Study Guide 6

This guide covers chapters 11 and 12. First you learn to read research fairly: name the design, hunt for bias and confounding, separate the placebo response from a specific effect, turn results into absolute differences and NNTs, read a confidence interval against the MCID, and judge a review with GRADE. Then you learn the machinery of stress: the fast sympathetic arm and the slow HPA axis, cortisol and its rhythm, the two autonomic divisions and their receptors, allostatic load, heart rate variability and how stress turns pain down or up. Do every calculation in the worked cases yourself, then try the ten board style self-test items for each chapter.

WHAT THIS GUIDE COVERS

- Chapter 11 · experimental versus observational designs, RCT variations, cohort, case control, case crossover and cross-sectional studies, the evidence pyramid, PICO, selection, information and attrition bias, blinding, intention to treat, confounding, regression to the mean, placebo, nocebo and contextual effects, shams, ARR, RRR, NNT, odds ratios, effect sizes, MCID, p values, power, confidence intervals, systematic reviews, forest and funnel plots, heterogeneity, GRADE, guidelines and the evidence for manipulation, acupuncture, massage, yoga, tai chi, mindfulness, herbs and homeopathy.
- Chapter 12 · stressors and the stress response, Cannon and Selye, the sympathetic adrenal medullary arm, the HPA axis, cortisol actions and rhythm, the sympathetic and parasympathetic divisions, neurotransmitters and receptors, vagal tone and the baroreflex, polyvagal theory, allostasis and allostatic load, chronic stress and the ACE study, HRV measures and bands, stress induced analgesia and hyperalgesia, CRPS and ways to break the stress and pain cycle.

CHAPTER 11

Reading the Evidence

Read it in full: **Chapter 11 in the textbook**. See it in motion: **Reading the Evidence Walkthrough** and **Reading the Evidence Lab**.

What to know

A paper's conclusion is only as strong as its design, so ask first how the authors found it. **Evidence based practice** integrates the best research evidence, clinical expertise and the patient's values and circumstances. One question sorts every design: did the investigators assign the exposure? If yes, it is **experimental**; if they only watched, it is **observational**. People who choose a treatment differ from those who do not; random assignment breaks that link.

The **randomized controlled trial** balances known and unknown characteristics by chance. Variations: parallel group, crossover (each person gets both treatments with a washout; fails if the first has lasting effects), cluster (randomize whole clinics), pragmatic (does it help in practice?) and explanatory (can it work, and how?). A non-randomized trial assigns by a rule such as alternating days.

Observational designs answer what trials cannot, including rare harms. A **cohort** follows exposed and unexposed people forward (prospective) or through records (retrospective) and gives relative risk. A **case control** study starts with the outcome and looks back at exposures; it is efficient for rare outcomes and gives an **odds ratio**. A case crossover study uses each case as his or her own control and has been used for manipulation and vertebral artery stroke. A cross-sectional study gives prevalence. Case reports raise hypotheses and flag harms. Cohort: cause first. Case control: cases first.

The evidence pyramid runs from systematic reviews and meta-analyses of good RCTs, through RCTs, cohorts, case control and cross-sectional studies, to case reports, expert opinion and lab research. It ranks designs, not individual studies. **Efficacy** is benefit under ideal conditions, **effectiveness** is benefit in ordinary practice and **mechanism** is how it works. Frame questions as **PICO**: population, intervention, comparison, outcome.

Random error shrinks with sample size; **bias** (systematic error) does not. **Selection bias** is prevented by randomization plus **allocation concealment**; poor concealment exaggerates effects. The healthy user effect inflates observational benefits. **Information bias** includes recall bias, detection bias and observer bias; patient reported outcomes such as pain are sensitive to expectation. **Blinding** can cover participants, clinicians, assessors, analysts and writers; in manual

therapy the clinician always knows, so blind the assessors and analysts and test whether blinding held.

Attrition bias comes from uneven dropout; **intention to treat** analysis keeps everyone in the group they were randomized to; per protocol analysis tends to overstate benefit; loss over about 20% raises concern. A **confounder** is linked to both exposure and outcome and is not on the causal path, such as income linking regular massage with fewer heart attacks. Design (randomization, restriction, matching) and analysis (stratification, adjustment) handle measured confounders; only randomization balances unmeasured ones.

Regression to the mean and natural history make nearly any treatment started at a peak look effective; only the difference between groups belongs to the treatment. The **placebo response** is all improvement in a placebo group; the narrower **placebo effect** is real psychobiological change from context, partly reversed by naloxone, strongest for pain, nausea and fatigue. The **nocebo** effect is harm from negative expectation. **Contextual effects** are real but not technique specific; a sham controlled trial estimates the specific effect. Shams for manual therapy and acupuncture are hard: too inert and blinding fails, too active and the difference shrinks. Other biases: performance, publication, selective outcome reporting, allegiance and funding, and spin.

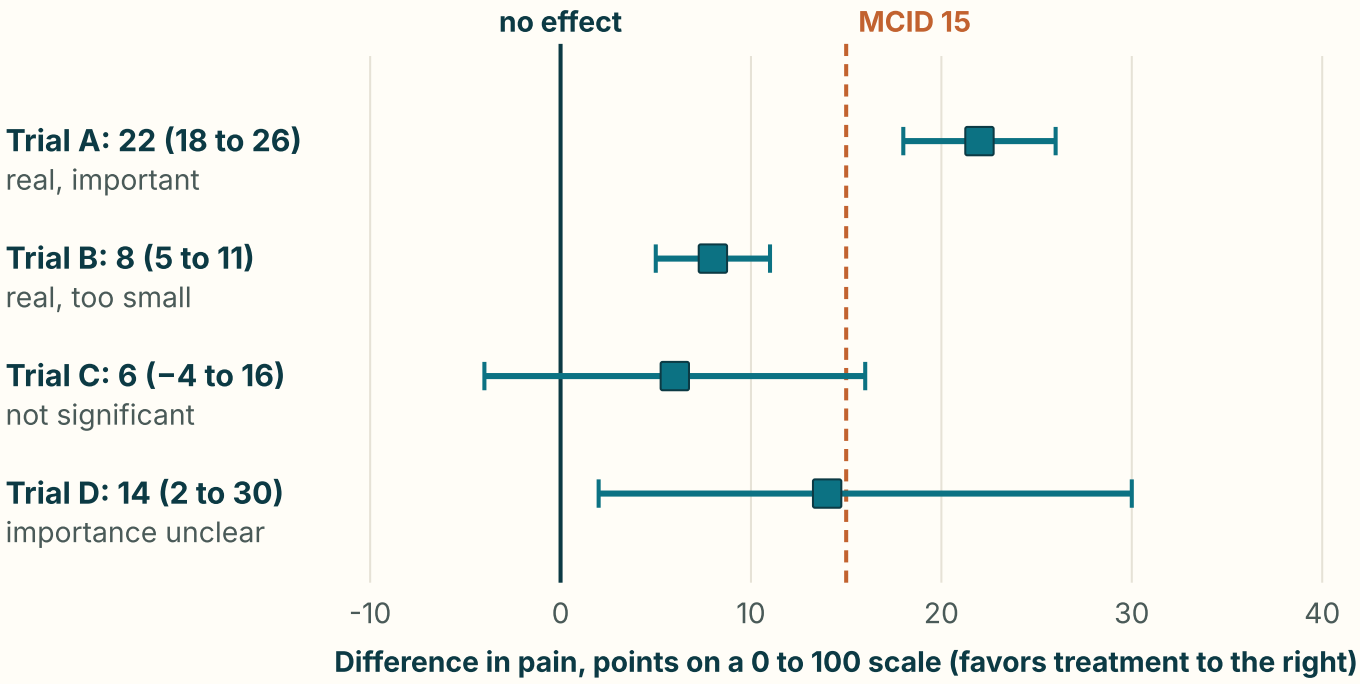
For yes or no outcomes, with control event rate (CER) and experimental event rate (EER): absolute difference = EER − CER; relative risk = EER ÷ CER; relative risk reduction = (CER − EER) ÷ CER; **NNT = 1 ÷ absolute difference**, rounded up; NNH is the same for harm. With CER 0.40 and EER 0.60: difference 0.20, RR 1.5, NNT 5, OR 2.25. Relative measures sound bigger; always find the absolute numbers. Case control studies give only odds ratios; for outcomes under about 10% the OR approximates the RR, and for common outcomes it exaggerates it.

Continuous outcomes give a mean difference or a **standardized mean difference** (Cohen's d: about 0.2 small, 0.5 moderate, 0.8 large). The **MCID** is the smallest change patients feel: about 2 points or 30% on a 0 to 10 pain scale, about 10 points on the Oswestry, about 2 to 5 on the 24 point Roland Morris. A **p value** is the probability of a result at least this extreme if there were no true difference; it is not the chance the null is true and says nothing about size. Type I error (alpha, usually 0.05) is a false positive; type II (beta) a false negative; power is 1 − beta, usually 80 or 90%. With 20 tests at 0.05, about one false positive is expected.

A 95% **confidence interval** gives the plausible range of the true effect. If it crosses zero (or 1 for a ratio), the result is not significant. Compare the whole interval with the MCID: entirely above it is real and important; above zero but below it is real but too small; spanning trivial to large means the study cannot tell. Reliability uses kappa (categorical) or the intraclass correlation coefficient (continuous); motion palpation reliability is low.

A **systematic review** has a registered protocol, a comprehensive search, two independent reviewers, risk of bias assessment and synthesis; PRISMA requires a flow diagram; Cochrane produces many. A **meta-analysis** pools studies, weighting larger ones more. In a **forest plot**, each square is a study (size is weight) with its CI line, and the diamond is the pooled result; if the diamond does not touch the line of no effect, it is significant. $\mathbf{I^2}$ measures heterogeneity (about 25% low, 50% moderate, 75% high); random effects models give wider intervals. A **funnel plot** with a missing lower corner suggests publication bias. **GRADE** starts RCTs high and observational studies low; it downgrades for risk of bias, inconsistency, indirectness, imprecision and publication bias, and upgrades observational evidence for a large effect, dose response, or confounding that would have shrunk the effect. Levels map to reviews' verbs: reduces, probably, may, uncertain. Guidelines make strong or conditional recommendations; AGREE II appraises them.

Applied fairly: spinal manipulation for acute low back pain gives modest improvement (about 10 points on a 100 point scale) with moderate certainty; for chronic low back pain it is similar to other recommended care; against sham the differences are small. Neck pain: short term benefit, especially with exercise; cervicogenic headache: several trials suggest benefit. No reliable evidence for non-musculoskeletal conditions. Mild soreness is common; serious events are rare; case crossover studies found a similar stroke association with primary care visits. Acupuncture beats sham by a small and no acupuncture by a moderate amount. Massage gives short term relief (low certainty). Yoga is similar to other exercise. Tai chi reduces falls. Mindfulness matched CBT for chronic low back pain. Herbs: St. John's wort has trial support for mild to moderate depression, but interactions, kava liver toxicity and contamination matter. Homeopathy and energy therapies show nothing beyond placebo or sham; the risk is delayed care. Three separate verdicts: beats no treatment? beats sham? matches other care?



Two reference lines, four verdicts. Zero tells you whether a difference is statistically significant; the minimal clinically important difference tells you whether it matters. Only interval A clears both.

LOCK THESE IN

- Experimental: investigators assign. Observational: investigators watch.
- Cohort gives relative risk; case control gives odds ratio. Cohort: cause first. Case control: cases first.
- Allocation concealment prevents selection bias; intention to treat preserves randomization.
- A confounder links to exposure and outcome; only randomization handles unmeasured ones.
- ARR = CER − EER (for harm). RRR = ARR ÷ CER. NNT = 1 ÷ ARR, rounded up.
- CI crossing 0 (or 1 for ratios) is not significant; compare the interval with the MCID.
- GRADE down: bias, inconsistency, indirectness, imprecision, publication bias. Up: large effect, dose response, confounding.
- Three verdicts: versus no treatment, versus sham, versus other recommended care.

Measures for yes or no outcomes (CER 0.40, EER 0.60)

Measure	Formula	Worked value	No effect
Absolute difference	EER − CER	0.20 (20 percentage points)	0
Relative risk	EER ÷ CER	1.5	1
Relative difference	(EER − CER) ÷ CER	0.50 (50% more)	0
Number needed to treat	1 ÷ absolute difference	5	Infinite
Odds ratio	[EER/(1 − EER)] ÷ [CER/(1 − CER)]	1.5 ÷ 0.667 = 2.25	1

Designs, error and certainty

Item	Key point	Watch for
RCT	Balances known and unknown confounders	Poor concealment, unblinded assessors, dropout
Cohort	Shows time order; relative risk	Confounding, healthy user effect
Case control	Efficient for rare outcomes; odds ratio	Recall bias, choice of controls
Cross-sectional	Prevalence at one time	Cannot show which came first
p value	Probability of data this extreme if no true difference	Not effect size; not the chance the null is true
MCID	Smallest change patients feel	Pain about 2 of 10; Oswestry about 10; Roland Morris 2 to 5
I^2	Share of variability from real differences	25 low, 50 moderate, 75 high
GRADE levels	High, moderate, low, very low	Reduces, probably, may, uncertain

Worked cases

WORKED CASE 1 · ARR, RRR, NNT AND THE ODDS RATIO

In a trial, 30% of control patients and 18% of treated patients develop chronic pain at one year. Find the ARR, RRR, NNT and odds ratio.

STEP 1 · FIND THE ARR

CER − EER = 0.30 − 0.18 = **0.12**, or 12 percentage points.

STEP 2 · FIND THE RRR

0.12 ÷ 0.30 = **0.40**, a 40% relative reduction.

STEP 3 · FIND THE NNT

1 ÷ 0.12 = 8.33, rounded up to **9** patients treated to prevent one case.

STEP 4 · FIND THE ODDS RATIO

Treated odds 0.18 ÷ 0.82 = 0.220; control odds 0.30 ÷ 0.70 = 0.429; OR = 0.220 ÷ 0.429 = about **0.51**.

CHECK IT

The relative risk is 0.18 ÷ 0.30 = 0.60. The OR (0.51) sits farther from 1 than the RR because the outcome is common, which is when ORs exaggerate.

WORKED CASE 2 · THE SAME RELATIVE EFFECT, TWO BASELINES

A treatment "reduces risk by 25%." Find the NNT when the baseline risk is 20% and when it is 2%.

STEP 1 · BASELINE 20%

ARR = 0.20 × 0.25 = 0.05. NNT = 1 ÷ 0.05 = **20**.

STEP 2 · BASELINE 2%

ARR = 0.02 × 0.25 = 0.005. NNT = 1 ÷ 0.005 = **200**.

STEP 3 · COMPARE

The same relative effect means ten times more patients treated per benefit when the outcome is rare.

THE HABIT

Turn every relative claim into an absolute difference and an NNT before deciding what it means for a patient.

WORKED CASE 3 · READING CONFIDENCE INTERVALS AGAINST AN MCID

The MCID for a 0 to 100 pain scale is 15 points. Four trials report differences favoring treatment: A, 22 (18 to 26); B, 8 (5 to 11); C, 6 (−4 to 16); D, 14 (2 to 30). Interpret each.

STEP 1 · TRIAL A

The whole interval lies above 15: **real and important**.

STEP 2 · TRIAL B

Above zero but entirely below 15: probably **real but too small** to matter.

STEP 3 · TRIAL C

The interval crosses zero: **not statistically significant**; the study cannot exclude no effect.

STEP 4 · TRIAL D

Excludes zero but spans trivial (2) to large (30): **real, importance uncertain**; a more precise study is needed.

TRAPS PEOPLE FALL INTO

- **Reading a p value as the chance the result is due to luck.** It is the probability of data this extreme if there were no true difference.
- **Equating significant with important.** A large trial can make a 2 point pain difference significant and meaningless.
- **Calling a nonsignificant small trial proof of no effect.** It may be underpowered. Absence of evidence is not evidence of absence.
- **Trusting a before and after story.** Natural history, regression to the mean and co-interventions can explain it.
- **Using relative risk without the baseline.** Halving 2 in 10,000 is 1 in 10,000.
- **Mixing up cohort and case control.** Cohorts start with exposure; case control studies start with the outcome.
- **Thinking adjustment removes all confounding.** Only measured, well measured variables are adjusted; randomization handles the rest.
- **Treating the pyramid as law.** A rigorous cohort can deserve more trust than a tiny, unblinded trial.

Chapter 11 self-test · ten items

1. Researchers find 300 people who had a vertebrobasilar stroke and 1,200 similar people who did not, then review visits in the prior month. What design is this, and what measure does it give?

A. Prospective cohort; relative risk
B. Randomized trial; risk difference
C. Case control study; odds ratio
D. Cross-sectional study; prevalence

C. Case control study; odds ratio It starts from the outcome and looks back at exposures. Because investigators chose the numbers of cases and controls, only an odds ratio can be calculated.

2. A trial uses a computer generated random sequence, but the enrolling clinician can see the next assignment. What problem does this create?

A. Attrition bias from uneven dropout rates
B. Selection bias from poor concealment
C. Recall bias from the patients' memories
D. Regression to the mean in the control arm

B. Selection bias from poor concealment If staff can predict the next assignment they may steer patients, recreating the selection bias that randomization was meant to remove.

3. Which analysis keeps every randomized participant in the assigned group regardless of adherence?

A. Prespecified subgroup
B. Sensitivity analysis
C. Per protocol only
D. Intention to treat

D. Intention to treat Intention to treat preserves the balance created by randomization. Per protocol analysis tends to overstate benefit.

4. A cohort finds that people who get regular massage have fewer heart attacks. Higher income makes massage affordable and independently lowers cardiac risk. What is income here?

A. A confounding variable
B. An effect modifier
C. A mediator on the causal path
D. A source of random error

A. A confounding variable Income is linked to both the exposure and the outcome and is not a step between them, so it can create an association even if massage does nothing to the heart.

5. Patients enrolled at their worst back pain improve by half in three weeks with a new treatment and no control group. Which explanation could account for this without any treatment effect?

A. Natural history and regression to the mean
B. Publication bias and spin in the abstract
C. Indirectness and imprecision of results
D. Allocation concealment and random error

A. Natural history and regression to the mean People enrolled at a peak drift toward average, and acute back pain usually improves on its own. Only a control group separates the treatment's share.

6. In a trial, 40% of controls and 60% of treated patients are much better. What is the NNT?

A. 3
B. 20
C. 2
D. 5

D. 5 The absolute difference is 0.60 − 0.40 = 0.20, and 1 ÷ 0.20 = 5.

7. A trial of 4,000 people finds a 2 point drop on a 0 to 100 pain scale, p = 0.001. Best interpretation?

A. Large and clinically important to patients
B. Probably real but too small to matter
C. Not statistically significant at all
D. Proof that the treatment has no effect

B. Probably real but too small to matter Large samples detect tiny differences. A 2 point change is far below typical MCIDs, so the p value shows the effect is probably real, not that it matters.

8. A 95% CI for a mean difference in disability is −3 to 12 points. What follows?

A. The treatment is certainly harmful to patients
B. The result is significant and important
C. The result is not statistically significant
D. The minimal important difference is reached

C. The result is not statistically significant An interval that crosses zero includes no effect, so the result is not significant at the 0.05 level.

9. In a forest plot, three small trials cross the line of no effect but the pooled diamond does not. Is that a contradiction?

A. No; pooling adds precision to a small effect
B. Yes; it proves that publication bias exists
C. Yes; the pooled result must be an error
D. No; small trials always carry most weight

A. No; pooling adds precision to a small effect Small trials are imprecise. Combining them narrows the interval, so a consistent small effect can become statistically clear.

10. Real acupuncture beats no acupuncture by a moderate amount but beats sham by a small amount. What does this suggest?

A. Needle location is the whole active ingredient
B. Acupuncture has no effect of any kind
C. Much of the benefit is shared with the sham
D. The sham was more effective than acupuncture

C. Much of the benefit is shared with the sham Contextual factors such as expectation, attention and skin stimulation contribute substantially; the specific effect of correct needling is small but not zero.

CHAPTER 12

Stress and the Autonomic Nervous System

Read it in full: **Chapter 12 in the textbook**. See it in motion: **Stress and Autonomic Balance Walkthrough** and **Stress and Autonomic Balance Lab**.

What to know

A **stressor** is any demand that challenges stability; the **stress response** is the coordinated neural, hormonal and behavioral reaction, a survival system that harms only when too strong, too long or too frequent. Walter Cannon described fight or flight and coined homeostasis. Hans Selye's

general adaptation syndrome has alarm, resistance and exhaustion stages, from rats that developed enlarged adrenals, shrunken thymus and lymphoid tissue, and ulcers. Unpredictable, uncontrollable, novel and socially evaluative stressors are the strongest triggers; control, predictability and social support blunt them.

The fast arm is the **sympathetic adrenal medullary** system. The amygdala signals the hypothalamus and brainstem; the locus coeruleus raises arousal with norepinephrine; preganglionic fibers reach the **adrenal medulla**, a modified sympathetic ganglion whose chromaffin cells release about 80% epinephrine and 20% norepinephrine into the blood within seconds.

The slow arm is the **HPA axis**: the paraventricular nucleus releases **CRH** (with vasopressin) into the hypophyseal portal veins; the anterior pituitary releases **ACTH**, cleaved from POMC (which also yields beta-endorphin); ACTH drives the zona fasciculata of the adrenal cortex to make **cortisol**, which rises within about 15 to 30 minutes and peaks at about half an hour. Cortisol acts through glucocorticoid and mineralocorticoid receptors and shuts the axis off by negative feedback on the hypothalamus, pituitary and hippocampus. The amygdala drives the axis; the hippocampus and prefrontal cortex restrain it.

Cortisol raises glucose (gluconeogenesis, less uptake in muscle and fat), supports blood pressure (permissive effect on catecholamines), suppresses inflammation, inhibits osteoblasts and collagen, and shapes memory and mood. Chronically high levels bring insulin resistance, central fat, hypertension, poor healing, infection risk and osteoporosis with vertebral fractures. Cushing syndrome shows excess; Addison disease shows deficiency with darkened skin from high ACTH. A patient on years of steroids with sudden mid back pain after a minor strain needs a fracture check before forceful treatment. Cortisol follows a **diurnal rhythm** set by the suprachiasmatic nucleus: lowest near midnight, peaking after waking, with a **cortisol awakening response** of about 50% in the first 30 to 45 minutes. A flattened slope goes with chronic stress, depression and poor sleep.

The ANS has sympathetic, parasympathetic and enteric divisions, integrated by the hypothalamus, the **nucleus tractus solitarius** and limbic areas. Output is a two neuron chain: a preganglionic (type B) fiber to a ganglion, then a postganglionic (type C) fiber to the target. The **sympathetic**

division is **thoracolumbar (T1 to L2)**, from the lateral horn, through white rami to the paravertebral chain beside the vertebral bodies, or on to prevertebral ganglia (celiac, superior and inferior mesenteric); postganglionic fibers return through gray rami. Short preganglionic, long postganglionic fibers, with wide divergence.

The **parasympathetic** division is **craniosacral**: cranial nerves III, VII, IX and X and the sacral cord at **S2 to S4**, with ganglia in or near the organs (long preganglionic, short postganglionic). The vagus carries about three quarters of parasympathetic fibers, supplying the heart, lungs and gut to about the left colic flexure; pelvic splanchnics from S2 to S4 supply the distal colon, bladder and reproductive organs, which is why cauda equina syndrome affects bladder and bowel. About 80% of vagal fibers are afferent, carrying interoception.

All preganglionic neurons release ACh onto **nicotinic** receptors. Parasympathetic postganglionic neurons release ACh onto **muscarinic** receptors; most sympathetic postganglionic neurons release norepinephrine onto adrenergic receptors. Exception: sympathetic fibers to most eccrine **sweat glands** release ACh onto muscarinic receptors, so anticholinergics reduce sweating. Receptors: alpha-1 constricts vessels and dilates the pupil; alpha-2 reduces NE release and insulin; beta-1 speeds and strengthens the heart and releases renin; beta-2 dilates bronchi and muscle arterioles; beta-3 drives lipolysis and relaxes the detrusor; M2 slows the heart; M3 drives glands, bronchoconstriction, gut motility, voiding and pupil constriction. Most blood vessels, sweat glands, arrector pili and the adrenal medulla get only sympathetic supply. Erection is parasympathetic, emission sympathetic.

A denervated SA node fires at about 90 to 110 per minute; a resting rate of 60 to 80 reflects **vagal tone**, which dominates at rest and acts within a beat, while sympathetic effects build over seconds. The **baroreflex** (carotid sinus via CN IX, aortic arch via CN X, to the NTS) raises vagal and lowers sympathetic output when pressure rises; its failure causes orthostatic hypotension. Healthy balance means **flexibility**: ramp up quickly, then withdraw and restore vagal activity. **Polyvagal theory** (Porges, 1990s) proposes ventral (social engagement) and dorsal (shutdown) vagal systems and neuroception; it is a helpful clinical language whose specific anatomical and evolutionary claims are disputed.

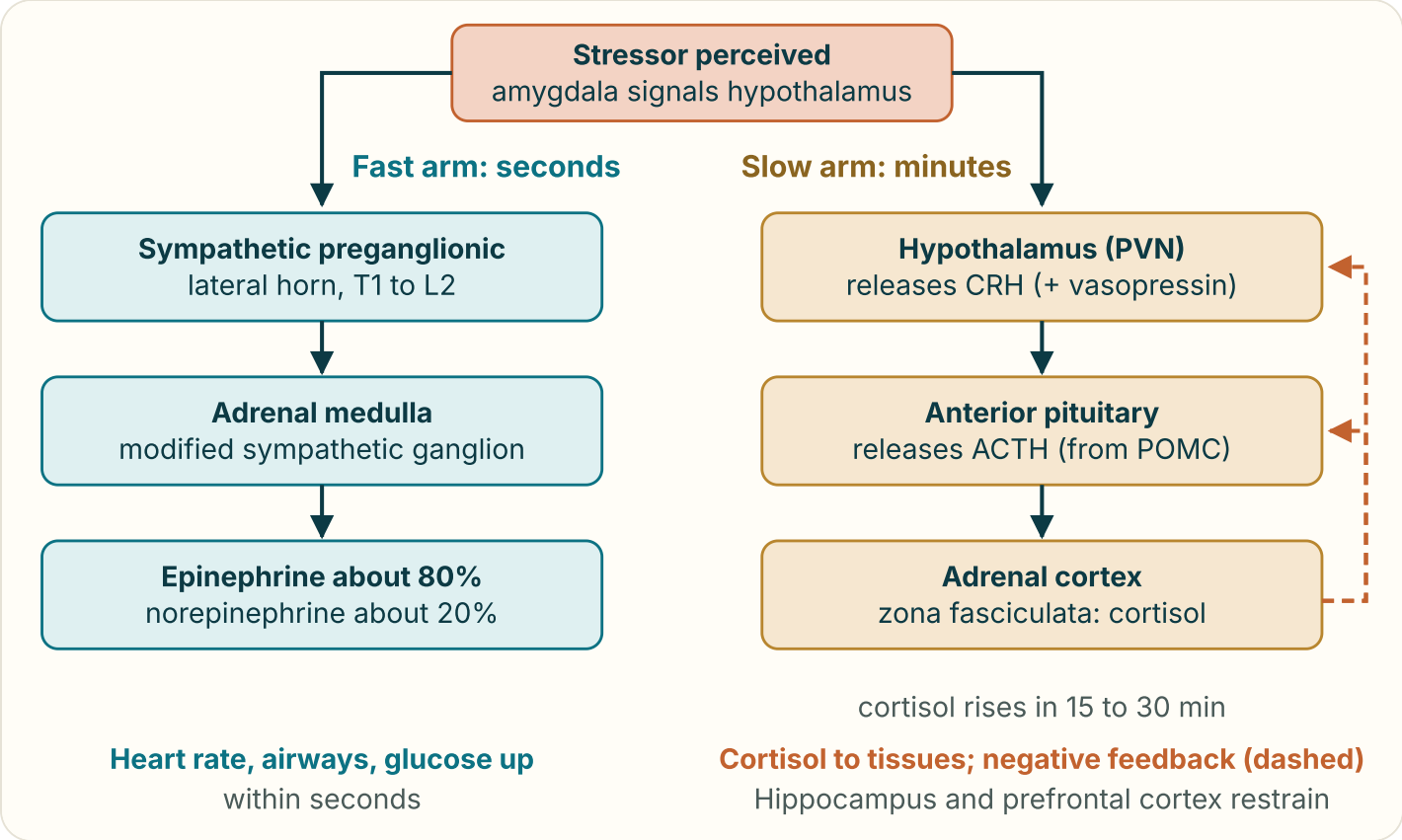
Allostasis (Sterling and Eyer, 1988) is stability through change. **Allostatic load** (McEwen) is the cumulative wear and tear; allostatic overload is when it causes disease. Four patterns: repeated hits, lack of adaptation, prolonged response and inadequate response. An allostatic load index counts primary mediators (cortisol, catecholamines, DHEA-S, IL-6, CRP), secondary outcomes (blood pressure, waist to hip ratio, HbA1c, glucose, cholesterol, resting heart rate) and tertiary disease. Chronic stress shrinks hippocampal and prefrontal dendrites and grows the amygdala in animal work, changes that can partly reverse. **Glucocorticoid resistance** explains why chronic stress brings more inflammation, not less. The ACE study found a dose response between childhood adversity and adult disease, with four or more categories markedly worse; it is observational, and safe, stable relationships buffer it.

Heart rate variability is the beat to beat variation in RR (NN) intervals; higher resting HRV signals adaptability. The biggest source at rest is **respiratory sinus arrhythmia**: inspiration shortens intervals, expiration lengthens them. **SDNN** is total variability (24 hour values below about 50 ms are markedly reduced, above about 100 ms healthy). **RMSSD** (root mean square of successive differences) and pNN50 mainly reflect vagal activity and work in 1 to 5 minute recordings. Bands: HF 0.15 to 0.40 Hz (breathing at 9 to 24 per minute; vagal), LF 0.04 to 0.15 Hz (baroreflex; mixed), VLF 0.0033 to 0.04 Hz, ULF below 0.0033 Hz. LF/HF is **not** a clean sympathetic index; slow breathing at 6 per minute (0.1 Hz) moves vagal RSA into LF.

HRV falls with age, rises with fitness, is highest in deep sleep, falls with stress, pain, alcohol, heavy meals, dehydration, fever and standing, and rises with beta blockers. Resonance breathing at about 6 per minute gives the largest oscillations (HRV biofeedback). ECG is the reference; chest straps are accurate at rest; PPG wrist and finger devices are fair at rest and poor in motion. Measure at the same time and position and follow weekly trends. After myocardial infarction, SDNN below 50 ms carried several times the mortality of SDNN above 100 ms; diabetic autonomic neuropathy produces a nearly fixed heart rate. Studies of manipulation and HRV are small and inconsistent; one reading is not proof of a balanced nervous system.

Stress induced analgesia comes with acute, intense danger: the PAG and rostral ventromedial medulla inhibit the dorsal horn with serotonin and norepinephrine, helped by endogenous opioids (some forms blocked by naloxone) and endocannabinoids. **Stress induced hyperalgesia** comes

with chronic, uncontrollable stress: descending facilitation, glial cytokines, glucocorticoid resistance and poor sleep feed central sensitization. Mental stress raises upper trapezius activity (the Cinderella hypothesis of always active low threshold units); guarding can outlast healing. In CRPS, injured neurons become sensitive to norepinephrine, with color, temperature, sweating and trophic changes. Ways out: pain education, graded activity, exercise, CBT, ACT, pain reprocessing, mindfulness, slow breathing, relaxation, yoga, tai chi, sleep and social connection. Manipulation produces brief autonomic changes; lasting health benefits are not shown, and trials for hypertension were negative or inconclusive.



Two arms, two time scales. The adrenal medulla belongs to the fast sympathetic arm and releases epinephrine within seconds; the adrenal cortex belongs to the slow HPA arm, where CRH drives ACTH and ACTH drives cortisol, which then shuts the axis off.

LOCK THESE IN

- HPA: hypothalamus CRH, pituitary ACTH, adrenal cortex (zona fasciculata) cortisol; negative feedback.
- Adrenal medulla = fast sympathetic arm, about 80% epinephrine. Adrenal cortex = slow HPA arm.
- Sympathetic T1 to L2 (thoracolumbar); parasympathetic CN III, VII, IX, X and S2 to S4 (craniosacral).
- Ganglia: nicotinic ACh. Parasympathetic targets: muscarinic ACh. Sympathetic targets: NE, except sweat glands (ACh).
- Intrinsic SA rate about 90 to 110; vagal tone brings it to 60 to 80.
- Allostatic load patterns: repeated hits, lack of adaptation, prolonged response, inadequate response.
- RMSSD, pNN50, HF: vagal. SDNN: total. LF/HF is not a sympathetic index.
- Acute danger: stress induced analgesia. Chronic stress: stress induced hyperalgesia.

Autonomic receptors and organ effects

Receptor or organ	Sympathetic	Parasympathetic
Heart	Faster, stronger (beta-1)	Slower (vagus, M2)
Bronchioles	Dilate (beta-2)	Constrict, mucus (M3)
Pupil	Dilates (alpha-1, radial muscle)	Constricts (CN III, sphincter)
Gut	Less motility; sphincters contract	More motility and secretion; sphincters relax
Bladder	Detrusor relaxes, internal sphincter contracts	Detrusor contracts (S2 to S4)
Salivary glands	Small volume, thick	Large volume, watery
Blood vessels	Constrict in skin and gut; dilate in muscle (beta-2)	Little direct effect
Sweat glands	ACh onto muscarinic receptors (exception)	None
Alpha-2 (presynaptic)	Less NE release, less insulin, lower central outflow	No parasympathetic counterpart

Heart rate variability measures

Measure	What it is	Main source
SDNN	Standard deviation of NN intervals	Total variability; 24 h below 50 ms reduced, above 100 ms healthy
RMSSD	Root mean square of successive differences	Vagal; reliable in 1 to 5 minutes
pNN50	% of successive differences over 50 ms	Vagal
HF power	0.15 to 0.40 Hz	Vagal, respiratory sinus arrhythmia
LF power	0.04 to 0.15 Hz	Baroreflex; vagal and sympathetic
VLF power	0.0033 to 0.04 Hz	Thermoregulation, renin angiotensin
ULF power	Below 0.0033 Hz	Circadian; needs 24 h
LF/HF	Ratio of the two bands	Not a clean sympathetic index

Worked cases

WORKED CASE 1 · COMPUTING RMSSD AND PNN50

Five RR intervals are recorded: 980, 910, 950, 1000 and 940 ms. Find the successive differences, RMSSD, pNN50 and mean heart rate.

STEP 1 · LIST SUCCESSIVE DIFFERENCES

910 − 980 = −70; 950 − 910 = 40; 1000 − 950 = 50; 940 − 1000 = −60 ms.

STEP 2 · SQUARE AND AVERAGE

4,900 + 1,600 + 2,500 + 3,600 = 12,600; 12,600 ÷ 4 = 3,150.

STEP 3 · TAKE THE SQUARE ROOT

RMSSD = √3,150 = about **56 ms**.

STEP 4 · COUNT PNN50

Differences larger than 50 ms: 70 and 60 (50 is not larger than 50), so 2 of 4 = **50%**.

STEP 5 · FIND HEART RATE

Mean RR = 4,780 ÷ 5 = 956 ms; 60,000 ÷ 956 = about **63 beats per minute**.

INTERPRET

One short recording means little alone. Follow one person's trend under the same conditions.

WORKED CASE 2 · WHY SLOW BREATHING FOOLS THE LF/HF RATIO

A user breathes at 6 breaths per minute during a relaxation exercise. The app reports a jump in LF/HF and labels her sympathetic dominant. Explain the error.

STEP 1 · CONVERT BREATHING TO FREQUENCY

6 breaths per minute ÷ 60 = **0.1 Hz**.

STEP 2 · PLACE IT IN A BAND

0.1 Hz lies in the LF band (0.04 to 0.15 Hz), not the HF band (0.15 to 0.40 Hz).

STEP 3 · NAME THE SOURCE

The oscillation is respiratory sinus arrhythmia, which is vagally mediated, now sitting in LF.

STEP 4 · CONCLUDE

LF rises, LF/HF rises, yet vagal activity is high. LF/HF is not a valid sympathetic index here; use RMSSD instead.

WORKED CASE 3 · READING STEROIDS AND THE HPA AXIS

A 68 year old has taken prednisone for months for an inflammatory condition. Predict her CRH and ACTH levels, what has happened to her adrenal cortex, and what it means for spinal care.

STEP 1 · APPLY NEGATIVE FEEDBACK

The synthetic glucocorticoid suppresses the hypothalamus and pituitary, so **CRH and ACTH fall**.

STEP 2 · FOLLOW THE ADRENAL

Without ACTH the adrenal cortex atrophies, which is why long term steroids must be tapered, not stopped abruptly.

STEP 3 · LINK TO BONE

Cortisol excess inhibits osteoblasts and collagen and reduces calcium absorption, causing osteoporosis, with vertebral bodies among the first affected.

STEP 4 · APPLY IT CLINICALLY

Sudden mid back pain after a minor strain needs evaluation for a compression fracture before any forceful spinal treatment.

TRAPS PEOPLE FALL INTO

- **Putting the adrenal medulla in the HPA axis.** The medulla is the fast sympathetic arm; the cortex makes cortisol in the HPA arm.
- **Saying all sympathetic targets use norepinephrine.** Most eccrine sweat glands receive ACh onto muscarinic receptors.
- **Calling the vagus a motor nerve.** About 80% of its fibers are afferent, carrying interoception.
- **Reading LF/HF as sympathetic balance.** LF includes baroreflex and vagal activity, and slow breathing moves vagal RSA into LF.
- **Expecting chronic stress to lower inflammation.** Glucocorticoid resistance weakens cortisol's brake, so inflammation rises.
- **Comparing HRV between two people from one reading.** HRV is individual; follow trends under consistent conditions.
- **Teaching polyvagal theory as settled physiology.** It is a useful clinical language whose specific claims are debated.
- **Treating balance as a fixed seesaw.** Healthy autonomic function is flexibility: quick ramp up and quick recovery.

Chapter 12 self-test · ten items

1. A patient has taken high dose prednisone for months. What happens to her CRH and ACTH?

A. Both rise to drive the adrenal cortex
B. Neither changes with synthetic steroids
C. Both fall from negative feedback
D. CRH rises while ACTH falls

C. Both fall from negative feedback The synthetic glucocorticoid feeds back on the hypothalamus and pituitary. The adrenal cortex then atrophies, which is why tapering is needed.

2. Why is the adrenal medulla called a modified sympathetic ganglion?

A. Its chromaffin cells act as postganglionic neurons
B. It releases cortisol under ACTH control
C. It is made of parasympathetic ganglion cells
D. It receives postganglionic fibers from the chain

A. Its chromaffin cells act as postganglionic neurons Preganglionic fibers synapse directly on chromaffin cells, which release epinephrine and norepinephrine into the blood instead of sending axons.

3. A heart transplant recipient has a resting heart rate of about 100. Why?

A. The new heart has extra pacemaker cells
B. Transplant drugs block beta-1 receptors
C. Baroreflex activity is doubled after surgery
D. The denervated heart has no vagal tone

D. The denervated heart has no vagal tone Without vagal restraint the SA node fires at its intrinsic rate of about 90 to 110 beats per minute.

4. A sympathetic response, sweating, is reduced by an anticholinergic drug. Why?

A. Sweating depends on nicotinic receptors alone
B. Its fibers release ACh onto muscarinic receptors
C. Sweat glands are parasympathetic structures
D. Anticholinergic drugs block alpha-1 receptors there

B. Its fibers release ACh onto muscarinic receptors Sympathetic fibers to most eccrine sweat glands are cholinergic, so blocking muscarinic receptors reduces sweating.

5. Where do sympathetic preganglionic neurons arise?

A. Dorsal root ganglia from C1 to S5
B. Lateral horn of the cord from T1 to L2
C. Sacral cord at the S2 to S4 segments
D. Brainstem nuclei of CN III, VII, IX and X

B. Lateral horn of the cord from T1 to L2 The sympathetic division is thoracolumbar, from the intermediolateral cell column at T1 to L2.

6. A caregiver's blood pressure stays high for hours after each difficult phone call. Which allostatic load pattern is this?

A. Lack of adaptation
B. Repeated hits
C. Inadequate response
D. Prolonged response

D. Prolonged response The response fails to shut off after the stressor ends, often kept going by rumination.

7. Chronic stress is linked to more inflammation even though cortisol is anti-inflammatory. What explains this?

A. Glucocorticoid resistance in immune cells
B. The adrenal medulla stops working
C. Cortisol levels fall to zero over time
D. Vagal tone rises and drives the cytokines

A. Glucocorticoid resistance in immune cells Prolonged exposure lowers immune cells' sensitivity to cortisol, weakening its brake while sympathetic signals promote inflammatory genes.

8. Which HRV measure mainly reflects vagal activity and works in a short recording?

A. SDNN over 24 hours
B. VLF power over 5 minutes
C. RMSSD over 1 to 5 minutes
D. The LF/HF ratio at rest

C. RMSSD over 1 to 5 minutes RMSSD captures fast beat to beat changes that only the vagus can produce and is reliable in 1 to 5 minutes.

9. A firefighter breaks a wrist during a rescue but feels little pain until afterward. What is this?

A. Stress induced analgesia
B. Complex regional pain syndrome
C. Stress induced hyperalgesia
D. Central sensitization

A. Stress induced analgesia Acute danger engages the PAG and medulla to inhibit the dorsal horn, aided by endogenous opioids, endocannabinoids and norepinephrine.

10. A patient with three weeks of back pain believes his spine is crumbling, has stopped walking and sleeps poorly. After red flag screening, what should come first?

A. An MRI to show him the crumbling spine
B. Daily manipulation for several months
C. Education, graded walking and better sleep
D. Strict bed rest until the pain has fully gone

C. Education, graded walking and better sleep Catastrophizing, fear avoidance and poor sleep predict chronic disability better than imaging, so care targets the fear avoidance cycle.

Cram sheet

Everything from chapters 11 and 12 in one place. Cover the right column and see if you can rebuild each row.

Equations

Name	Formula	Note
Absolute risk reduction	CER − EER (harm) or EER − CER (benefit)	Percentage points
Relative risk	EER ÷ CER	No effect = 1
Relative risk reduction	(CER − EER) ÷ CER	Sounds bigger than ARR
NNT	1 ÷ absolute difference, rounded up	Carries baseline risk inside it
Odds	p ÷ (1 − p)	0.60 is odds of 1.5
Odds ratio	Odds treated ÷ odds control	Approximates RR under about 10%
Power	1 − beta	Usually 80 or 90%
RMSSD	√[mean of squared successive RR differences]	Vagal, short recordings
Heart rate from RR	60,000 ÷ mean RR in ms	Beats per minute
Breathing frequency	Breaths per minute ÷ 60	12/min = 0.2 Hz (HF); 6/min = 0.1 Hz (LF)

Numbers to know

Item	Value	Note
Effect sizes	SMD 0.2 small, 0.5 moderate, 0.8 large	Conventions
MCID	Pain about 2 of 10 or 30%; Oswestry about 10; Roland Morris 2 to 5	Guides, not laws
Alpha	0.05	20 tests give about one false positive
Loss to follow up	Over about 20% raises concern	Attrition bias
I^2	25 low, 50 moderate, 75 high	Heterogeneity
SMT acute LBP	About 10 points on a 100 point scale	Moderate certainty
Adrenal medulla	About 80% epinephrine, 20% norepinephrine	Seconds
Cortisol	Rises in 15 to 30 min; peaks about 30 min	Awakening response about 50% in 30 to 45 min
SA node	Intrinsic 90 to 110; resting 60 to 80	Vagal tone
Vagus	About 75% of parasympathetic fibers; about 80% afferent	Interoception
SDNN (24 h)	Below 50 ms reduced; above 100 ms healthy	After MI, low SDNN raised mortality
HRV bands	HF 0.15 to 0.40; LF 0.04 to 0.15; VLF 0.0033 to 0.04; ULF below 0.0033 Hz	Resonance breathing about 6 per minute
ACE study	Four or more categories markedly raise risk	Dose response; observational

Rules that are not equations

Topic	The rule
Design	Who assigned the exposure? Cohort: cause first. Case control: cases first.
Bias	Bigger samples shrink random error, not bias.
Confounding	Only randomization balances unmeasured confounders.
Before and after	Natural history, regression to the mean and co-interventions can explain improvement.
CI reading	Crosses 0 (or 1): not significant. Compare the interval with the MCID for importance.
GRADE	Down: bias, inconsistency, indirectness, imprecision, publication. Up: large effect, dose response, confounding.
Three verdicts	Versus no treatment, versus sham, versus other recommended care.
HPA	CRH to ACTH to cortisol; feedback shuts it off; steroids suppress it.
Divisions	Sympathetic T1 to L2; parasympathetic CN III, VII, IX, X and S2 to S4.
Receptors	Ganglia nicotinic; parasympathetic targets muscarinic; sweat glands cholinergic sympathetic.
HRV	Vagal: RMSSD, pNN50, HF. LF/HF is not a sympathetic index.
Stress and pain	Acute danger: analgesia. Chronic uncontrollable stress: hyperalgesia.

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