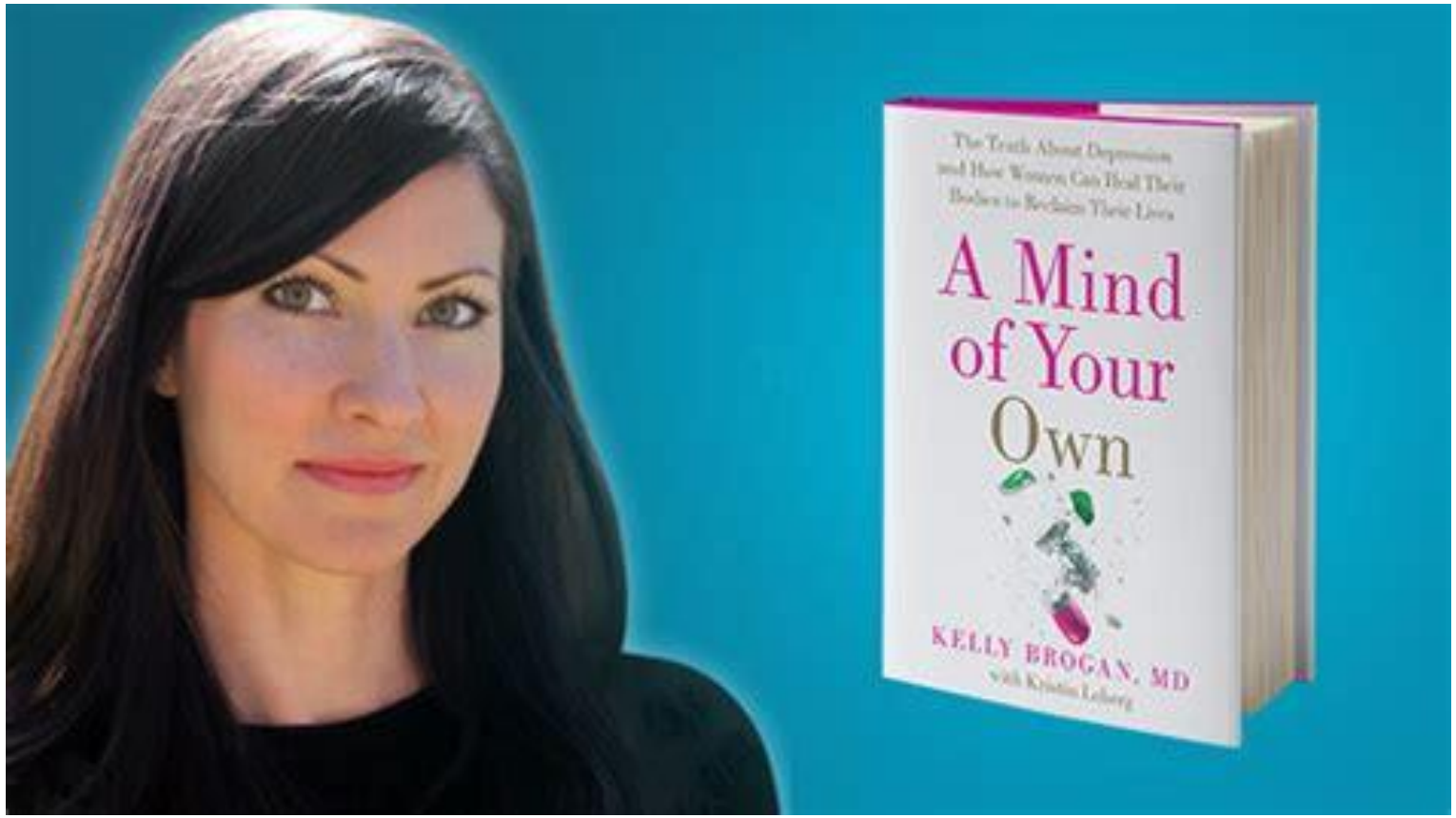
カイロプラクターのための栄養学
第Ⅶ期　第2回
うつ、不安障害

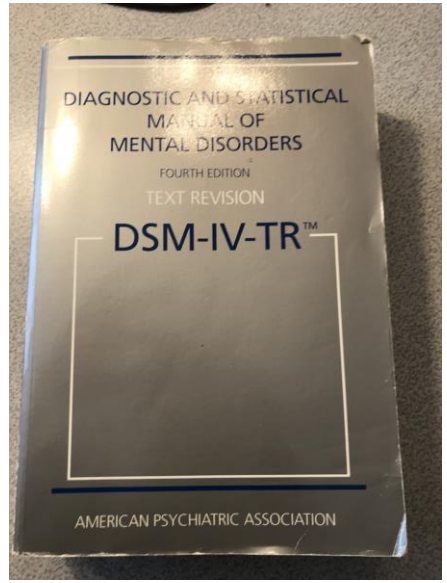
Hiro Izumi, DC

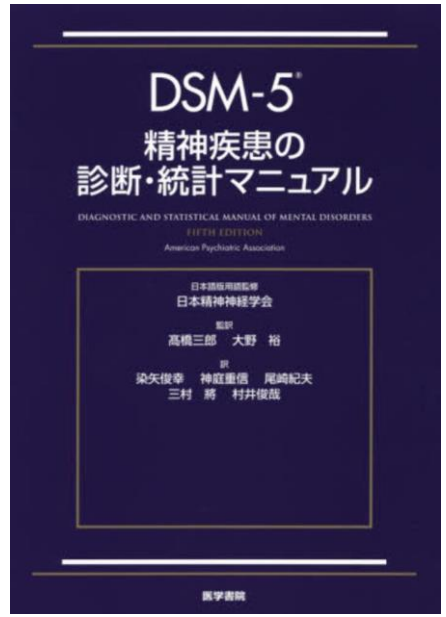
Kelly Brogan, MD



DSM-IV　DSM-5

- DSMとは、アメリカ精神医学会が出版している、精神疾患の診断基準・診断分類です。正式名称は「精神疾患の診断・統計マニュアルDiagnostic and Statistical Manual of Mental Disorders）」と言い、その頭文字を略してDSMと呼びます
- DSMは、精神医学の研究や治療を行っている人に、精神疾患の基本的な定義などを示したものです。元々はアメリカでつくられたものですが、現在は国際的に利用されていて、日本でも精神疾患の診断に用いられています





うつ病診断基準

以下の症状のうち、少なくとも1つある

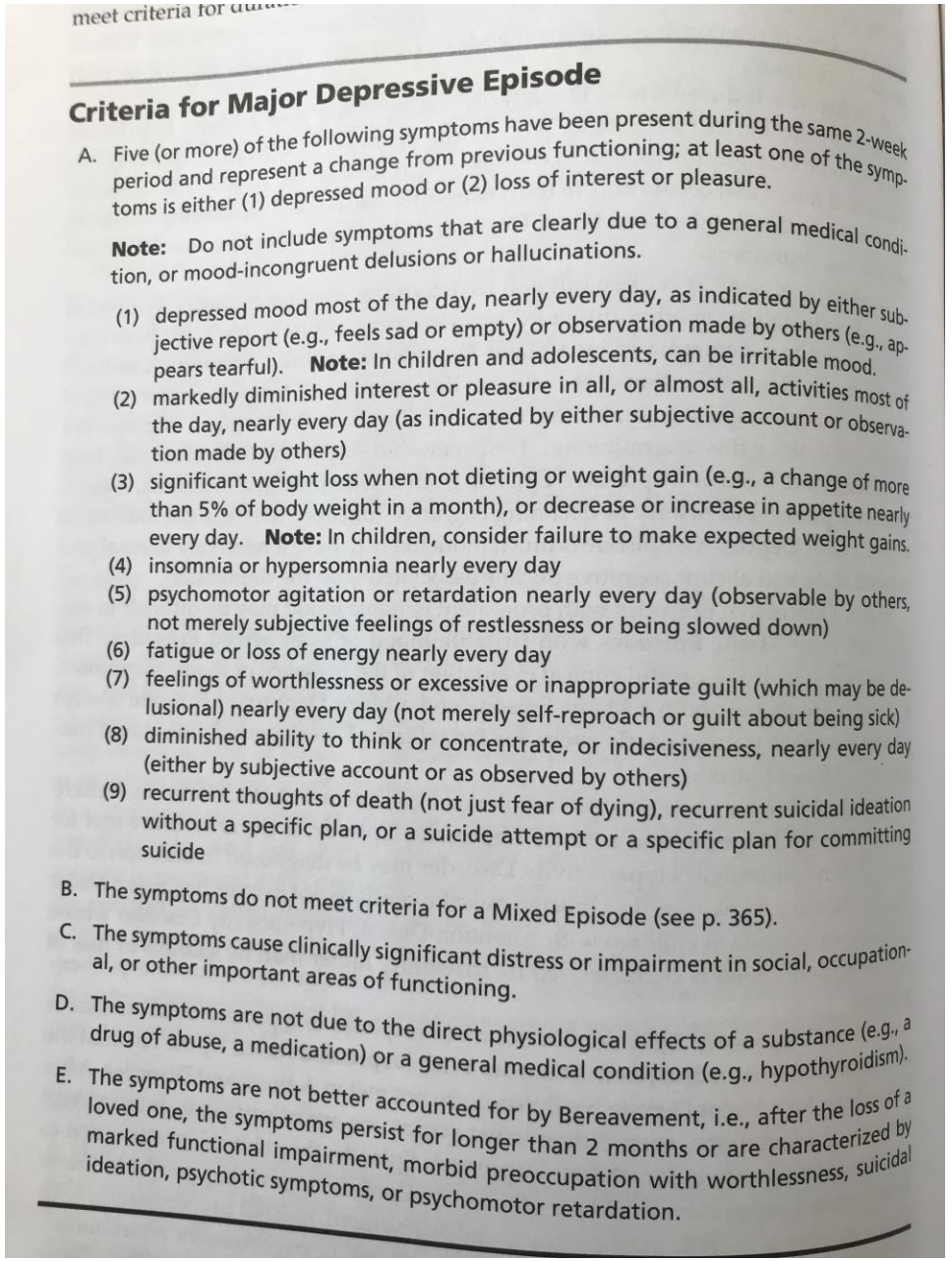
1. 抑うつ気分
2. 興味または喜びの喪失

さらに、以下の症状を併せて、合計で5つ以上が認められる

3. 食欲の減退あるいは増加、体重の減少あるいは増加
4. 不眠あるいは睡眠過多
5. 精神運動性の焦燥または制止(沈滞)
6. 易疲労感または気力の減退
7. 無価値感または過剰(不適切)な罪責感
8. 思考力や集中力の減退または決断困難
9. 死についての反復思考、自殺念慮、自殺企図

うつ病診断基準

- 上記症状がほとんど１日中、ほとんど毎日あり、２週間にわたっている症状のために、著しい苦痛または社会的、職業的、または他の重要な領域における機能障害を引き起こしている。これらの症状は、一般身体疾患や物質依存(薬物またはアルコールなど)では説明できない



meet criteria for

Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
(4) insomnia or hypersomnia nearly every day
(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
(6) fatigue or loss of energy nearly every day
(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode (see p. 365).

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

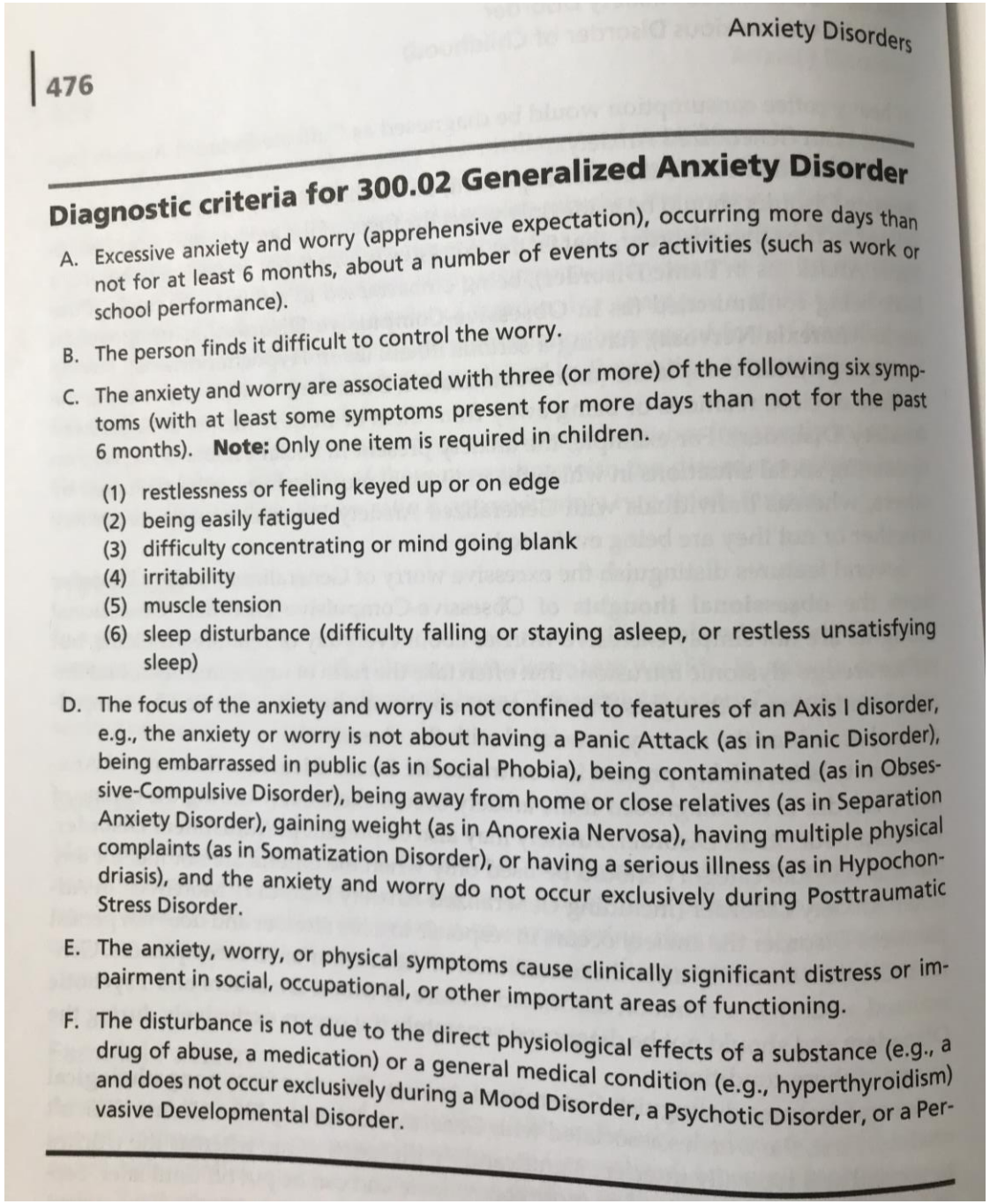
E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

不安障害

- いろいろな要素が原因になっている、生い立ち、虐待、栄養状態、持病、金銭問題、人間関係など

不安障害

- 過剰な不安や心配がある
- 不安や心配がコントロールできない
- 精神症状や身体症状がある
- 苦痛や生活への支障がある
- 他の病気や物質のせいではない



Diagnostic criteria for 300.02 Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). **Note:** Only one item is required in children.

(1) restlessness or feeling keyed up or on edge
(2) being easily fatigued
(3) difficulty concentrating or mind going blank
(4) irritability
(5) muscle tension
(6) sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a Panic Attack (as in Panic Disorder), being embarrassed in public (as in Social Phobia), being contaminated (as in Obsessive-Compulsive Disorder), being away from home or close relatives (as in Separation Anxiety Disorder), gaining weight (as in Anorexia Nervosa), having multiple physical complaints (as in Somatization Disorder), or having a serious illness (as in Hypochondriasis), and the anxiety and worry do not occur exclusively during Posttraumatic Stress Disorder.

E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder.

一般的治療のアプローチ

- 心理療法　精神療法
  - 物理的また化学的手段に拠らず、教示、対話、訓練を通して行う治療法
- 心療内科、精神科の治療
  - 西洋医学
  - 主に薬を使う治療

抗うつ薬

- SSRI（選択的セロトニン再取り込み阻害薬）
  - シナプスにおけるセロトニンの再吸収に作用する
- MAOI（モノアミン酸化酵素阻害薬）
  - モノアミン酸化酵素の働きを阻害することによって、脳内の主なモノアミン神経伝達物質であるドーパミンやセロトニン、アドレナリンのような物質を分解されないようにする薬剤の総称

抗不安薬

- ベンゾジアゼピン、バルビツール
  - GABAの働きを促す
  - 中枢神経系の働きを抑制する
  - 過剰服用は危険、耐性、依存性が高い
- SSRI
  - シナプスにおけるセロトニンの再吸収に作用する
  - 抗不安薬としても使用される

SSRIの副作用

- 体重増加
- 暴力的になる
- 自殺
- 血糖値の問題
- 片頭痛
- 性欲減退
- うつ

ノセボ効果

- フルオキセチン（SSRI）を使って、ノセボ効果を調べる実験が行われた。
- 最初の3か月は全員薬を摂取していた
- その後、半分のグループは薬を摂取し、残りの半分は偽薬を摂取
- 全員自分がどちらのグループに属しているかは知らされていない
- 結果は所属グループ関係なしに、全員うつ症状が同レベルに悪化した

The role of patient expectancy in placebo and nocebo effects in antidepressant trials

DOI: 10.4088/JCP.13m08797

うつ、不安障害は病気？？？

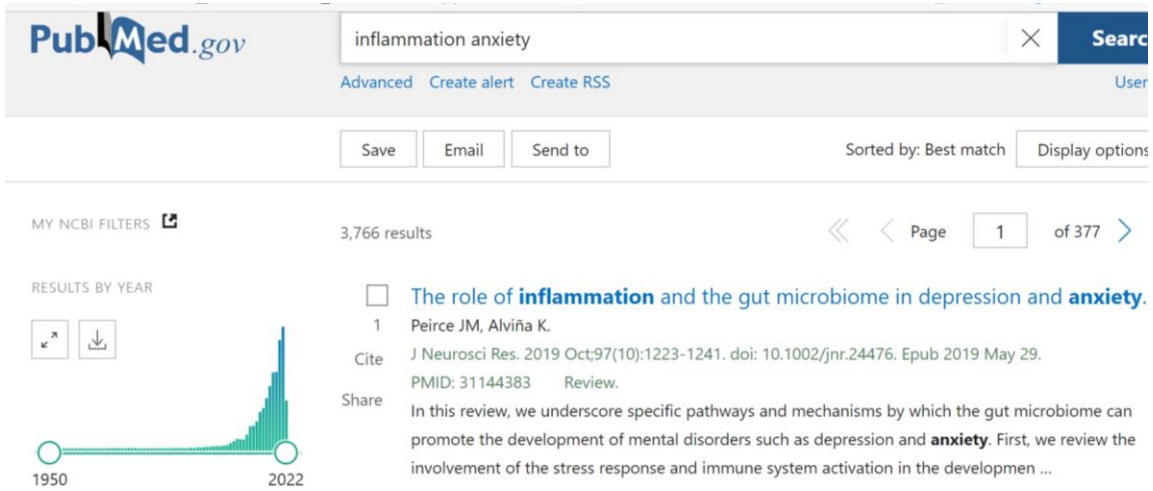
- 脳内のケミカルバランスが、うつや不安障害の原因であることを示す証拠はどこにもない
- 診断基準は極めて主観的であり、客観的検査に基づかない
- ＳＳＲＩの長期使用が有効であるという研究結果はない、むしろ
- 「１００ほどある脳内伝達物質の中から１つだけを選び出し、それを操作することで、すべての精神疾患を治癒できると考えることは、あまりにも馬鹿げている」 Dr. Daniel Carlat

うつのような、不安障害のような症状

- 炎症モデルのうつ、不安障害
- 脳は痛みを感じないため、炎症が起きていても見逃されることが多い
- 炎症マーカーが高い（CRPなど）場合、抗うつ剤よりも抗炎症薬の方が効き目がある、クルクミンがうつに有効なのもこれで説明がつく

うつ、不安障害に炎症が関係していることを示唆する文献は多数ある

- **Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study** PMID: 23760347
- **So depression is an inflammatory disease, but where does the inflammation come from?** PMID: 24228900
- **Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression** PMID: 19150053



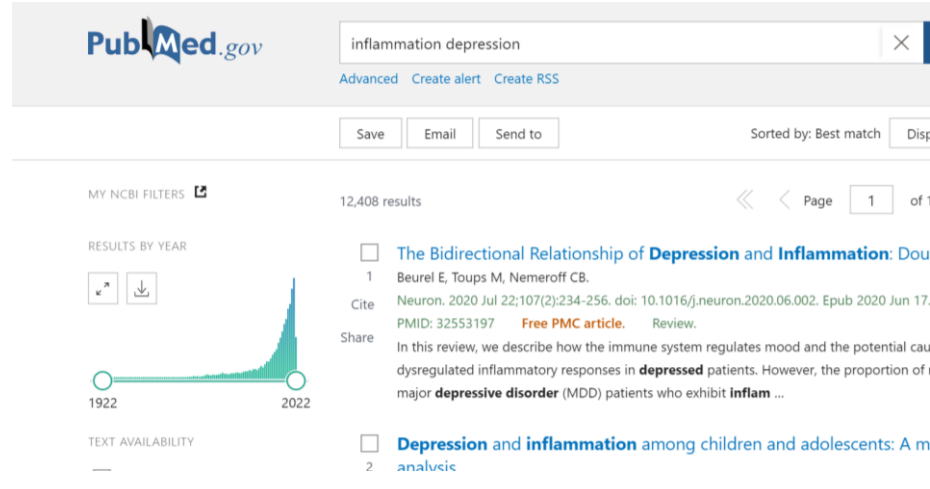
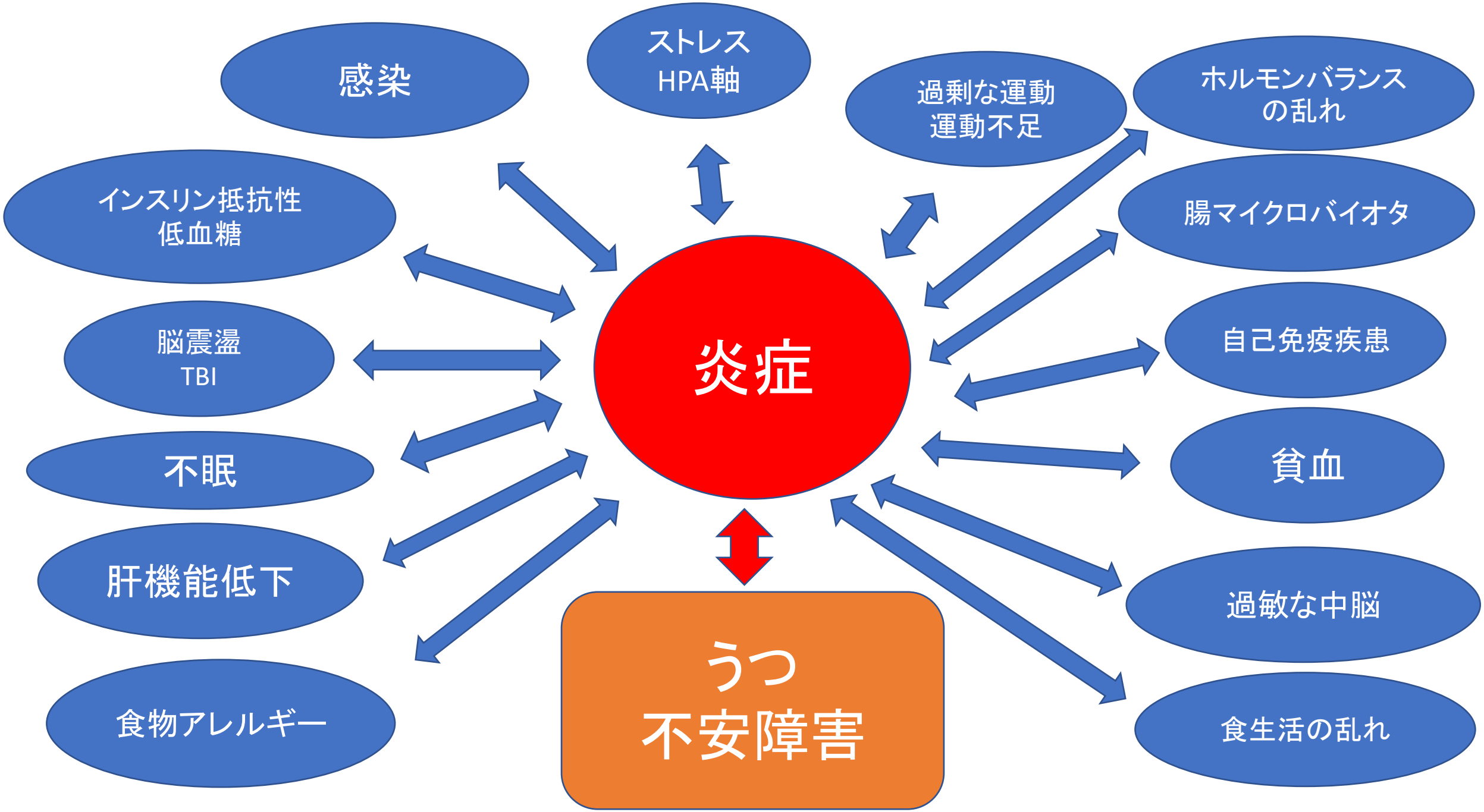


Table 1
Clinical and preclinical evidence for the antidepressant and anxiolytic properties associated with targeting the gut microbiota (modified from reference (Sherwin et al., 2016)).

	Behavioural outcomes	Physiological outcomes	References
Clinical evidence			
B-GOS	Increased cognitive processing of positive versus negative attentional vigilance	Reduced cortisol awakening response	(Schmidt et al., 2015)
Lactobacillus casei strain Shirota	Reduced anxiety scores in patients with chronic fatigue syndrome	Increased numbers of *Lactobacillus* and *Bifidobacterium* in faecal samples	(Rao et al., 2009)
	Improved mood in individuals with a low mood prior to taking the probiotic	NA	(Benton et al., 2007)
Probiotic formulation: *Lactobacillus helveticus* and *Bifidobacterium longum*	Reduced psychological distress as measured by the HADS	Reduced 24-h UFC levels	(Messaoudi et al., 2011a)
Multispecies probiotic formulation: *Lactobacillus* and *Bifidobacterium* species	Reduced cognitive processing of sad mood; decreased aggressive feelings and rumination	NA	(Steenbergen et al., 2015)
Preclinical evidence			
Prebiotic- FOS and GOS	Antidepressant and anxiolytic-like effects in adult mice. Reversed the behavioural effects of chronic psychosocial stress in mice.	Increased BDNF, NR1 and NR2A mRNA, and protein expression in the dentate gyrus and frontal cortex Reduced acute and chronic stress-induced corticosterone release. Modified specific gene expression in the hippocampus and hypothalamus. Reduced chronic stress-induced elevations in pro-inflammatory cytokines levels	(Savignac et al., 2013; Burokas et al., 2017)
Prebiotic- 3'Sialyllactose and 6'sialyllactose	Anxiolytic effect in mice exposed to SDR	Prevented SDR-mediated reduction in the number of immature neurons	(Tarr et al., 2015)
Prebiotic- GOS & polydextrose with lactoferrin (Lf) and milk fat globule membrane	Reduced immobility time of maternally separated rats in a forced swim test	Improves NREM Sleep, Enhance REM Sleep Rebound and Attenuate the Stress-Induced Decrease in Diurnal Temperature	(Thompson et al., 2016)
Bifidobacterium infantis		Attenuated exaggerated IL-6 response in maternally separated rats following concanavalin A stimulation	(Desbonnet et al., 2010)
Bifidobacterium breve	Improved depressive and anxiety-related behaviours in mice	No effect upon circulating corticosterone	(Savignac et al., 2014)
Bifidobacterium longum	Anxiolytic effect in step-down inhibitory avoidance	Anxiolytic effect mediated via the vagus nerve	(Bercik et al., 2011b)
Lactobacillus plantarum PS128	Reduced immobility time and increased sucrose preference in ELS mice	Decreased basal and stress-induced circulating corticosterone levels; attenuated circulating TNF-α and IL-6 levels while increasing IL-10 levels in ELS mice	(Liu et al., 2016b)
Lactobacillus rhamnosus	Reduced immobility time in the forced swim test Decreased stress-induced anxiety-like behaviour	Decreased stress-induced circulating corticosterone secretion and altered central GABA receptor subunit expression Attenuated chronic stress-related activation of dendritic cells while increasing IL-10 + regulatory T cells	(Bravo et al., 2011) (Bharwani et al., 2017)
Lactobacillus fermentum NS9	Reduced ampicillin-induced anxiety behaviour	Decreased ampicillin-induced corticosterone secretion and increased hippocampal mineralocorticoid receptor and NMDA receptor levels	(Wang et al., 2015)
Butyric acid	Reduced immobility time in Flinders sensitive line rats exposed to a forced swim test	Increased BDNF expression within the prefrontal cortex	(Wei et al., 2014)

Abbreviations used in Table 1. BDNF brain-derived neurotrophic factor, *ELS* early life stress–exposed, *FOS* fructo-oligosaccharide, *GABA* γ-aminobutyric acid, *GOS* galacto-oligosaccharide, *HADS* Hospital Anxiety and Depression Scale, *IL* interleukin, *mRNA* messenger RNA, *NA* not assessed, *NMDA* *N*-methyl-d-aspartate, *SDR* social disruption stress, *TNF* tumour necrosis factor, *UFC* urinary free cortisol, *NR* NMDA Receptor.


感染
ストレス
HPA軸
過剰な運動
運動不足
ホルモンバランス
の乱れ
インスリン抵抗性
低血糖
腸マイクロバイオタ
脳震盪
TBI
炎症
自己免疫疾患
不眠
貧血
肝機能低下
過敏な中脳
うつ
不安障害
食物アレルギー
食生活の乱れ

リポポリサッカライドという爆弾

- リポポリサッカライドは腸内細菌を胆汁や消化酵素から守っている
- リポポリサッカライドは細菌同志のコミュニケーションのために不可欠な物質
- しかし、体内にリポポリサッカライドが侵入した場合は、極度な炎症を引き起こす
- リーキーガットがあると、リポポリサッカライドが腸壁を通って体内に侵入する
- リポポリサッカライドはブラッド ブレイン バリア（BBB)を破壊し、脳内に炎症を引き起こす

Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression PMID: 19150053

うつ⇒炎症⇒うつ

もしくは

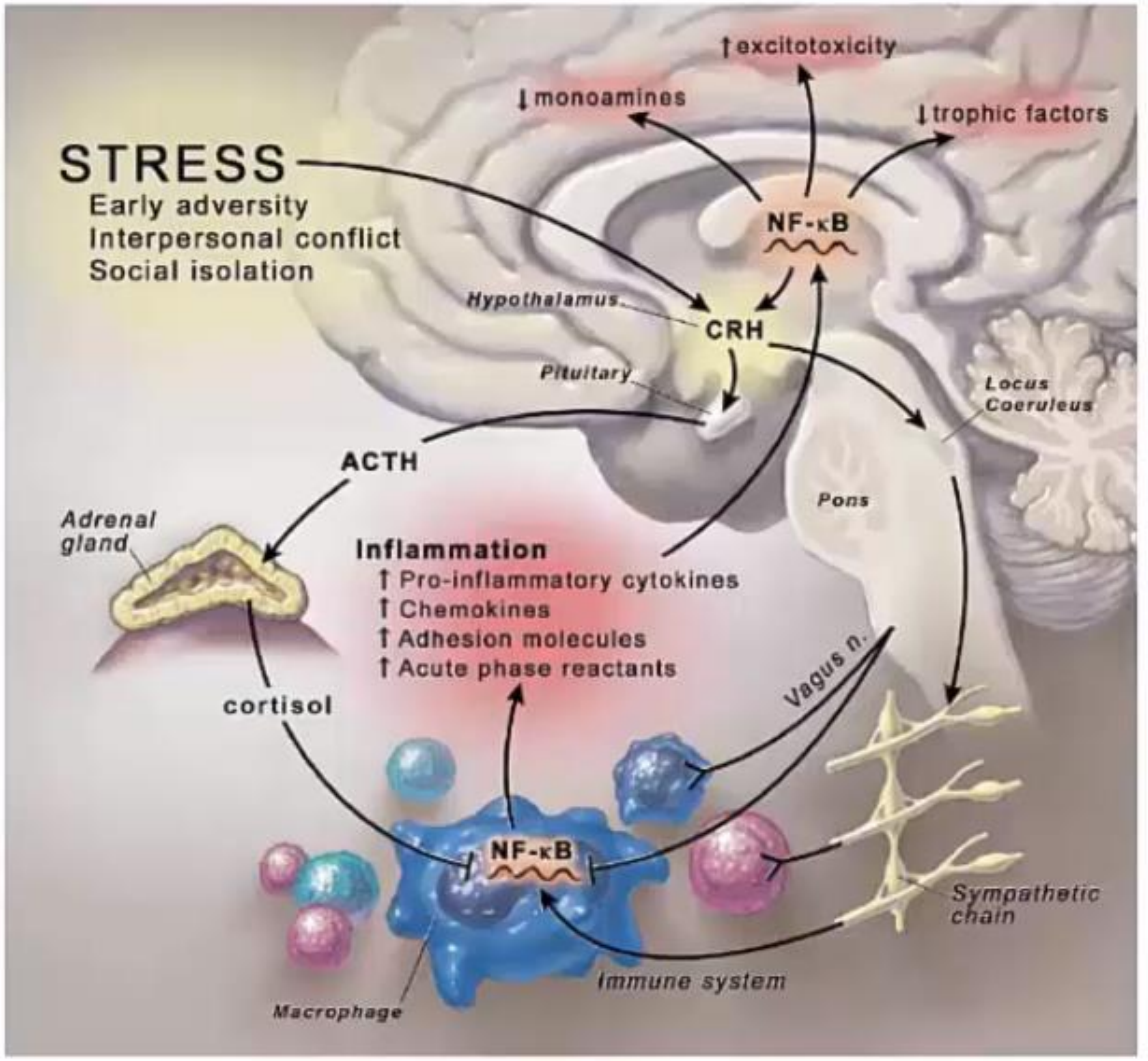
炎症⇒うつ⇒炎症

「ただ単にうつ」であるというのは、基本的にはあり得ない

もしも「ただ単にうつ」であったとしても、やがて脳炎症が始まるのは時間の問題である

Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression

Biol Psychiatry. 2009 May 1;65(9):732-41. Miller AH, Maletic V, Raison CL.



右脳と左脳

左脳

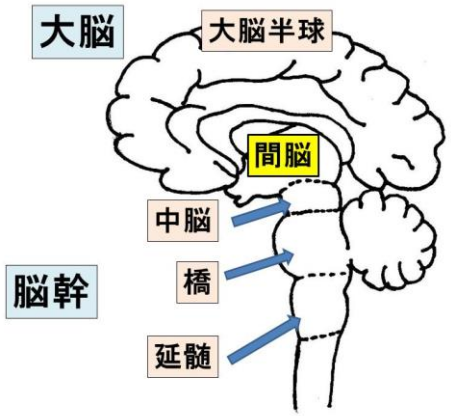
- 話す
- 書く
- 読む
- 分析力
- 理論的
- 数学的理解

右脳

- ひらめき
- 身体感覚
- 空間の把握
- 芸術性
- 音楽性
- 表情の認識
- 自律神経のバランス

脳幹

- 脳幹内の網様体が自律神経のコントロールに深く関係している
- 網様体
  - MRF（Mesencephalic Reticular Formation)
  - 脳幹の上部1/3（中脳）
    - 交感神経の働きを促す
  - PMRF(pontmedullary Reticular Formation)
  - 脳幹の下部2/3 (橋、延髄）
    - 副交感神経の働きを促す、交感神経の働きを抑制する



- ストレス（特に目と耳からの刺激）で中脳が反応する
  - 危険な状態から身を守る仕組み、しかし過剰な刺激は中脳の働きを過剰／高効率に働かせてしまい、結果慢性的な交感神経優勢にさせてしまう

The Role of Spinal GABAergic Circuits in the Control of Phrenic Nerve Motor Output

Am J Physiol Regul Integr Comp Physiol. 2015 Jun 1;308(11):R916-26. Marchenko V, Ghali MG, et al.

"While supraspinal mechanisms underlying respiratory pattern formation are well characterized, the contribution of spinal circuitry to the same remains poorly understood. In this study, we tested the hypothesis that intraspinal GABAergic circuits are involved in shaping phrenic motor output. To this end, we performed bilateral phrenic nerve recordings in anesthetized adult rats and observed neurogram changes **in response to knocking down expression of both isoforms (65 and 67 kDa) of glutamate decarboxylase (GAD65/67) using microinjections of anti-GAD65/67 short-interference RNA (siRNA) in the phrenic nucleus.** The number of GAD65/67-positive cells was drastically reduced on the side of siRNA microinjections, especially in the lateral aspects of Rexed's laminae VII and IX in the ventral horn of cervical segment C4, but not contralateral to microinjections. We hypothesize that intraspinal GABAergic control of phrenic output is primarily phasic, but also plays an important role in tonic regulation of phrenic discharge. Also, we identified respiration-modulated GABAergic interneurons (both inspiratory and expiratory) located slightly dorsal to the phrenic nucleus. **Our data provide the first direct evidence for the existence of intraspinal GABAergic circuits contributing to the formation of phrenic output.** The physiological role of local intraspinal inhibition, independent of descending direct bulbospinal control, is discussed."

↓ GABA (GAD65 ab's or other) → ↓ Respiratory Volume
→ ↓ O2 → ↑ HIF1α → ↑ NFkB → ↑ Inflammation

健全な脳神経機能の必須条件

- 安定したブドウ糖の供給
  - インスリン抵抗性
  - 糖代謝改善
  - ケトジェニック ダイエット
  - ケトン体サポート（MCT Oil）
- 安定した酸素の供給
  - 血圧の正常化
  - 血流促進（Ginkgo，HuperzineA、運動）
  - 自律神経バランス改善
- 刺激
  - 運動
  - 脳トレ