

Hypersomnia of central origin

15th - 18th September | Newcastle

Ivana Rosenzweig • BSS ISMC 2026 • Thursday 17 September • 09:30–10:30



British Sleep Society



UK Multidisciplinary Sleep Professionals



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Historical Milestones

1880

Gelineau publishes the first clinical description of narcolepsy with excessive daytime sleepiness and cataplexy

1960s

Sleep-onset REM periods (SOREMPs) discovered — narcolepsy linked to fundamental REM sleep dysregulation

1998

Orexin/Hypocretin discovery — de Lecea and Sakurai identify novel neuropeptides in the lateral hypothalamus

1999

Canine narcolepsy gene identified — mutation in hypocretin receptor 2 (HCRTR2) causes narcolepsy in dogs

2000

Human orexin neuron loss confirmed — 90% loss of hypothalamic hypocretin neurons in NT1; CSF hypocretin-1 deficiency established

2005

ICSD-2 classification separates narcolepsy with/without cataplexy; CSF hypocretin-1 becomes a diagnostic biomarker

2009

H1N1/Pandemrix — AS03-adjuvanted vaccine triggers narcolepsy outbreak, confirming autoimmune etiology

2014

ICSD-3 introduces NT1 and NT2 classification; central disorders of hypersomnolence formally defined

Sleep-Wake Neurocircuitry

Wake-Promoting Nuclei

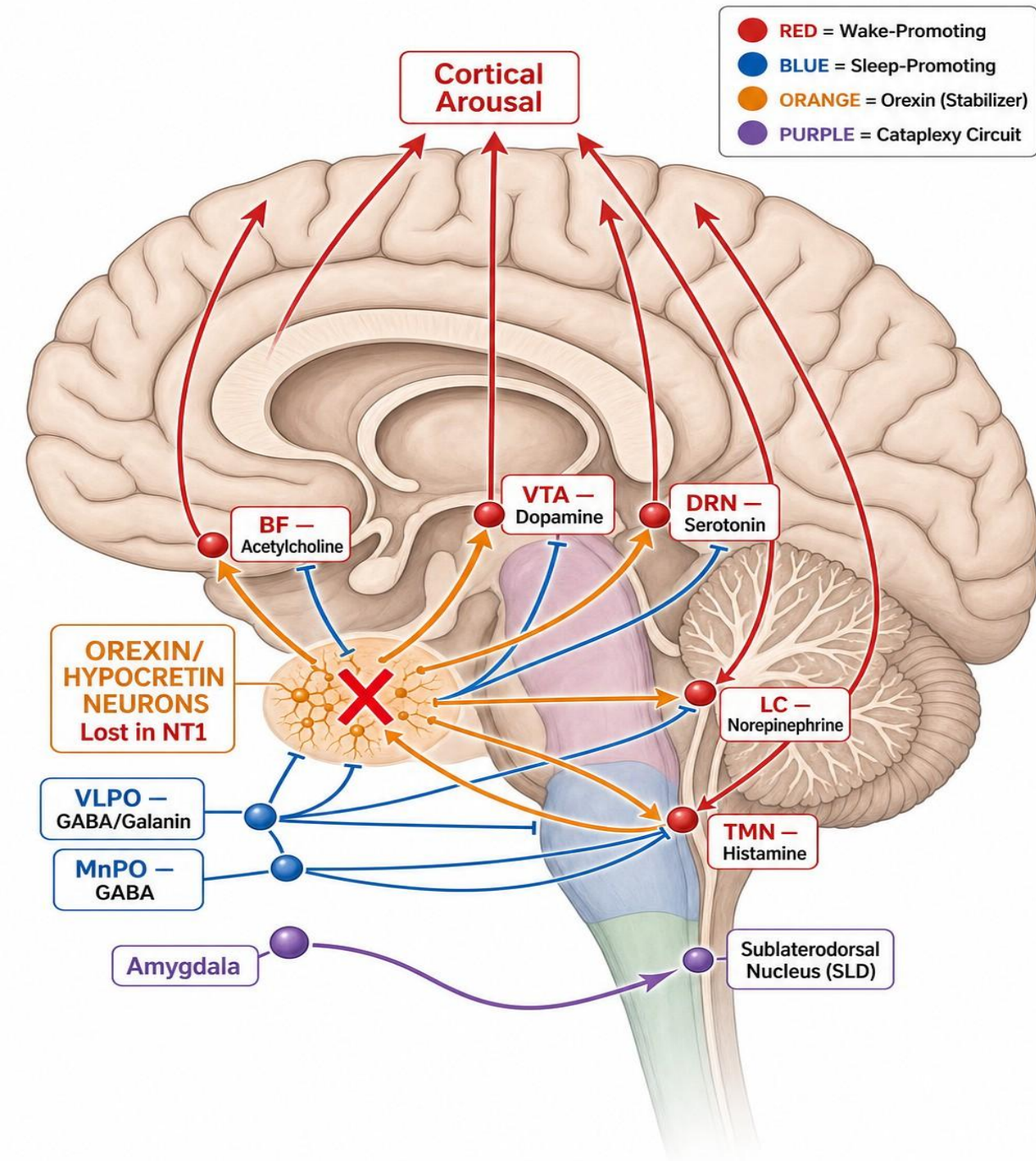
- Locus Coeruleus (LC) — Norepinephrine
- Tuberomammillary Nucleus (TMN) — Histamine
- Dorsal Raphe Nucleus (DRN) — Serotonin
- Ventral Tegmental Area (VTA) — Dopamine
- Basal Forebrain (BF) — Acetylcholine

Sleep-Promoting Nuclei

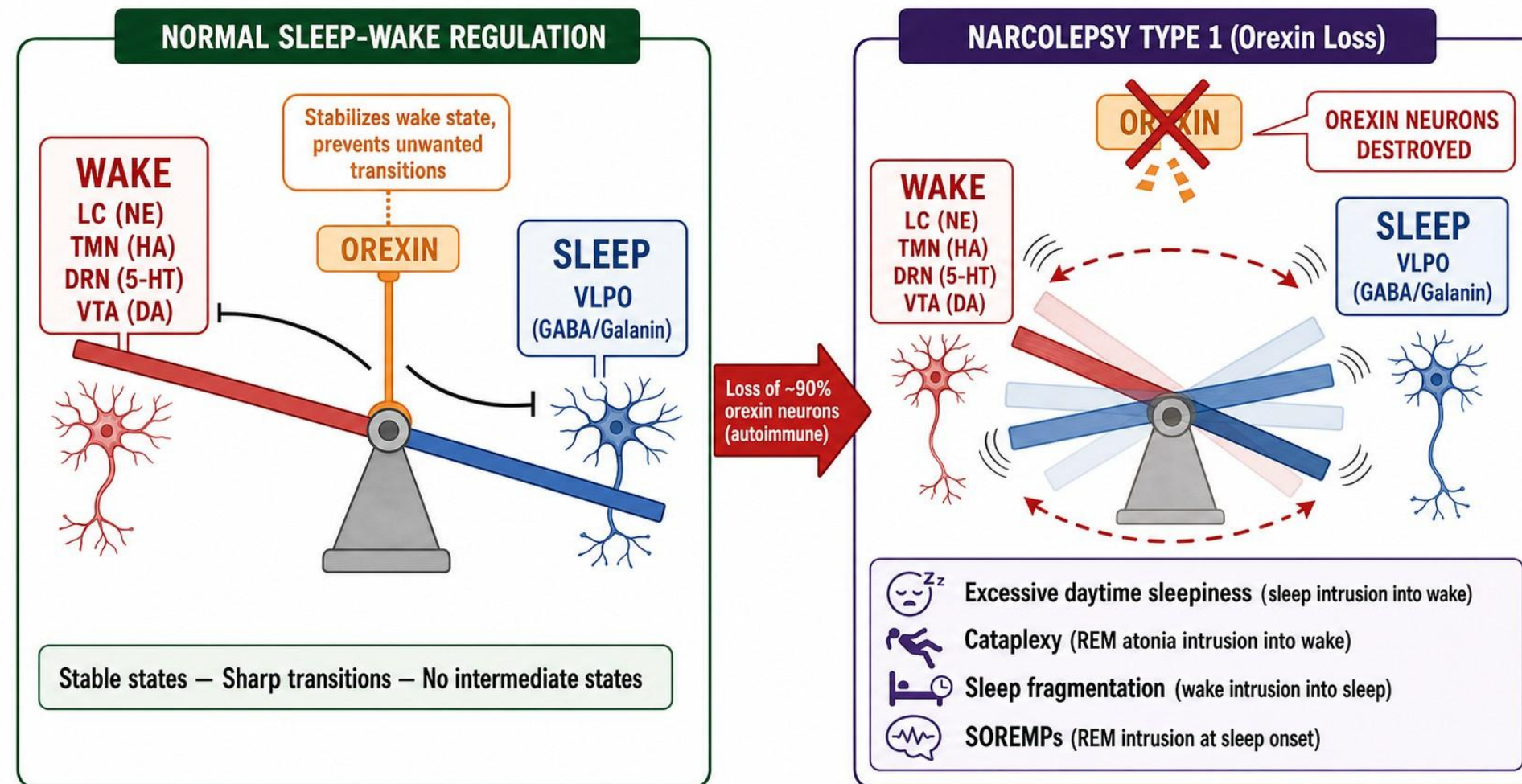
- VLPO — GABA/ Galanin
- Median Preoptic Nucleus (MnPO) — GABA
- Parafacial Zone (PZ) — GABA

Orexin/Hypocretin System (Stabilizer)

- Lateral hypothalamus — exclusive source of Orexin A and B
- Projects to ALL wake-promoting nuclei
- OX1R and OX2R receptors widely distributed
- Stabilizes the wake state; prevents unwanted transitions



The Flip-Flop Switch Model and Orexin's Role



Orexin neurons stabilize the wake state by reinforcing monoaminergic wake-promoting nuclei. Their destruction in NT1 destabilizes the switch, causing rapid, unwanted transitions between wake and sleep — producing EDS, cataplexy, SOREMPs, and sleep fragmentation.

Pathophysiology Across Central Hypersomnias

Narcolepsy Type 1

- Autoimmune destruction of orexin neurons in lateral hypothalamus
- HLA-DQB1*06:02 in >90% of patients
- T-cell mediated attack on hypocretin-producing neurons
- Loss of up to 95% of orexin neurons
- CSF hypocretin-1 below 110 pg/mL

H1N1/Pandemrix confirmed autoimmune trigger (2009-2010)

NT2 and Idiopathic Hypersomnia

- NT2: Normal orexin, unknown mechanism; possible partial orexin loss
- IH: Enhanced GABAergic inhibitory tone ("endogenous somnogen")
- Reduced CSF histamine levels
- Dopaminergic dysfunction
- Altered circadian clock gene dynamics in IH

Rare prepro-orexin cleavage site variant linked to IH

Kleine-Levin Syndrome

- Episodic thalamic and hypothalamic dysfunction
- Hypoperfusion of thalamus and hypothalamus during episodes
- Possible autoimmune/post-infectious etiology
- Male predominance (2:1)
- Episodes resolve spontaneously; disorder often self-limiting

CSF orexin A levels abnormal during episodes

ICSD-3 Classification of Central Hypersomnias

Narcolepsy Type 1

Hallmark: Cataplexy + orexin deficiency. **CSF hypocretin-1 below 110 pg/mL**

Key features: EDS, cataplexy, sleep paralysis, hypnagogic hallucinations, disrupted nocturnal sleep

MSLT: Mean sleep latency below 8 min with 2+ SOREMPs (including nocturnal SOREMP)

Narcolepsy Type 2

Hallmark: No cataplexy, normal CSF hypocretin-1. **Diagnosis of exclusion**

Key features: EDS without cataplexy; positive MSLT (mean SL below 8 min, 2+ SOREMPs)

Note: Up to 30% may develop cataplexy over time, converting to NT1

Idiopathic Hypersomnia

Hallmark: Prolonged sleep, severe sleep inertia. **No SOREMPs on MSLT**

Key features: EDS, sleep drunkenness, unrefreshing naps, total 24h sleep above 11 hours

Mechanism: Enhanced GABAergic tone; possible "endogenous somnogen" in CSF

Kleine-Levin Syndrome

Hallmark: Recurrent episodes of hypersomnia + cognitive/behavioral changes

Key features: Episodes lasting days-weeks; hyperphagia, hypersexuality, derealization

Course: Self-limiting; median 14 years; episodes decrease in frequency over time

ORIENTATION

What the examiner is really testing

Can you prove central hypersomnolence — after excluding the commoner explanations?

Then distinguish narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia and recurrent syndromes.

Phenotype

Valid testing

Exclusion

Safety

This lecture maps primarily to ESRS Textbook Section E, chapters E1–E3 and E5.

Source: <https://esrs.eu/wp-content/uploads/2021/07/Table-of-Contents-and-Preface-Sleep-Medicine-Textbook-2nd-edition-2021-ESRS.pdf>

CASE

Start with the patient, not the MSLT

OPENING CASE

A 24-year-old sleeps 10–12 hours, needs three alarms, feels ‘drunk’ for an hour after waking, and naps without refreshment. No definite cataplexy.

ESS 18/24 • rotating shifts until 6 weeks ago • sertraline stopped 5 days before MSLT

What must be fixed before interpreting the test?

Sleep opportunity
Circadian stability
Medication washout

Answer: all three. Recent shift work and inadequate antidepressant washout can distort sleep latency/SOREMPs; document adequate, stable sleep first.

Central hypersomnolence is a small family with several look-alikes

CORE**Narcolepsy type 1**

Orexin deficiency and/or cataplexy with characteristic REM intrusion.

CORE**Narcolepsy type 2**

Narcoleptic MSLT phenotype without cataplexy or proven orexin deficiency.

CORE**Idiopathic hypersomnia**

Persistent sleepiness, often long sleep, severe inertia and unrefreshing naps.

EPISODIC**Kleine–Levin syndrome**

Recurrent episodes with near-normality between episodes.

SECONDARY**Medical / neurological**

Attributed to a condition, injury, infection or genetic disorder.

OTHER**Medication / psychiatric**

Causal attribution is essential; symptoms alone do not define a primary disorder.

the diagnostic sequence is: symptom → phenotype → objective evidence → exclusions → attribution.

PHENOTYPE

Sleepiness is not the same as fatigue

SLEEPINESS

Propensity to fall asleep

Unintended dozing or sleep attacks
Reduced alertness in passive settings
May improve briefly after sleep

FATIGUE

Low energy or effort intolerance

Can be severe without sleep onset
Often described as exhaustion
Points toward broader medical and psychiatric differential

Both can coexist.

DIFFERENTIAL

Before 'central', clear five gates



A positive MSLT does not rescue a poor pre-test history.

Use this as the differential checklist. The commonest errors occur before the laboratory.

WORK-UP

The diagnostic sequence is deliberately slow



The MSLT answers a constrained question after preparation; it is not a general sleepiness biomarker.

A technically valid MSLT begins before admission

Adequate and stable sleep

Document with sleep diary and preferably actigraphy; avoid testing after chronic restriction or unstable shift work.

Treat comorbid sleep disorders

Use usual effective OSA therapy during the preceding night and each nap where appropriate.

Plan medication changes

Taper alerting, sedating and REM-modulating drugs safely; record what cannot be stopped.

Control the test day

Five nap trials, low stimulation, toxicology when indicated, and transparent protocol reporting.

Do not prescribe a universal washout without considering half-life and rebound; the protocol recommends a clinician-led plan.

EXAM NUMBERS

Know the thresholds — then ask whether they are credible

Mean sleep latency

≤ 8 min

Objective sleepiness threshold used in narcolepsy criteria and one IH pathway.

Narcoleptic REM

≥ 2 SOREMPs

Across MSLT; an eligible nocturnal SOREMP may count depending on diagnosis.

Long sleep

≥ 660 min / 24 h

Supports IH when documented by 24-h PSG or averaged actigraphy plus sleep log.

Numbers are necessary, never sufficient. For NT1, ICSD-3-TR also allows cataplexy plus a nocturnal SOREMP to fulfil the objective arm.

Orexin loss destabilises the borders of sleep and wake

Wake instability

Irrepressible sleepiness and rapid transitions into sleep.

REM intrusion

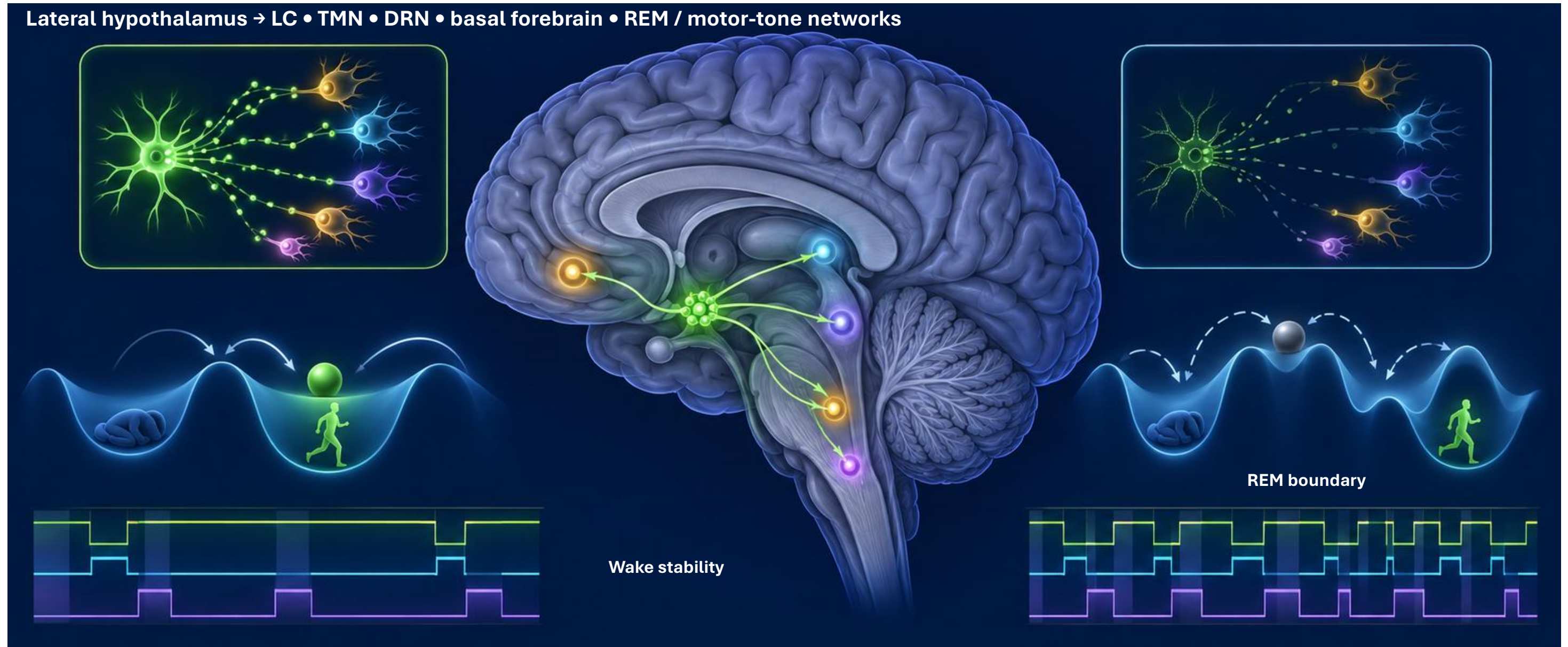
Cataplexy, sleep paralysis, hallucinations and SOREMPs.

Night fragmentation

Narcolepsy is not simply 'too much sleep'; nocturnal sleep may be disrupted.

Consider orexin as a stabilising signal rather than an on/off sleep switch. Cataplexy is emotion-triggered loss of tone with preserved awareness.

Orexin stabilises state boundaries

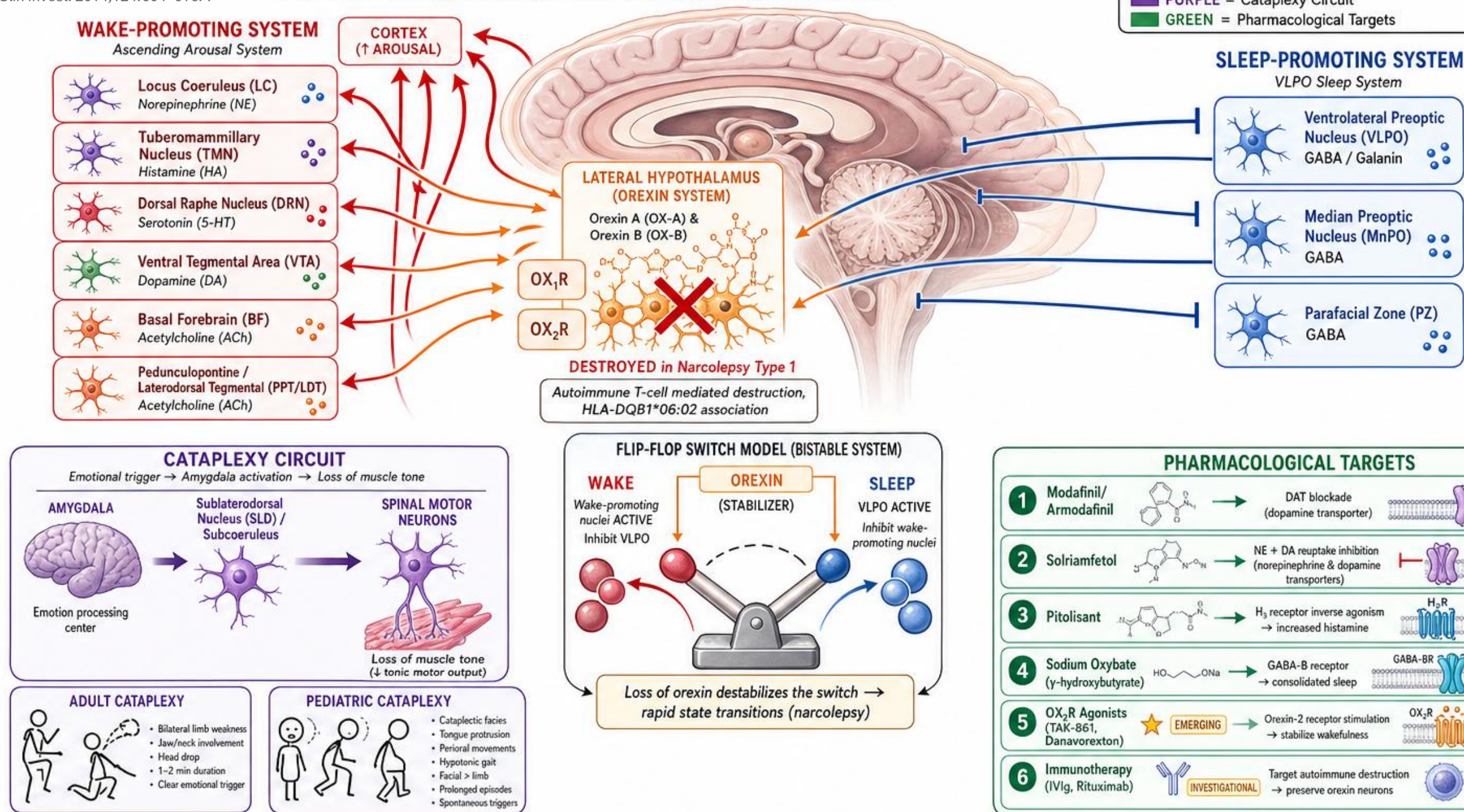
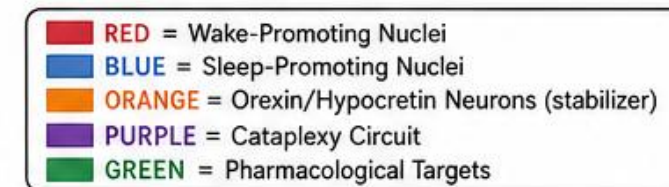


Orexin neurons recruit distributed arousal systems and stabilise transitions. Loss of that stabilising signal explains wake-state fragmentation, REM intrusion and cataplexy better than the phrase “excess sleep”.

HYPERSOMNIAS OF CENTRAL ORIGIN: Neurocircuitry & Pathomechanisms

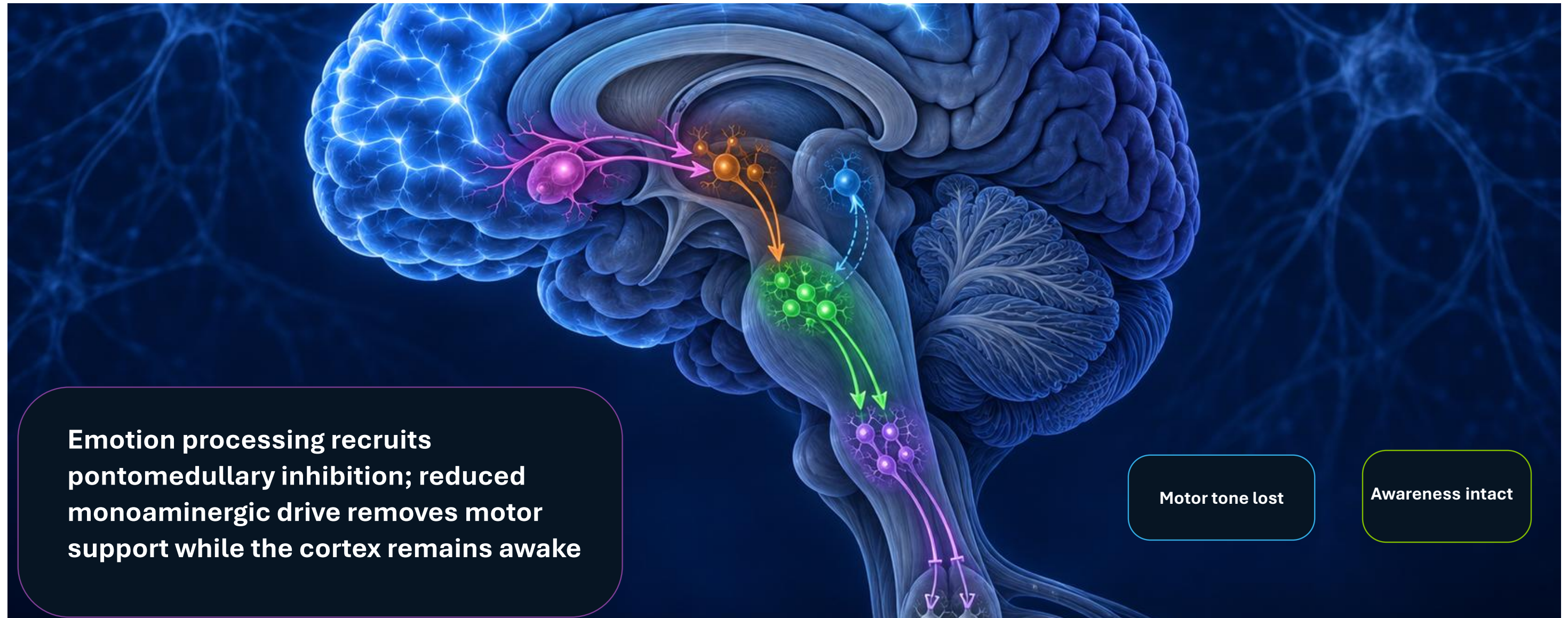
Hasegawa E et al. J Clin Invest. 2014;124:604–616. .

Sleep-Wake Circuitry, Orexin/Hypocretin System, and Disease Mechanisms



In orexin-receptor-null mice, targeted receptor restoration in the locus coeruleus consolidated wake, whereas restoration in dorsal raphe serotonergic neurons suppressed cataplexy-like episodes. The result argues that sleepiness and cataplexy can arise through partly separable orexin outputs.

Cataplexy recruits the REM-atonia pathway during wake



Positive emotion engages amygdala and medial prefrontal pathways. Pontine and medullary REM-atonia circuits increase GABAergic and glycinergic inhibition of motor neurons, while noradrenergic excitation falls. The patient remains conscious because cataplexy recruits motor atonia rather than the full REM state.

Cataplexy spans partial weakness and complete collapse



Cataplexy is bilateral, although one side may appear more affected. Awareness and memory remain intact. The diaphragm and extraocular muscles are spared. About half of patients in the cited clinical synthesis reported both partial weakness and complete paralysis, while about 30% reported partial attacks only. Ask specifically about jaw or head drop, slurred speech, dropped objects and knee buckling.

Childhood cataplexy can resemble a movement disorder

NEAR CHILDHOOD ONSET

Facial and axial hypotonia dominate

- Droopy eyelids, mouth opening and tongue protrusion
- Head and trunk drops with a floppy or unsteady gait
- Active perioral or dyskinetic movements can coexist
- Episodes may occur without an obvious emotional trigger

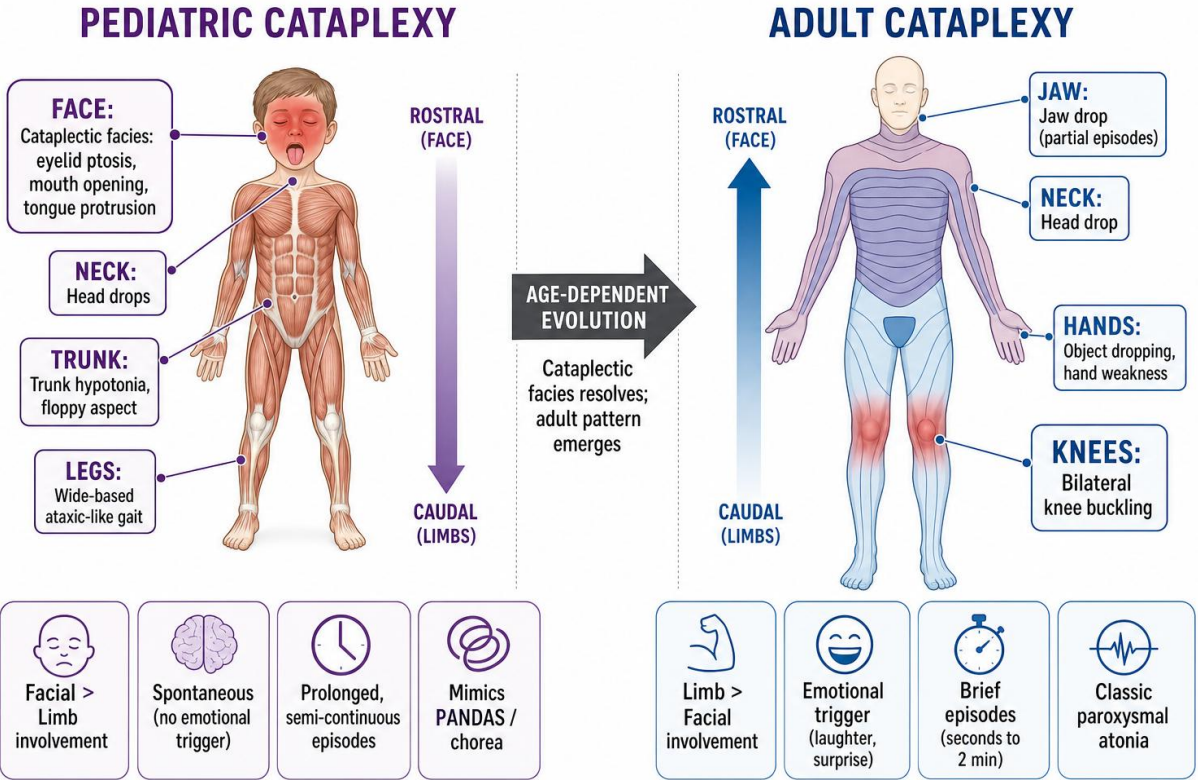
CLASSIC ADULT PATTERN

Brief emotion-triggered loss of tone

- Jaw or head drop, slurred speech and dropped objects
- Bilateral knee buckling or complete collapse
- Normal neurological examination between attacks
- Consciousness and recall remain intact

The childhood phenotype may look like epilepsy, a neuromuscular disorder, tics or a hyperkinetic movement disorder. A strong emotional trigger can be absent close to onset. Avoid demanding the adult stereotype before considering NT1. Ask families for safe home video when the history remains unclear.

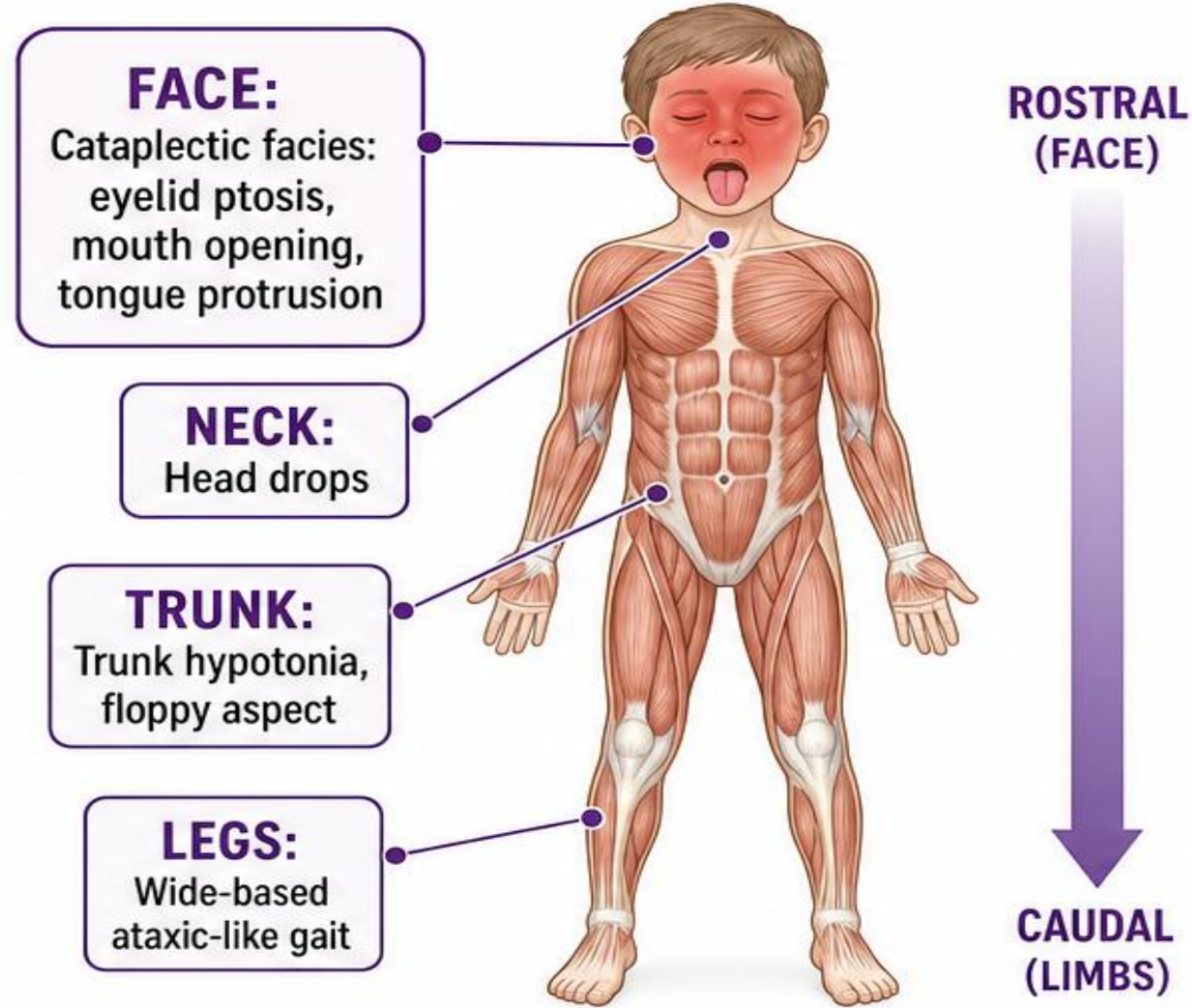
Paediatric vs Adult Cataplexy



Feature	Paediatric	Adult
Facial muscles	Predominant: jaw dropping, tongue protrusion, periorbital "cataplectic facies"	Less prominent; jaw sag only in severe attacks
Axial tone	Global hypotonia ("cataplectic walk"), trunk collapse	Knee buckling with preserved trunk
Attack pattern	Continuous/sub-continuous ("status cataplecticus")	Discrete, brief episodes (seconds to 2 min)
Triggers	Negative emotions common; spontaneous attacks	Laughter, surprise, positive emotions
Motor features	Perioral dyskinesia, active motor phenomena	Pure atonia without active movements
Misdiagnosis	Epilepsy, ataxia, neuromuscular (48%)	Syncope, drop attacks (15-20%)
Evolution	Transitions to adult phenotype over 2-4 years	Stable phenotype; severity may decrease

Key Insight: Pediatric cataplexy is a distinct motor phenotype, not simply milder adult cataplexy. The "cataplectic facies" (facial hypotonia + dyskinesia) is virtually pathognomonic for childhood-onset NT1.

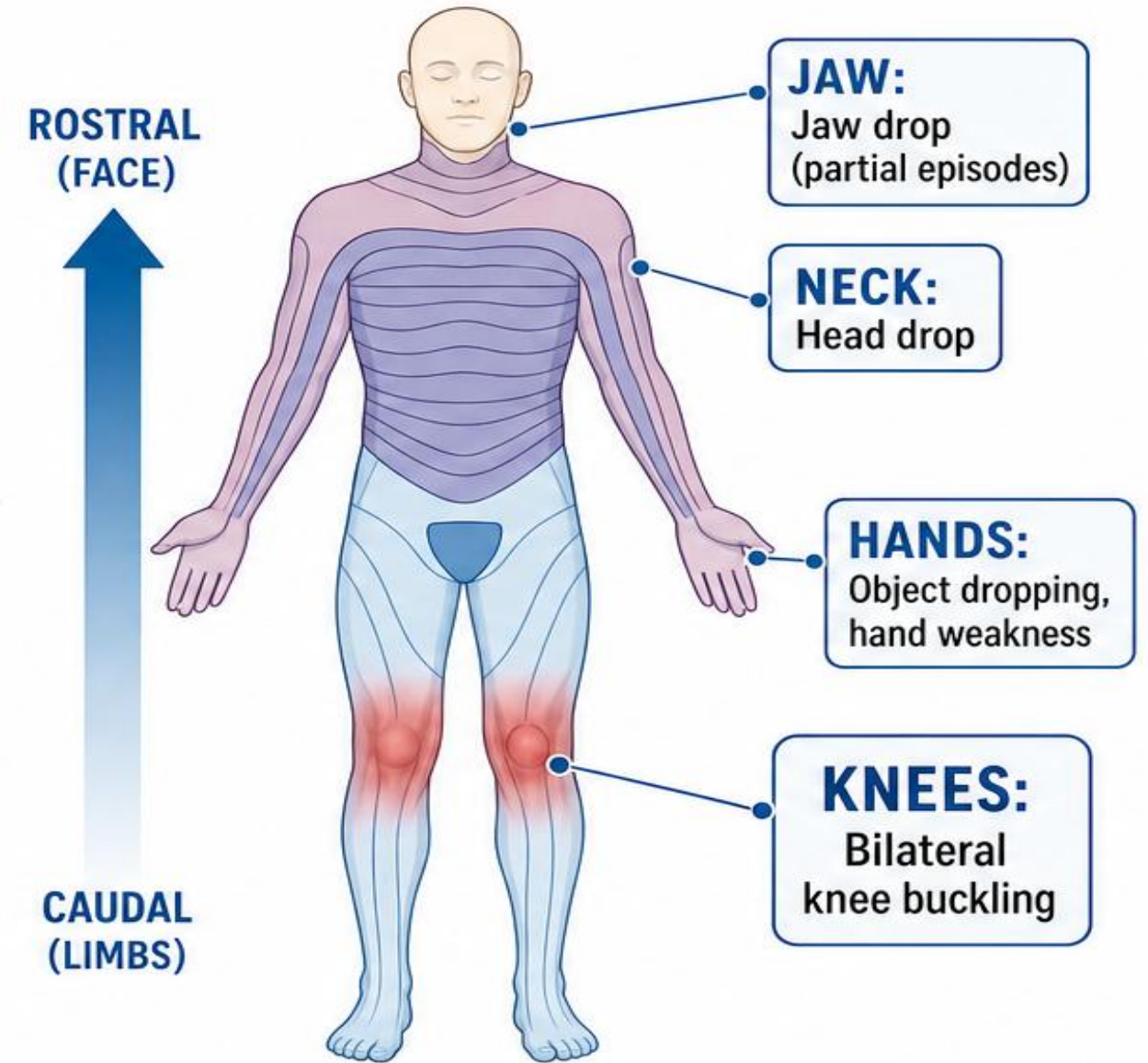
PEDIATRIC CATAPLEXY



AGE-DEPENDENT EVOLUTION

Cataplectic facies resolves; adult pattern emerges

ADULT CATAPLEXY



Facial > Limb involvement



Spontaneous (no emotional trigger)



Prolonged, semi-continuous episodes



Mimics PANDAS / chorea



Limb > Facial involvement



Emotional trigger (laughter, surprise)



Brief episodes (seconds to 2 min)



Classic paroxysmal atonia

Childhood cataplexy evolves toward the adult pattern

Untreated children showed a marked change in motor phenotype over the first years after onset

Adult pattern at first assessment

9.5%

Spontaneous hypotonia and active movements were common

Mean age 10 years

Adult pattern at follow-up

71.4%

Classic emotion-triggered episodes became predominant

Mean age 12 years

Prospective cohort

n = 21

Drug-naïve children with narcolepsy and cataplexy

Median 3 years from onset

Early cataplexy is a changing motor phenotype; time from onset alters what the examiner sees.

ICSD-3-TR: two routes to objective confirmation

ROUTE A

Cataplexy + REM evidence

MSLT mean latency ≤ 8 min and ≥ 2 SOREMPs

OR cataplexy plus a nocturnal SOREMP

Use current standard MSLT protocol

ROUTE B

Low CSF orexin

≤ 110 pg/mL using Stanford reference sample

OR $<$ one-third of normal assay mean

Can establish NT1 even when MSLT is non-diagnostic

cataplexy plus a nocturnal SOREMP can fulfil criterion B. Persistent daily sleepiness ≥ 3 months and exclusion criteria still apply

NT2 is a positive test inside a diagnosis of exclusion

Sleepiness + narcoleptic MSLT — but no cataplexy and no proven orexin deficiency

Recheck sleep sufficiency, circadian alignment, medicines, OSA and test reproducibility before attaching a lifelong label.

No cataplexy

≥ 2 SOREMPs

MSL ≤ 8 min

Exclusions

NT2 is more heterogeneous and less biologically anchored than NT1. If cataplexy later develops or orexin is low, reclassify as NT1.

IDIOPATHIC HYPERSOMNIA

IH is often a disorder of waking as much as sleeping

Long, unrefreshing sleep

Some—but not all—patients sleep ≥ 11 hours across 24 hours.

Severe sleep inertia

Prolonged impaired awakening: ‘sleep drunkenness’.

Long, unrefreshing naps

Unlike classic narcolepsy, naps frequently fail to restore alertness.

ICSD-3-TR added an explicit requirement that PSG/MSLT findings are not consistent with NT1 or NT2. Symptoms persist ≥ 3 months and are not better explained by other causes.

Source: <https://aasm.org/wp-content/uploads/2023/05/ICSD-3-Text-Revision-Supplemental-Material.pdf>

DIFFERENTIATION

NT2 versus IH: the boundary rests heavily on REM

Feature	Narcolepsy type 2	Idiopathic hypersomnia
Cataplexy	Absent	Absent
MSLT	Mean latency ≤8 min; ≥2 SOREMPs	Not consistent with narcolepsy; often <2 SOREMPs
Long total sleep time	May occur, not defining	May establish objective sleepiness (≥660 min/24 h)
Naps	Often short and refreshing	Often long and unrefreshing
Sleep inertia	Can occur	Often prominent
Diagnostic stability	MSLT phenotype can vary	Reassess if phenotype and testing disagree

However, the symptom overlap is substantial and the MSLT has imperfect repeatability. A forced binary label should never override the longitudinal phenotype.

NEW FINDING

NT2 and IH do not form stable biological islands



In 1,078 unmedicated people, unsupervised clustering across 97 variables found seven clusters. NT2 and IH diagnoses were evenly mixed within the two main non-cataplexy clusters. The study questions whether SOREMP count alone is the right boundary in patients without cataplexy. This is a classification insight, not permission to ignore current criteria.

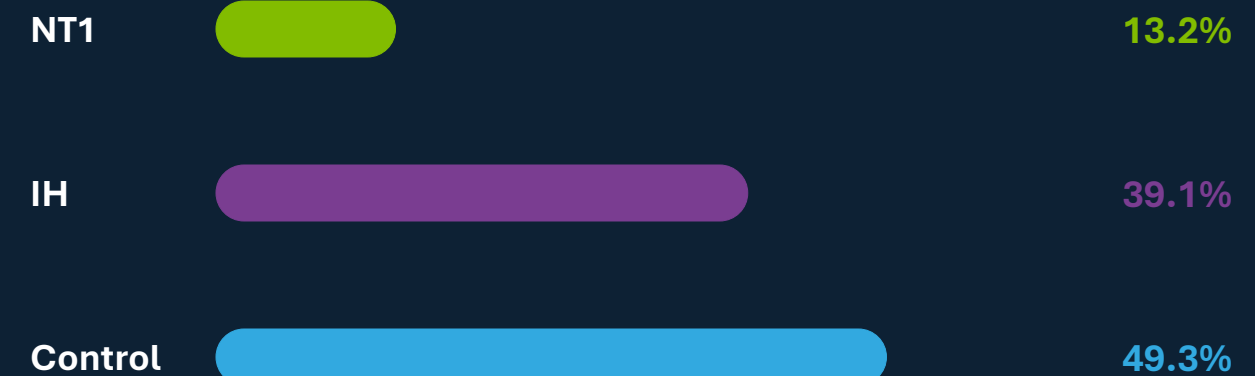
A 2026 imaging signal is promising, not yet diagnostic

Dynamic resting-state connectivity distinguished NT1 from IH in one drug-naïve cohort

State II: coupled DMN / sensorimotor / visual pattern



State I: sparse intrinsic-network connectivity

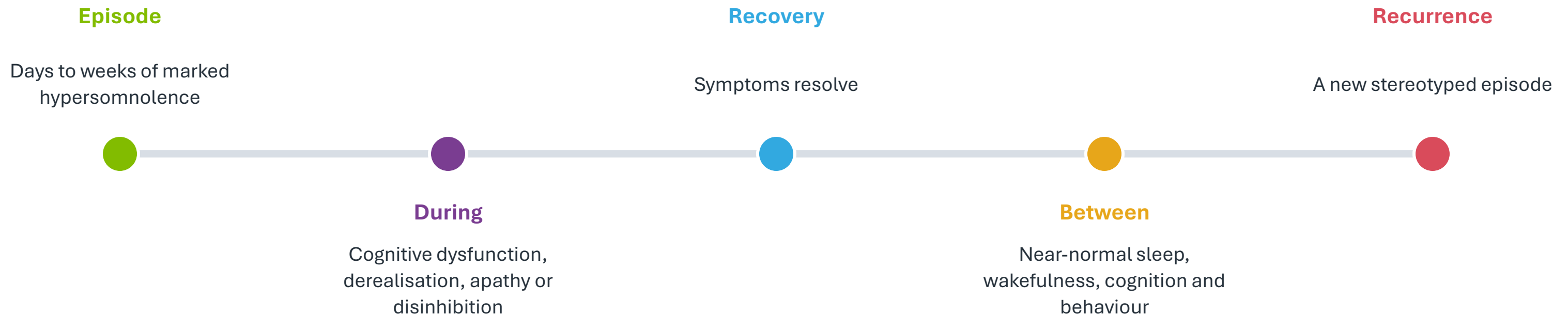


Random-forest AUC 0.90 in this dataset • n = 50 NT1, 31 IH, 50 controls • external validation is required

Five recurring connectivity states were identified. A random-forest model using State II features achieved AUC 0.90 for NT1 versus IH. The cohort is modest and independent external validation is needed.

RECURRENT HYPERSOMNIA

Kleine–Levin syndrome is episodic — normality between attacks matters



Exam discriminator: episodic pattern with recovery between episodes. ICSD-3-TR modernised associated features, including derealisation and major apathy.

Source: <https://aasm.org/wp-content/uploads/2023/05/ICSD-3-Text-Revision-Supplemental-Material.pdf>

SECONDARY CAUSES

Ask whether the hypersomnolence is primary — or attributed

Neurological

Head injury, tumour, stroke, encephalitis, neurodegeneration, hypothalamic lesions.

Genetic / systemic

Myotonic dystrophy and selected syndromic disorders.

Medication / substance

Sedatives, antipsychotics, antihistamines, opioids, alcohol and withdrawal states.

Psychiatric

Hypersomnolence can accompany mood disorders; distinguish sleep propensity from fatigue.

Sleep fragmentation

OSA, PLMS, pain and nocturnal epilepsy can mimic a central disorder.

Circadian / behavioural

Irregular schedules, delayed phase and chronic sleep restriction.

Attribution requires a plausible temporal and mechanistic relationship, not merely coexistence.

The phenotype often tells you which confounder to hunt

Clue	Think first	Confirm with
Weekend catch-up + short weekdays	Insufficient sleep	Diary / actigraphy and sleep opportunity
Late sleep onset, normal sleep when free	Delayed phase	Clock history, diary / actigraphy
Snoring, witnessed apnoea, morning headache	OSA	PSG or validated sleep study
Temporal link to a drug change	Medication effect	Reconciliation and supervised adjustment
Low energy without dozing	Fatigue syndrome / mood / medical	Broader medical and psychiatric assessment

Children may look hyperactive; older adults may look ‘slowed’

CHILD / ADOLESCENT

Behaviour can mask sleepiness

Irritability, hyperactivity, school decline
Facial hypotonia or complex cataplexy
Rapid weight gain around NT1 onset
Protect development, education and family function

OLDER ADULT

Polypharmacy dominates

Sedating medicines and comorbidity
Neurodegenerative or structural causes
Falls and driving risk
Interpret tests in the full clinical context

Do not insist on the adult stereotype. Age changes the presentation, risk balance and practical management.

CASE RESOLUTION

Case 1: the first diagnosis is 'test not yet interpretable'

Stabilise sleep and circadian timing; complete a safe medication plan; then retest only if needed

A premature NT2 or IH label would convert confounding into disease.

Document

Correct

Repeat

Reclassify

Case 2: two SOREMPs after abrupt REM-suppressant withdrawal

The MSLT shows mean sleep latency 6 minutes and 2 SOREMPs. What is the best interpretation?

A Definite NT2

B REM rebound is a major confounder

C Definite IH

D No sleep disorder

Correct answer: B.

Abrupt withdrawal of REM-suppressing medication may create REM rebound and false-positive SOREMPs. Reconstruct the preparation and clinical phenotype before diagnosing.

Treat the mechanism you can identify — and the risk you cannot ignore

Cause-specific

Correct restriction, circadian misalignment, OSA, medication burden or underlying disease.

Symptom-targeted

Wake-promoting therapy and structured behavioural strategies when appropriate.

Function and safety

Driving, work, education, pregnancy, mental health and social support.

For IH, AASM strongly recommends modafinil in adults; other options are conditional and local licensing varies.

Source: https://aasm.org/wp-content/uploads/2022/03/Treatment_Central_Disorders_Hypersomnolence_Guideline_at_a_Glance.pdf

A diagnosis is incomplete until risk is managed

Driving and safety-critical work

Assess real-world sleep attacks, treatment response and local legal duties; objective wakefulness testing answers only selected questions.

Pregnancy and contraception

Review treatment before conception; modafinil is associated with congenital-malformation risk and reduces effectiveness of steroidal contraception.

Mental health and stigma

Screen actively; validate invisible disability and support adjustments.

Follow-up

Track function, symptoms, adverse effects, blood pressure/weight where relevant, and diagnostic stability.

EXAM CHECKPOINT

One minute: choose the single best answer

Which finding can now pair with cataplexy to fulfil the objective arm of NT1 criteria without an MSLT?

A ESS ≥ 16

B HLA-DQB1*06:02

C Nocturnal SOREMP

D Sleep time ≥ 660 min

Correct answer: C — a SOREMP within 15 minutes of sleep onset on nocturnal PSG, alongside cataplexy, can fulfil ICSD-3-TR criterion B. HLA supports susceptibility but is not diagnostic.

Source: <https://aasm.org/wp-content/uploads/2023/05/ICSD-3-Text-Revision-Supplemental-Material.pdf>

TAKE-HOME

Five rules that survive the exam — and the clinic

Central hypersomnolence is a diagnosis of disciplined context.

- 1: Separate sleepiness from fatigue.
- 2: Prove adequate sleep and circadian stability before PSG/MSLT.
- 3: Use cataplexy and orexin biology to anchor NT1.
- 4: Treat NT2 versus IH as a longitudinal distinction, not a single-number contest.
- 5: Finish with function, driving, pregnancy and follow-up.

SOURCES

Core reading

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