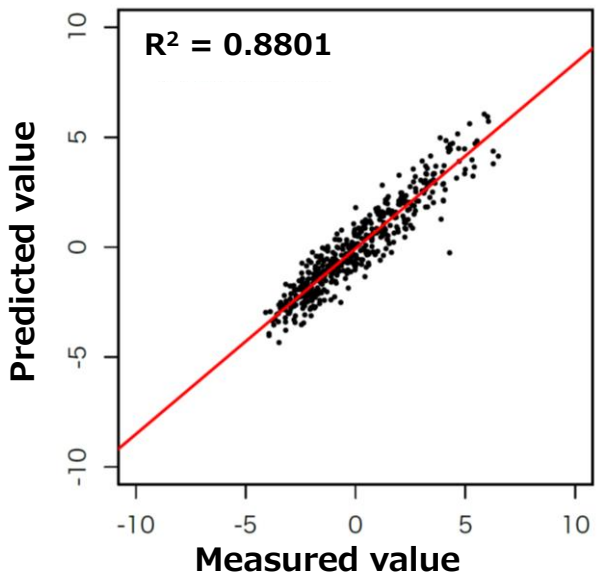
by only 15 items of non-invasive measurements

RIKEN BDR RIKEN Center for Biosystems Dynamics Research

x-axis



y-axis



High-precision prediction of health level

Achievement

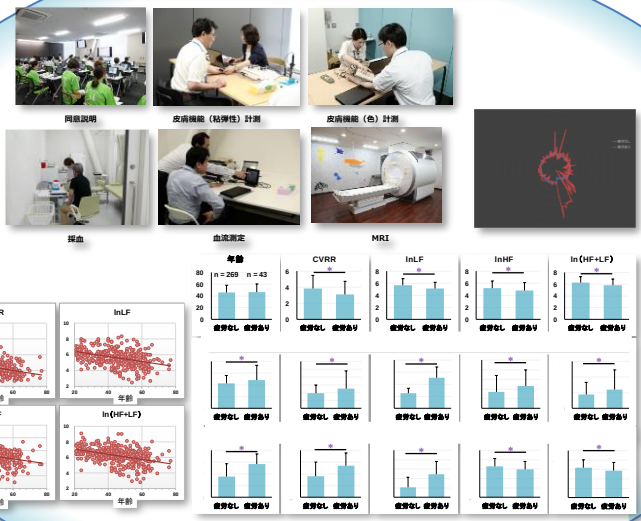
Patent (2018-207611)

Non-invasive measurements

Drug shop, Office, Caffe, Community center, etc.

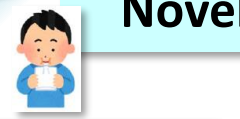
Toward Maximization of Individual Health

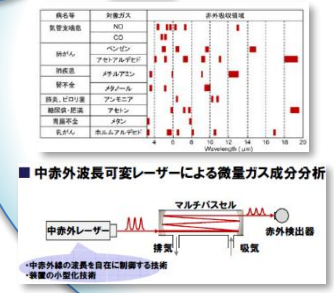
Health Quotients

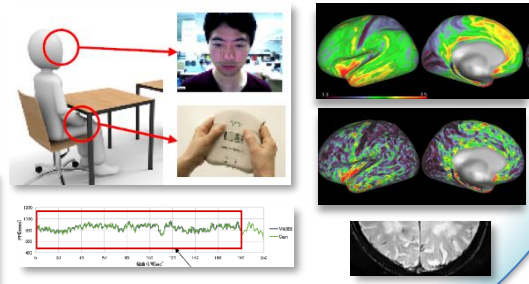


Perturbation by Various Solutions

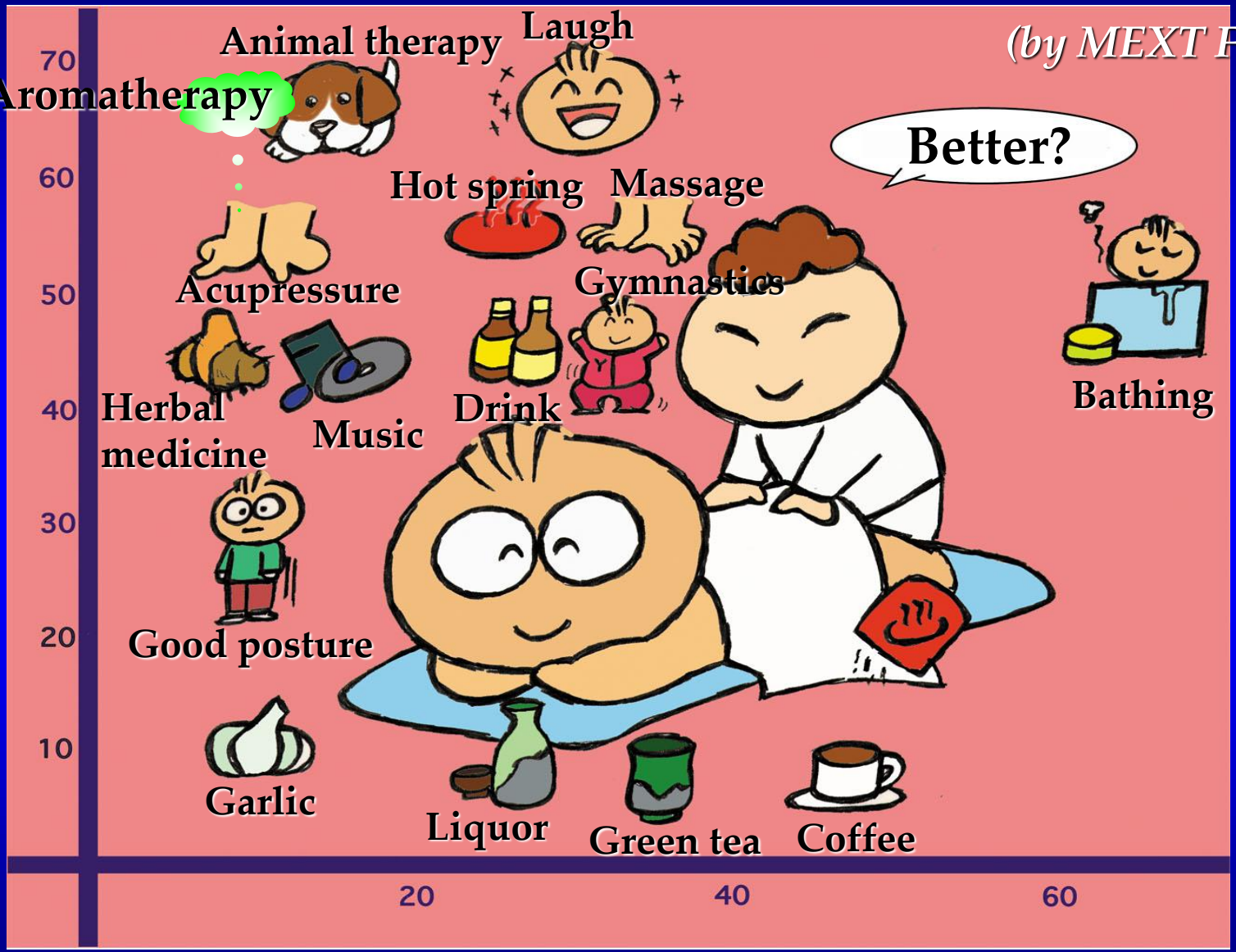
Novel methodologies







Methods for Recovery from Fatigue: 1,300 Japanese



(by MEXT Fatigue Res. 2001)

Anti-fatigue solutions with scientific evidence

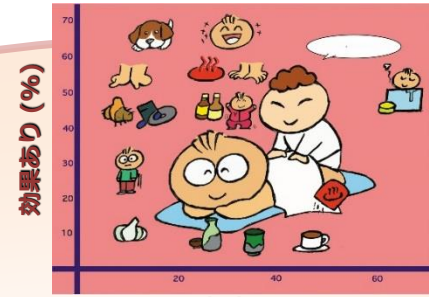
RIKEN

Food / Nutrition / Supplement


Imidazole dipeptide


ImDP + CoQ10


Reduced CoQ10



More than 80 RCT

→Clinical trials→Evidence

Anti-fatigue recepe

Carbonated water


Lemon (Citrate)

Fulsultiamine (Vitamin B1 der.)


Healing pictures

Healing music


Wooden room

Elecrolyzed & bubbled Hydrogen-rich water


Green odor


Ge-carbonate SPA


Pellet stove


Air condition


Communication robot


Micro-bubble bath Flow Massage bath

Communication / Entertainment

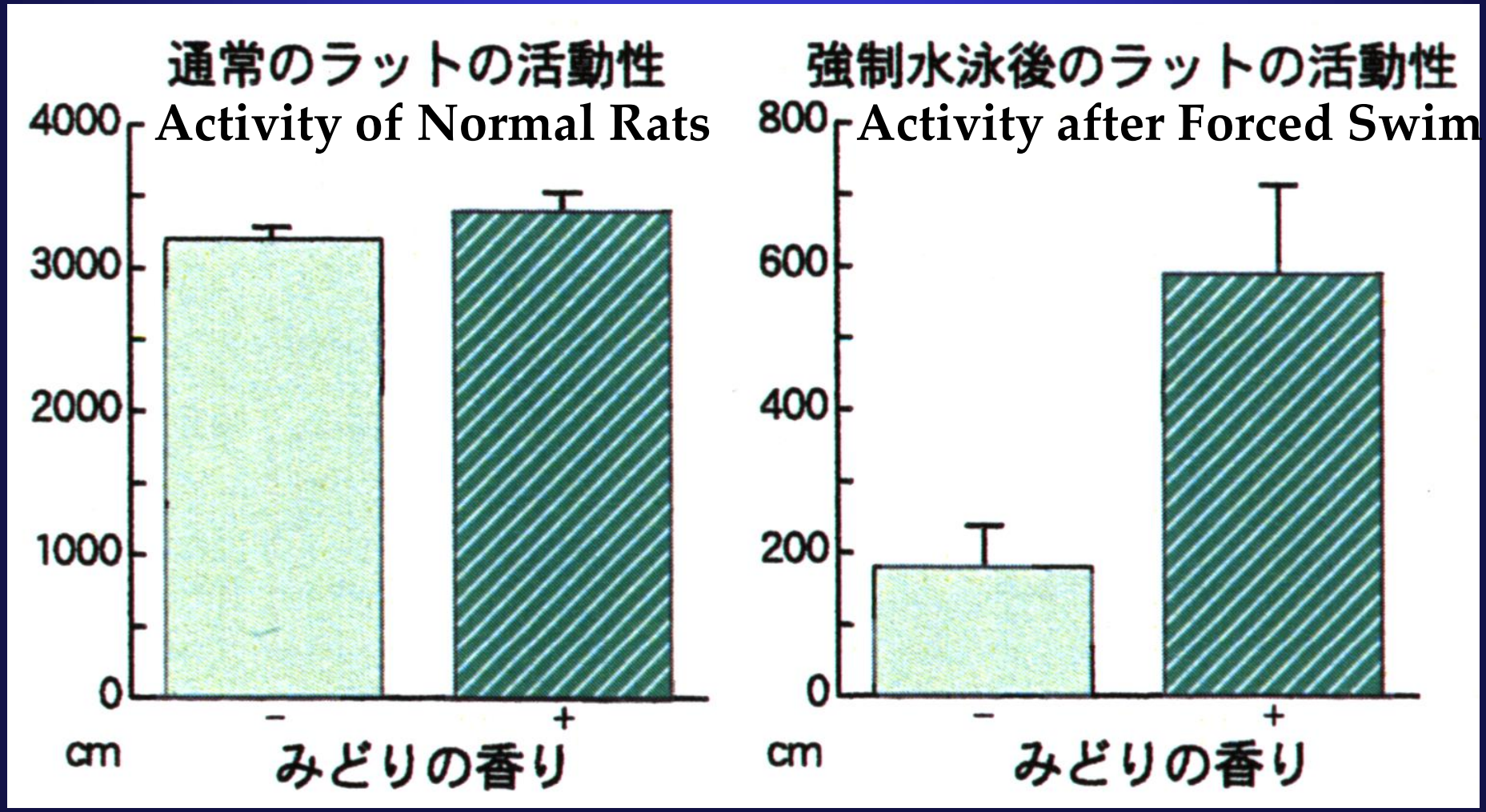
Space / Housing

Green Odor(s)
緑のかおり

cis **- 3 - hexenol**

trans **- 2 - hexenal**

Anti-fatigue effect by Green Odor



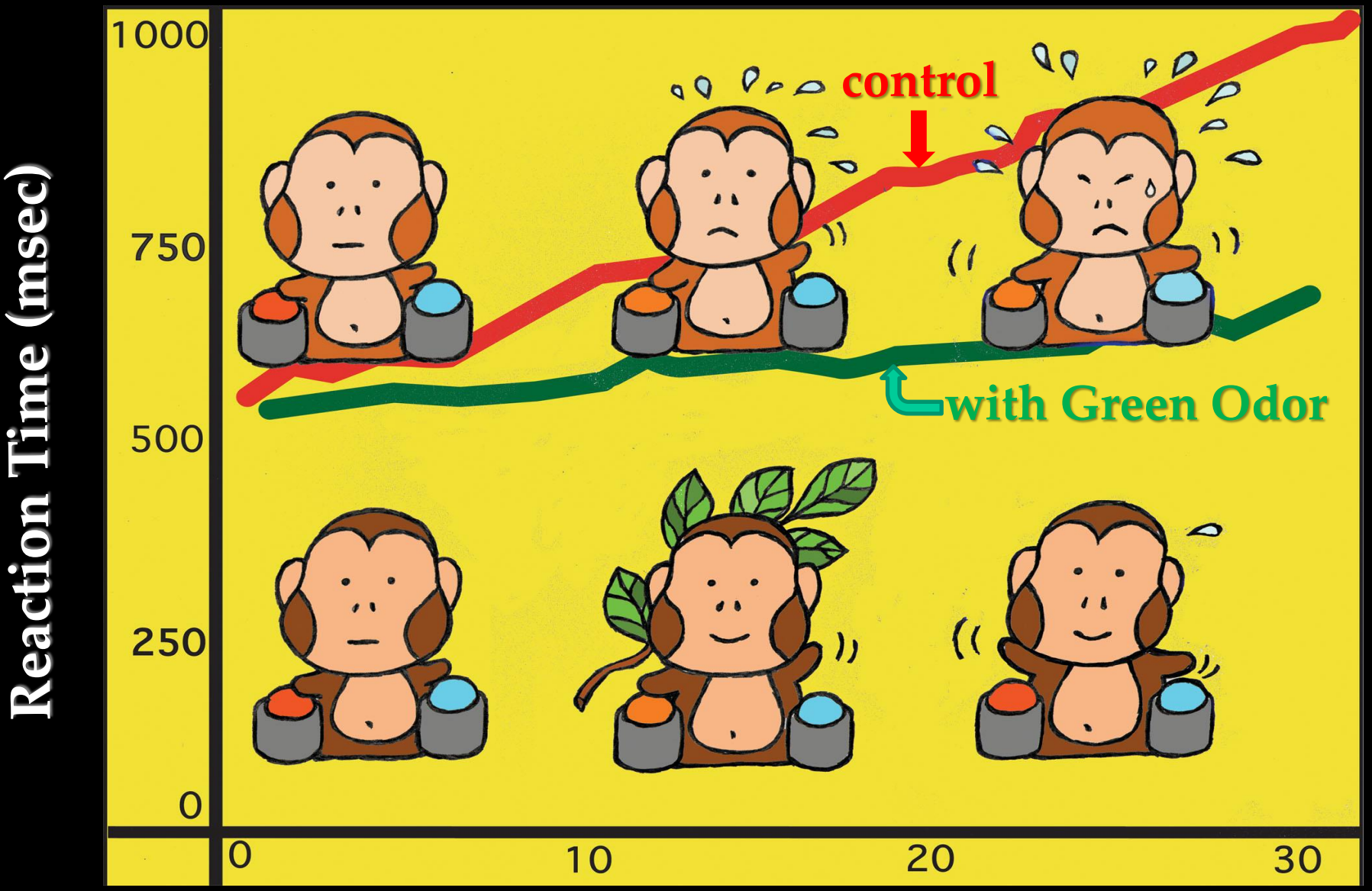
Control

+ Green Odor

Control

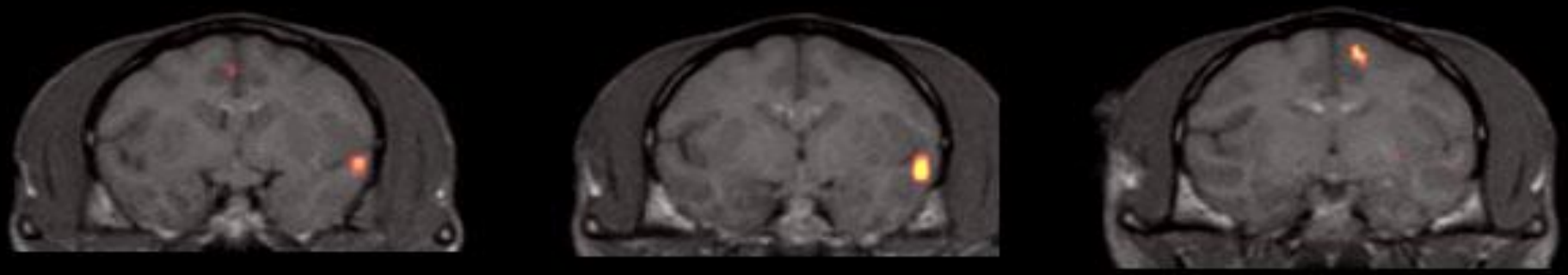
+ Green Odor

Change of Reaction Time during Simple Task by Mokeys
サル単純課題遂行の反応時間の推移



Activation by Green odor(s) in Anterior Cingulate and Dorsolateral Prefrontal Cortices of Monkey Brain: PET study

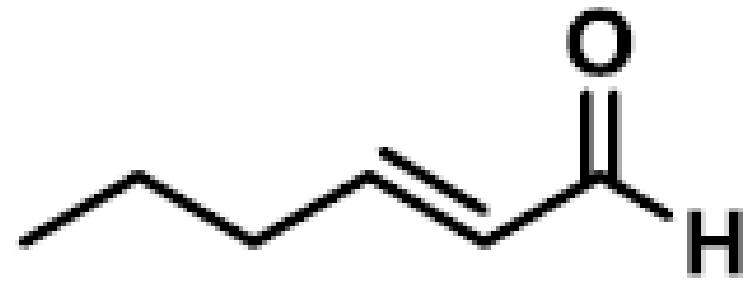
Control (solvent)



Green Odor : Activating frontal and anterior cingulate cortices

Hex-Hex Mix (green odor)

cis-3-Hexenol



trans-2-Hexenal

Sasabe et al., 2003.

Watanabe et al., 2005.

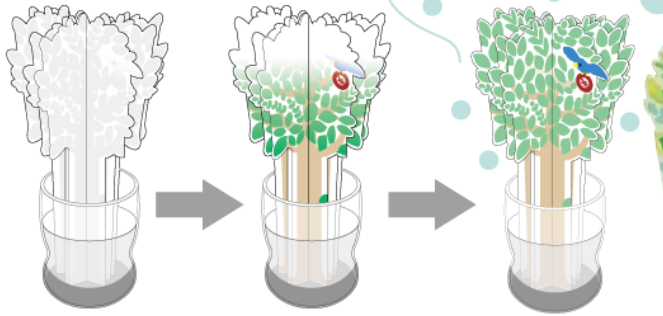
New product derived from collaboration

Japan Preventive Medicine 日本予防医薬

集中力を高め、ぐったり感を癒す「確か」な香り

「緑林の香り」を簡単に体感

周囲の湿度に合わせて水を吸収して蒸発させる自然気化式のペーパー加湿器です。
電源が不要なので、室内のいろいろな所でお使いいただけます。



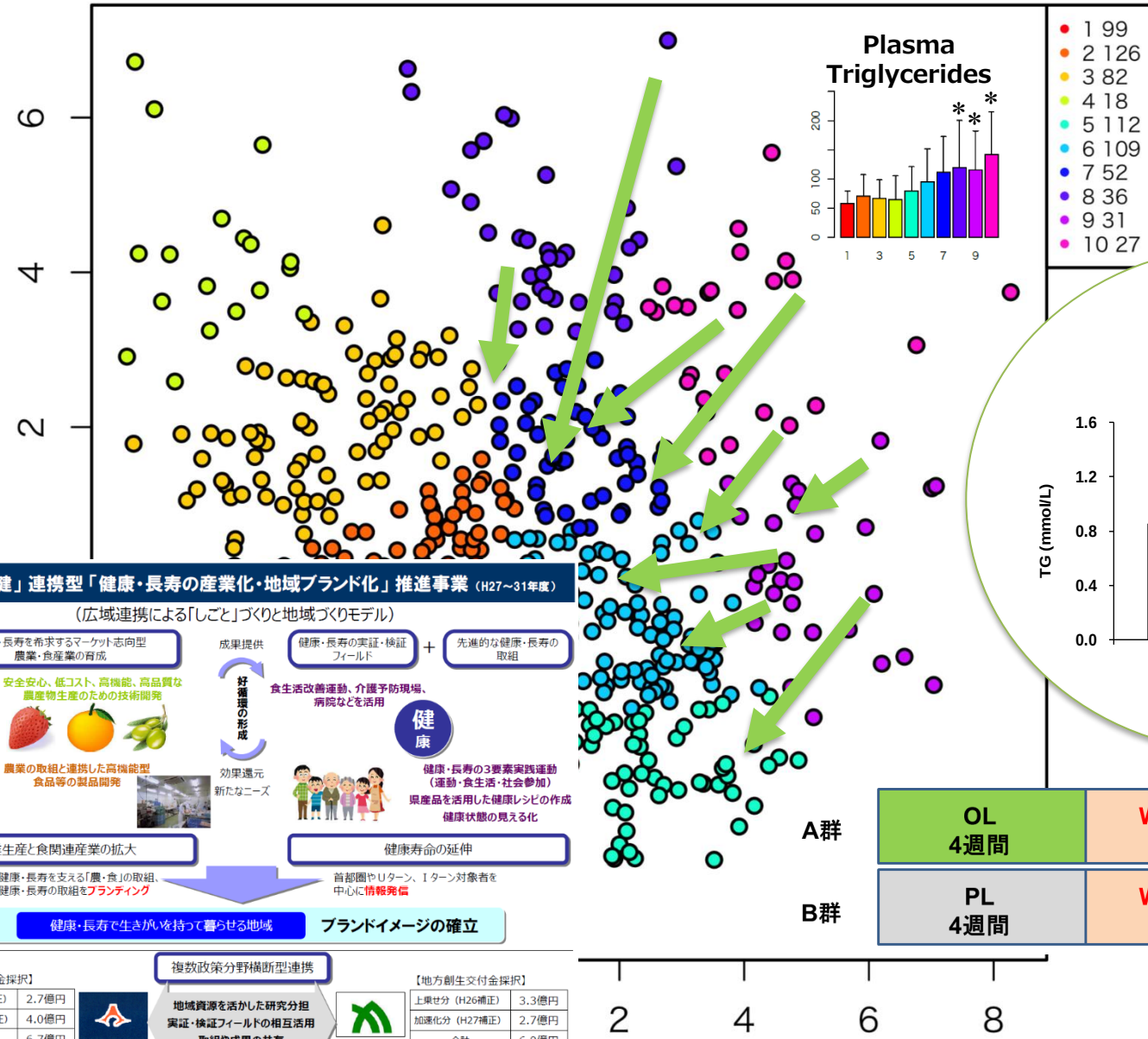
水に緑林の香りエキスを加え、ペーパーディフューザーを挿したら…

水を吸い上げて色づき始め…

緑林の香り成分を発散させながら加湿します。

使用量の目安：水・150ml、緑林の香りエキス・約2.5ml
緑林の香りエキス：水、エタノール、香料、界面活性剤、防腐剤
ペーパーディフューザー使用時サイズ：高さ約21cm×幅約15cm

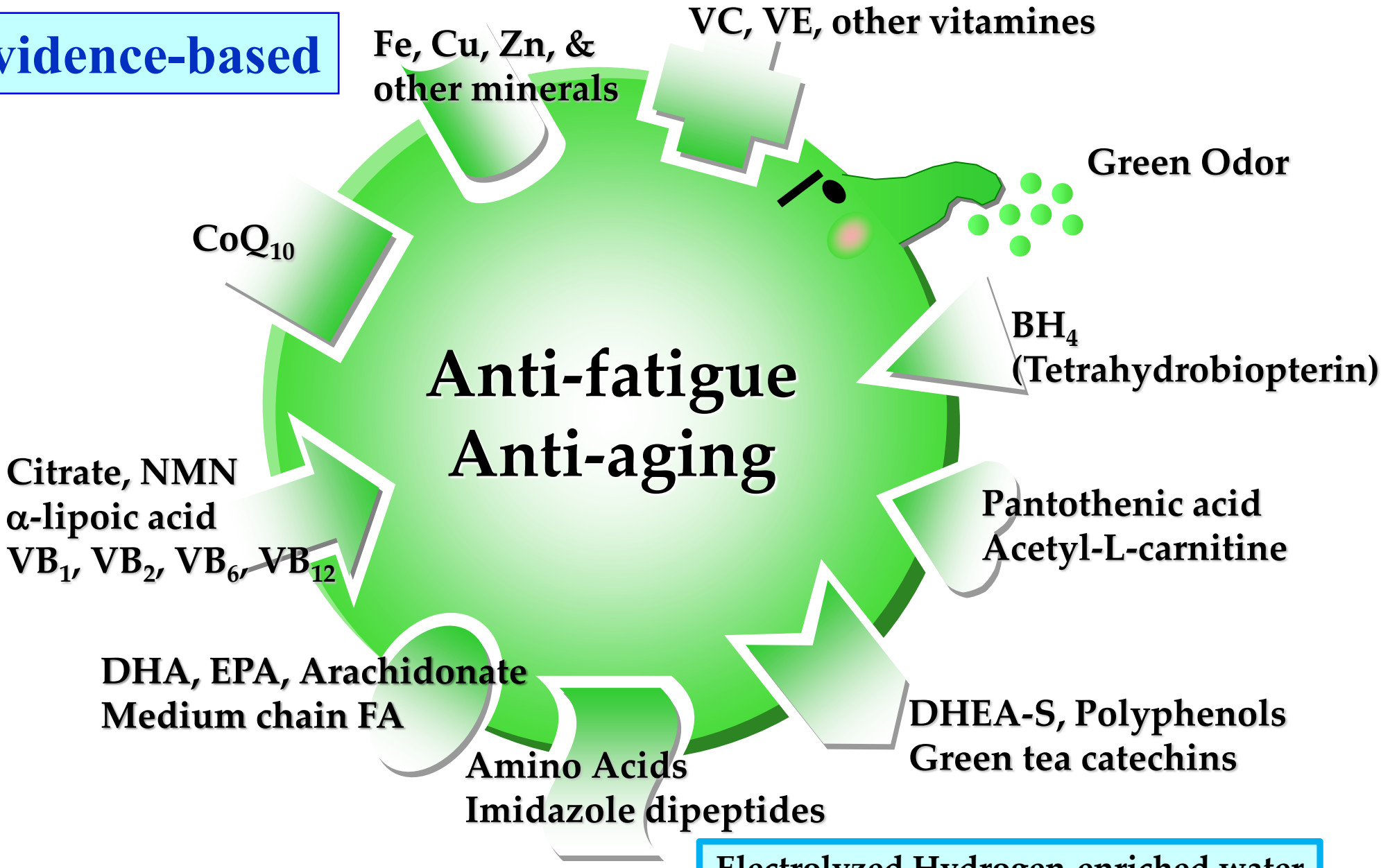
Effects of Olive Oil for individuals



Anti-Fatigue Substances with Evidence

- **Applephenon®** (Polyphenol extract from unripe apples) for Physical Fatigue: *Ataka, S. et al., Nutrition 23:419-423, 2007*
- **Coenzyme Q10** for Physical Fatigue: *Mizuno, K. et al., Nutrition 24: 293-299, 2008*
- **(-)-Epigallocatechin gallate** for Complex Fatigue (an animal model): *Tanaka, M. et al., Nutrition 24: 599-603, 2008*
- CBEX-Dr-containing Drink (**Imidazole dipeptide**) for Physical Fatigue: *Tanaka, M. et al., Jpn Phramacol Ther 36: 199-212, 2008*
- **Crocetin** (a natural carotenoid dicarboxylic acid from crocus flower) for Physical Fatigue: *Mizuma, H. et al., Nutrition Res. in press, 2009*

Evidence-based



in best combination!!

Electrolyzed Hydrogen-enriched water
Rich hydrogen-dissolved water
Carbonated water

Anti-fatigue food book

published in September, 2016

金曜日 6日目

主菜 若鶏のやわらか照り煮

きつね色に焼いた鶏肉に、野菜を加えて甘辛のたれをからめた子どもも喜ぶ疲労回復料理。高タンパク低カロリー、皮はコラーゲンも豊富で女性にもうれしい限り。ごぼうの食感も楽しんで。

材料（2人分）
若鶏むね肉(皮付)…200g
ごぼう…3分本(100g)
にんじん…3分本(100g)
生しいたけ…4枚
きぬさや…10枚(20g)
油…適量
A［片栗粉…大さじ2.5 酒…大さじ1と1/3］
B［水…1カップ しょうゆ…1/3カップ みりん…小さじ4 砂糖…小さじ4 酒…1/4カップ］

作り方
❶鶏肉は1cm幅にそぎ切りにし、Aに10分漬ける。
❷ごぼう、にんじんは乱切りにし、ごぼうは湯がく。
❸しいたけはひと口大に切る。
❹フライパンに油を入れて熱し、①の鶏肉を焼いてとり出す。
❺④のフライパンに②を入れ、よく混ぜ合わせたBを加えて20分煮る。
❻仕上げに鶏肉と③のしいたけときぬさやを入れて5～6分煮る。

ポイント
鶏肉を焼いてから煮ると鶏の脂が出て、しつこさがなくなります。肉のうま味も逃げずに、仕上がりにコクと深みが出ます。

副菜 ほうれん草とうなぎのごま和え

ほうれん草は抗酸化成分カロテン、うなぎは高たんぱく、高カロリーで疲労回復を促すビタミンB1、B2、ごまは神経伝達物質をつくるトリプトファンが豊富。黄金のごま和えで頭と体をリフレッシュ。

材料（2人分）
ほうれん草…1/2束(65g)
うなぎ(かば焼)…1/2枚(30g)
油…小さじ1/2
A［薄口しょうゆ…小さじ1 砂糖…小さじ1 だし汁…小さじ2 ねりごま(白)…30g］

作り方
❶ほうれん草は根元を切って洗い、ゆでて水気を切って5cmの長さに切る。
❷うなぎのかば焼きは1cm角に切る。
❸ボウルにAを入れ、よく混ぜ合わせてから①と②を入れて和える。

ポイント
ほうれん草のような葉野菜は葉と茎では、火の通りが違うので切り分けて時間差でゆがきます。ちょっと硬めの方がいいです。

副菜 わかめのきのこ炒め

ビタミン、ミネラルたっぷりの元気回復料理。わかめとしめじはビタミンB2、いたけはビタミンB1が豊富。B1の吸収を助けるねぎも加わり、代謝を高めて活力をアップし、ストレスの改善を。

材料（2人分）
わかめ(刺身用)…40g
しめじ…1/2パック(60g)
生しいたけ…2枚(20g)
白ねぎ…1/3本(30g)
油…小さじ1/2
A［しょうゆ…小さじ2と2/3 みりん…小さじ2と2/3 酒…小さじ2と2/3 こしょう…少々］

作り方
❶わかめはひと口大に切る。
❷しめじはほぐす。
❸しいたけは石づきをとって薄切りにする。白ねぎは斜めに5mm幅に切る。
❹フライパンに油を入れて熱し、①②③を炒め、混ぜ合わせたAで味つけする。

ポイント
わかめはきのこと相性もよく、より栄養が多く摂れます。わかめは洗いすぎないでおくと、手早く炒められ歯ごたえがよくおいしい。

土曜日 14日目

主菜 豚肉のピカタ

豚肉にチーズと卵をつけて焼いた、やわらかくておいしいひと皿。ビタミンB1を含む豚肉、神経や脳の働きをサポートするテロシンを含むチーズ、栄養の宝庫、卵とのベストマッチで脳も全開。

材料（2人分）
豚ロース(厚カツ用)…200g
卵…2個
粉チーズ…14g
カレー粉…少々
塩…少々
こしょう…少々
油…小さじ2/3

作り方
❶豚肉は塩とこしょうをふる。
❷フライパンに油を入れて熱し、①の豚肉の片面をこんがり焼いたら、裏返して同様に焼いて火を通す。
❸ボウルに卵を割り入れて溶き、粉チーズとカレー粉を加え、よく混ぜ合わせる。
❹②の豚肉に③をからめて、フライパンでさらに軽く焼く。同様にしながら③がなくなるまで繰り返す。

ポイント
豚肉にチーズと卵をつけて焼いた、やわらかくて子どもにも人気のおかず。豚肉と神経や脳の働きを助けるテロシンを含むチーズ、栄養の宝庫、卵とのベストマッチは頭も身体もホットに。

副菜 きぬさやとちくわの彩り炒め

抗酸化作用を持つきぬさやは、ビタミンB1も豊富。ビタミンB1の吸収をよくする玉ねぎと 魚のたんぱく質を含むちくわを組み合わせた料理で、頭と身体も活発に。お弁当のおかずにもぴったり。

材料（2人分）
絹さや…30枚(60g)
玉ねぎ…小1/4(40g)
ちくわ…1本(40g)
ごま油…適量
A［しょうゆ…小さじ1 みりん…小さじ1 酒…小さじ1］

作り方
❶絹さやは筋をとり除き、縦に半分に切り、玉ねぎはくし切りにする。
❷ちくわは長さ5cmの棒状に切る。
❸フライパンにごま油を入れて熱し、①と②を炒める。
❹混ぜ合わせたAで③を和える。

ポイント
しょうゆ、みりん、酒など、合わせ調味料の割合を覚えておくと炒め物や和え物、煮物などに応えて便利です。料理もらくに。

副菜 桜えびのクルミ炊き

材料のハーモニーが見事。抗酸化作用を持つ桜えび、体内でDHAやEPAに変換されるαリノレン酸を含むクルミ、ナイアシンを含むじゃこが三位一体でストレスをブロックし、頭もシャープに。

材料（2人分）
板麩…60g
じゃこ…10g
クルミ…40g
しょうが…1/2かけ
A［薄口しょうゆ…小さじ2 みりん…大さじ1と1/3 砂糖…小さじ1と2/3 酒…大さじ1と1/3］

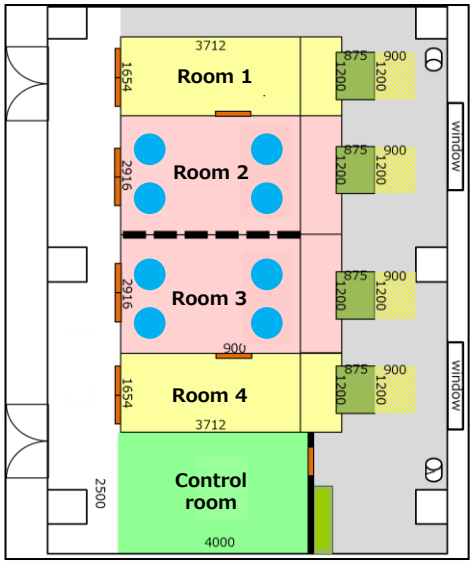
作り方
❶クルミは食べやすい大きさに割る。
❷しょうがはせん切りにする。
❸鍋にAを入れて煮たたせ、桜えび、じゃこ、①のクルミを加え、水分がなくなるまで煮る。

ポイント
材料を合わせて火にかけるだけの料理ですが、絶えず混ぜながら火を通して全体をからめるように仕上げるのがコツです。

RIKEN BDR-DAIKIN Collaboration Center
Fatigue and Hygrothermal Environment

RIKEN BDR RIKEN Center for Biosystems Dynamics Research

Experimental rooms



Experiments

Summer exp.
24, 26, 28, 30 [℃]
40, 55, 70 [%RH]

Winter exp.
20, 22, 24, 26 [℃]
30, 50, 70 [%RH]

Summer res.

30℃×70%RH = bad
30℃×50%RH = good
30℃×30%RH = good
Key is humidity control!!

Winter res.

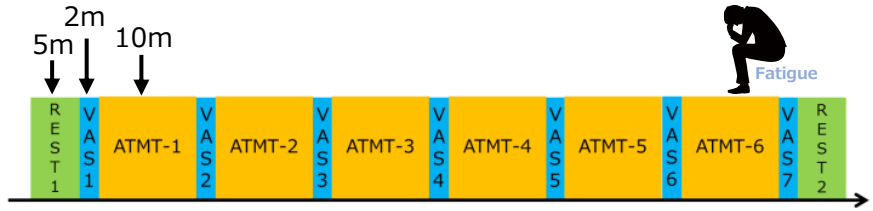
Best condition
Female =
22℃×50%RH
Male =
20℃×30%RH
20℃×50%RH
Sex differences!!

Achievement

Patent (2019-207611)

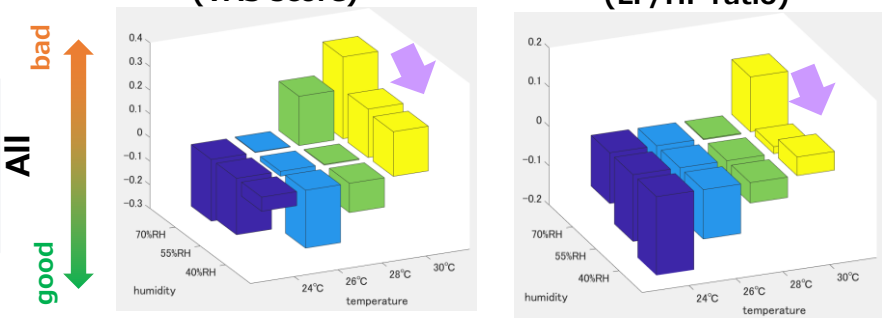
ECG record (wireless type)

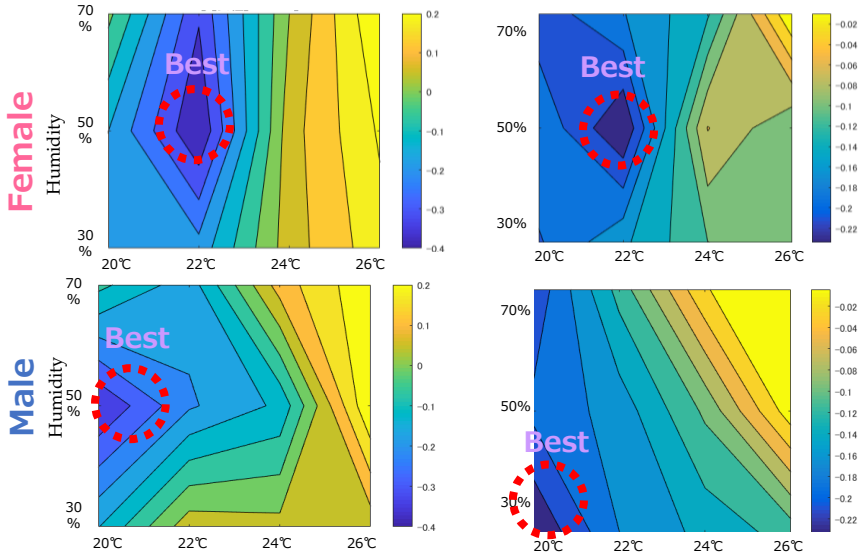
Fatigue-inducing cognitive task for 60 min



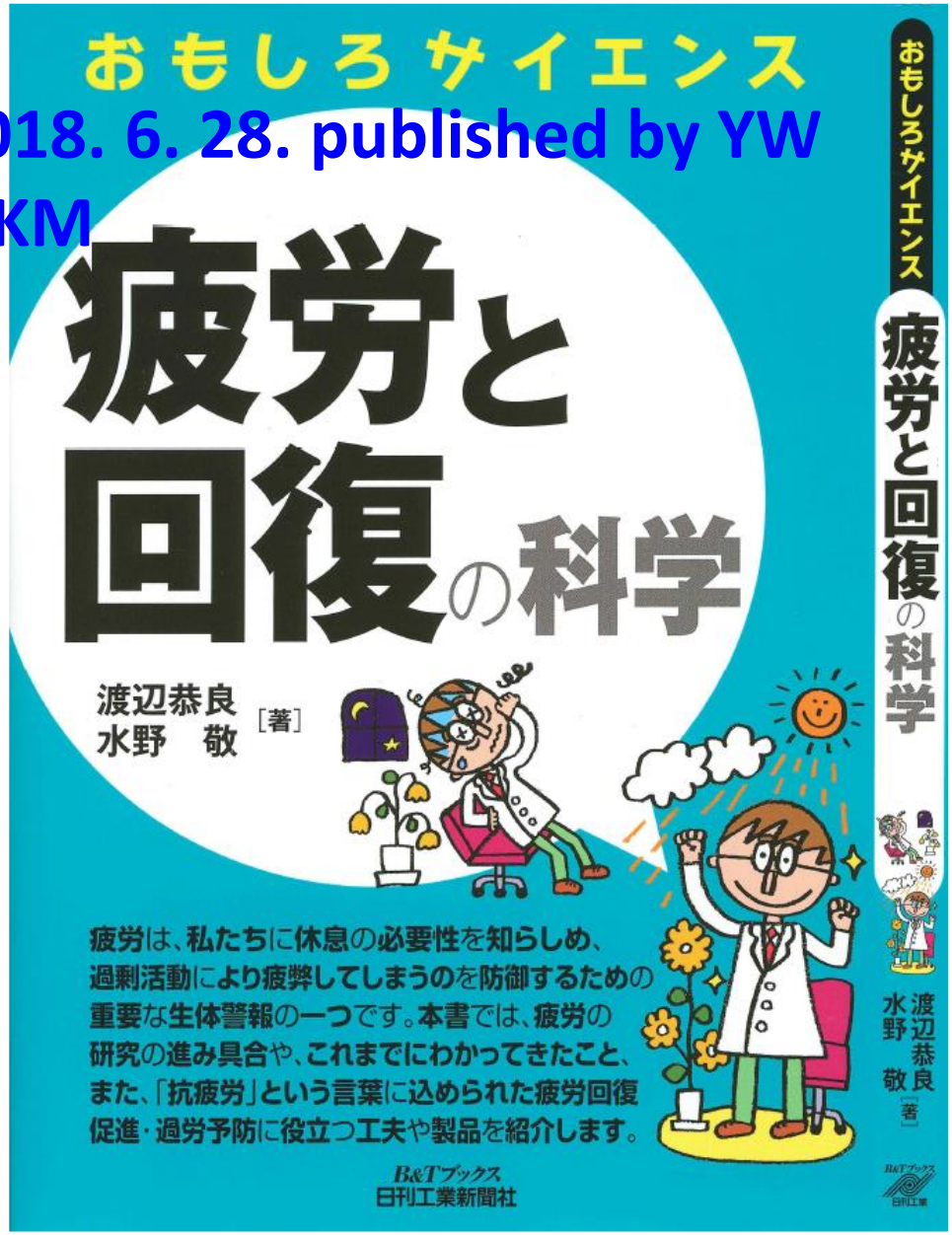
Mental fatigue (VAS score)

Sympathetic nerve activity (LF/HF ratio)





Thank you for your attention!! Wishing your better health!!



2018. 6. 28. published by YW &KM

2021. 6. 17. published Edited by Drs. Masaaki Sugino & Hideki Katano