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EXIT EXAMINATION • SOLVED PREVIOUS-YEAR QUESTIONS

DM Neurology

Solved Previous-Year Questions with Textbook-Cited Answers

VOLUMES I • II • III



VOLUME I

Neuroanatomy, Localisation
and Investigation

VOLUME II

Disorders
of the Brain

VOLUME III

Immune-Mediated and
Neuromuscular Disease

REVIEWED BY

Dr Abhishek Tiwari • Dr Divya Gupta

both DM Neurology

*Based on Bradley & Daroff's Neurology in Clinical Practice 8e, DeJong's The Neurologic Examination 8e
and Preston & Shapiro's Electromyography and Neuromuscular Disorders 4e*

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SAMPLE EDITION • 100 PAGES FROM THE THREE-VOLUME SET

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About this book

This is a solved question bank for the **DM Neurology exit examination**. It answers every question of the topic-wise compilation and of all eight DM Neurology papers of 2025 — **436 questions**, written as **286 answers**, because repeated and near-identical questions share one answer.

Every answer is written from three standard texts and nothing else: **Bradley & Daroff 8e** as the primary source, **DeJong 8e** for neuroanatomy and bedside technique, and **Preston & Shapiro 4e** for all electrodiagnosis. Each answer cites chapter, section and page range, and the diagrams are the actual textbook figures, cited by figure number and printed page — so every line can be checked against the book on your shelf.

Answers are point-wise and in simple language: elaborate enough to score, short enough to reproduce in the exam hall. Depth is scaled to the marks, and every answer carries its original paper, year and question number.

The set at a glance

Volume	Parts	Answers	Pages
Volume I	Neuroanatomy, Localisation and Investigation — Part 1 Systems and Pathways · Part 2 Short Notes and Clinical Correlates · Part 3 Neuroimaging and Clinical Neurophysiology	81	358
Volume II	Disorders of the Brain — Part 4 Stroke · Part 5 Epilepsy, EEG and Status Epilepticus · Part 6 Movement Disorders · Part 7 Dementia, Cognition, Sleep and Headache · Part 8 Infections	108	487
Volume III	Immune-Mediated and Neuromuscular Disease — Part 9 Demyelinating, Autoimmune and Cerebellar · Part 10 Peripheral Nerve, NMJ, Muscle and Anterior Horn Cell · Part 11 Drugs, Recent Advances and Research Methods	97	385
Complete set		286	1,230

Reviewed by

Dr Abhishek Tiwari

DM Neurology

Dr Divya Gupta

DM Neurology

How to read an answer

LONG · 10 marks

INTERMEDIATE · 6-8 marks

SHORT · 5 marks

Under each question: the paper, year and question number, an *Also asked as* line listing every other form of it, and the **Source** line with chapter, section and pages.

HIGH-YIELD / CLINICAL PEARLS

Ends every answer — the points to revise the night before.

GUIDELINE UPDATE

Management that post-dates the textbooks, kept apart from textbook content.

NOT COVERED

Where the sources are silent — never a silent omission, never an invented citation.

FIGURES AND TABLES

Real textbook figures with what to label; tables numbered within each part.

Inside this sample

These 100 pages are taken unchanged from the three volumes: the opening pages and the full index of Volume I, followed by complete answers from five of the eleven parts. Each answer is shown from its first line to its high-yield box.

Contents	Part · type	Page
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Standard DM Neurology reading list — current editions		6
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Q2. Management of multiple sclerosis — a critical evaluation	Part 9 · Long	75
Q1. Causes of neuropathy; GBS in India versus the rest of the world	Part 10 · Long	85
Q2. Electrophysiological evaluation of AIDP	Part 10 · Intermediate	97

Page numbers above are pages of this sample. The number printed at the foot of each answer page is its page in the full volume, so the index can be followed straight into the complete book.

Get the complete three-volume set

All 436 questions · 286 answers · about 1,230 pages in full colour

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How this book is built

The three volumes

- The bank answers every question of the topic-wise compilation and of the eight DM Neurology papers of 2025 — **436 questions**, written as **286 answers**, because repeated and near-identical questions share one answer.
- **Volume I — Neuroanatomy, Localisation and Investigation** (Parts 1–3): the pathways, the short anatomy notes, and imaging and neurophysiology.
- **Volume II — Disorders of the Brain** (Parts 4–8): stroke, epilepsy, movement disorders, dementia and headache, and infection.
- **Volume III — Immune-Mediated and Neuromuscular Disease** (Parts 9–11): demyelination and autoimmunity, nerve, junction and muscle, and drugs and recent advances.
- The index in **every** volume lists all 436 questions and says which volume, part and answer covers each one — with a page number when the answer is in the volume you are holding.

Source discipline

- Every answer is written **only** from Bradley & Daroff 8e, DeJong 8e and Preston & Shapiro 4e. Nothing is taken from the web or from memory of other texts.
- **Bradley & Daroff 8e is the primary source.** DeJong is used for neuroanatomy and bedside technique, Preston & Shapiro for all electrodiagnosis.
- Where a topic is **not covered** in those sources it carries a red **NOT COVERED** box naming exactly what was searched for and what came back — never a silent omission, never an invented citation.
- Management that post-dates the textbooks appears **only** inside an amber **GUIDELINE UPDATE** box, so textbook and outside content never mix on the page.

Answer format and citation

- Point-wise, simple language — elaborate but reproducible in the exam hall. Depth is scaled to the marks: **LONG** ≈ 10, **INTERMEDIATE** ≈ 6–8, **SHORT** ≈ 5.
- Each answer keeps its **original paper, year and question number** (or topic-bank section and number) and an “Also asked as” line listing every other form of it.
- **Diagrams are the actual textbook figures**, cropped from the source PDFs and cited by figure number and printed page; each caption says what to label when reproducing it.
- Citations give **chapter, section and page range**. Bradley and Preston are cited by printed page number; the DeJong copy is a reflowed electronic edition with no printed pagination and is cited by chapter, section and figure.
- Every answer ends with a green **HIGH-YIELD / CLINICAL PEARLS** box.

Finding your way around

- Question and table numbers restart in each part, so a reference reads **Part 10 · Q12**. Parts are numbered straight through the three volumes, 1 to 11.
- The PDF carries **bookmarks** for the index, every part and every answer — use your reader’s sidebar rather than scrolling.

Standard DM Neurology reading list — current editions

- The texts a DM / DrNB Neurology candidate is expected to have read or to have at hand, grouped by subject, with the edition and the reason each one earns its place on the list.
- Editions below were current in **September 2026**. Confirm the edition when you order, since publishers reissue these on a three-to-five year cycle.

Core reference

Title	Author	Edition	Publisher	Why it is on the list
Bradley and Daroff's Neurology in Clinical Practice	Jankovic, Mazziotta, Pomeroy, Newman	9th · 2025	Elsevier	The standard two-volume reference; this bank is written from the 8th
Adams and Victor's Principles of Neurology	Ropper, Samuels, Klein, Prasad	12th · 2023	McGraw Hill	Classic single-volume text; superb on approach and syndromes
Merritt's Neurology	Louis, Mayer, Noble	14th · 2021	Wolters Kluwer	Concise, fact-dense; good for rapid revision
Neurology: A Queen Square Textbook	Clarke, Howard, Rossor, Shorvon	3rd · 2024	Wiley	Strong clinical reasoning and investigation chapters

Examination, localisation and neuroanatomy

Title	Author	Edition	Publisher	Why it is on the list
DeJong's The Neurologic Examination	Campbell, Barohn	8th	Wolters Kluwer	Bedside technique and the anatomy behind every sign
Localization in Clinical Neurology	Brazis, Masdeu, Biller	8th · 2021	Wolters Kluwer	The localisation book; invaluable for viva
Neuroanatomy through Clinical Cases	Blumenfeld	3rd · 2022	Oxford / Sinauer	Anatomy taught through cases; best diagrams for drawing

Clinical neurophysiology

Title	Author	Edition	Publisher	Why it is on the list
Electromyography and Neuromuscular Disorders	Preston, Shapiro	4th · 2020	Elsevier	The practical EMG/NCS text; used throughout Part 10 and Part 3
Electrodiagnosis in Diseases of Nerve and Muscle	Kimura	4th	Oxford	The theory behind the waveforms; deeper than Preston
Niedermeyer's Electroencephalography	Schomer, Lopes da Silva	7th	Oxford	Reference EEG text for the neurophysiology rotation

Imaging

Title	Author	Edition	Publisher	Why it is on the list
Osborn's Brain: Imaging, Pathology and Anatomy	Osborn	3rd · 2024	Elsevier	Pattern-based neuroimaging; the standard for image-based vivas

Subspecialty

Title	Author	Edition	Publisher	Why it is on the list
Caplan's Stroke: A Clinical Approach	Caplan	5th	Cambridge	Vascular syndromes and mechanism-based stroke thinking
Wyllie's Treatment of Epilepsy: Principles and Practice	Wyllie	8th · 2025	Wolters Kluwer	Comprehensive epilepsy reference including surgery
Principles and Practice of Movement Disorders	Jankovic, Fahn, Tolosa	3rd	Elsevier	Phenomenology, genetics and treatment of movement disorders
Swaiman's Pediatric Neurology: Principles and Practice	Ashwal, Ferriero, Gropman	7th	Elsevier	Paediatric neurology, metabolic and developmental disease

Continuing education

Title	Author	Edition	Publisher	Why it is on the list
Continuum: Lifelong Learning in Neurology	American Academy of Neurology	Bi-monthly	AAN / Wolters Kluwer	Issue-per-topic reviews; the fastest route to current practice

Index — every question in the bank

- Every question of the compilation, in its original order: the topic-wise bank section by section, then the eight DM Neurology papers of 2025.
- **Vol II · P5 · Q12 · p. 233** — volume, part, answer number and, when the answer is in **this** volume, its page. Answers in the other two volumes are given without a page.

Volume	Part	Title	Where
Vol I	Part 1	Neuroanatomy and Localisation — Systems and Pathways	this volume
Vol I	Part 2	Neuroanatomy — Short Notes and Clinical Correlates	this volume
Vol I	Part 3	Neuroimaging and Clinical Neurophysiology	this volume
Vol II	Part 4	Stroke and Cerebrovascular Disease	Volume II
Vol II	Part 5	Epilepsy, EEG and Status Epilepticus	Volume II
Vol II	Part 6	Movement Disorders	Volume II
Vol II	Part 7	Dementia, Cognition, Sleep and Headache	Volume II
Vol II	Part 8	Infections of the Nervous System	Volume II
Vol III	Part 9	Demyelinating, Autoimmune and Cerebellar Disorders	Volume III
Vol III	Part 10	Peripheral Nerve, NMJ, Muscle and Anterior Horn Cell	Volume III
Vol III	Part 11	Drugs, Recent Advances, Investigations and Research Methods	Volume III

The eleven parts across the three volumes.

Anatomy

No.	Question	Answered at
§Long Q1	Anatomy of visual pathway and its clinical correlates.	Vol I · P1 · Q5 · p. 43
§Long Q2	Anatomy and connections of basal ganglia and describe its involvement in pathogenesis of different movement disorders.	Vol II · P6 · Q1
§Long Q3	Describe pain pathway and molecular drug targets of pain therapy.	Vol I · P1 · Q14 · p. 91
§Long Q4	What is muscle tone? Draw labelled diagram of myotatic reflex and describe pathophysiology of spasticity?	Vol I · P1 · Q12 · p. 79
§Long Q5	Thalamus functions, pathology and association with movement disorder surgery.	Vol I · P1 · Q4 · p. 38
§Long Q6	Anatomy, neural connection and function of thalamus in respect of sensation, behaviour, and memory.	Vol I · P1 · Q4 · p. 38
§Long Q7	Anatomy and physiological pathway of basal ganglia along with clinical implication.	Vol II · P6 · Q1
§Long Q8	Discuss organisation of speech and various aphasias.	Vol I · P1 · Q1 · p. 26
§Long Q9	Utility of implantable and non-implantable devices in neurological disorders.	Vol I · P1 · Q25 · p. 152
§Long Q10	How chemical toxins act at different levels of central and peripheral nervous system? What are the usual way of presentation?	Vol I · P1 · Q24 · p. 146
§Long Q11	How you will approach a patient of aged 65 years presented with episodic loss of consciousness.	Vol II · P7 · Q10
§Long Q12	How you will approach a patient of aged 15 years presented with abnormal gait.	Vol I · P1 · Q13 · p. 85
§Long Q13	Discuss anatomy and blood supply of thalamus. Describe clinical syndromes associated with thalamic lesions.	Vol I · P1 · Q4 · p. 38
§Long Q14	What do you mean by gait cycle? Describe post stroke gait disorder and rehabilitative measures.	Vol II · P4 · Q18
§Long Q15	Discuss CSF pathways and abnormal intracranial pressure syndromes.	Vol I · P1 · Q15 · p. 100
§Long Q16	Classify neuromodulators in brain. What are the neuropeptide families? What are their broad lines of functions?	Vol I · P1 · Q19 · p. 127
§Long Q17	Role of antibodies	Vol III · P9 · Q18
§Long Q18	Discuss the structure and function of mitochondria and their relevance in neurological diseases.	Vol I · P1 · Q20 · p. 131
§Inter Q1	Descending tracts of spinal cord and their clinical significance.	Vol I · P1 · Q11 · p. 75
§Inter Q2	Limitation of current BBB models for the study of neurodegenerative disorders.	Vol I · P1 · Q21 · p. 136
§Inter Q3	Neurobiology of memory.	Vol II · P7 · Q1

No.	Question	Answered at
§Inter Q4	Neurophysiology of urinary bladder control explaining with appropriate diagrams.	Vol I · P1 · Q18 · p. 118
§Inter Q5	Role of cytokines in modulating learning, memory and brain plasticity.	Vol I · P1 · Q22 · p. 139
§Inter Q6	Thalamus	Vol I · P1 · Q4 · p. 38
§Inter Q7	Gut microbiome and CNS	Vol I · P1 · Q23 · p. 142
§Inter Q8	Describe the corpus callosum and discuss the clinical features of lesions involving the corpus callosum.	Vol I · P1 · Q3 · p. 34
§Short Q1	Frontal lobe	Vol I · P2 · Q1 · p. 161
§Short Q2	Autonomic nervous system	Vol I · P1 · Q17 · p. 112
§Short Q3	Anatomical and clinical correlation in cavernous sinus syndrome	Vol I · P2 · Q9 · p. 184
§Short Q4	Gate theory of pain	Vol I · P1 · Q14 · p. 91
§Short Q5	Basal ganglia	Vol II · P6 · Q1
§Short Q6	Anatomy of visual pathway	Vol I · P1 · Q5 · p. 43
§Short Q7	Anatomy of ventricular system of brain	Vol I · P1 · Q15 · p. 100
§Short Q8	Ondine curse	Vol I · P2 · Q20 · p. 218
§Short Q9	Retrochiasmal lesion	Vol I · P1 · Q5 · p. 43
§Short Q10	Horner syndrome	Vol I · P1 · Q16 · p. 106
§Short Q11	Papez circuit	Vol II · P7 · Q1
§Short Q12	Neurogenic bladder	Vol I · P1 · Q18 · p. 118
§Short Q13	Difference between metabolic and structural coma.	Vol II · P7 · Q11
§Short Q14	Anocioceptive action of botulinum toxin	Vol I · P2 · Q25 · p. 233
§Short Q15	Vein of Galen	Vol I · P2 · Q19 · p. 215
§Short Q16	Anatomy of visceral brain and rationality of connections	Vol I · P2 · Q2 · p. 163
§Short Q17	Anatomy and function of cerebellum – motor and non motor	Vol III · P9 · Q23
§Short Q18	Draw a section of medulla showing structures involved in Wallenberg syndrome.	Vol II · P4 · Q8
§Short Q19	Dopaminergic pathways in CNS	Vol II · P6 · Q3
§Short Q20	Spinal dysraphism syndrome	Vol I · P2 · Q22 · p. 224
§Short Q21	CGRP receptors	Vol II · P7 · Q15
§Short Q22	Axonal transport and neurological diseases	Vol I · P2 · Q28 · p. 243
§Short Q23	Neurobiology of broken heart syndrome	Vol I · P2 · Q21 · p. 220
§Short Q24	Trinucleotide repeat disorders	Vol I · P2 · Q30 · p. 248

No.	Question	Answered at
§Short Q25	NMDA receptors	Vol I · P2 · Q32 · p. 254
§Short Q26	Inclusion bodies in brain	Vol I · P2 · Q29 · p. 245
§Short Q27	Persistent vegetative state	Vol II · P7 · Q12
§Short Q28	Neurological complications of uremia	Vol I · P2 · Q34 · p. 259
§Short Q29	Neurological complications of CRF	Vol I · P2 · Q34 · p. 259
§Short Q30	Primary position nystagmus	Vol I · P2 · Q15 · p. 202
§Short Q31	DMPK protein kinase enzyme	Vol I · P2 · Q31 · p. 251
§Short Q32	NO synthase enzyme	Vol I · P2 · Q33 · p. 256
§Short Q33	Brain death	Vol II · P7 · Q12
§Short Q34	BPPV	Vol I · P2 · Q16 · p. 206
§Short Q35	Plantar reflex	Vol I · P2 · Q26 · p. 236
§Short Q36	Air pollution and smoke	Vol I · P1 · Q24 · p. 146
§Short Q37	Role of neurotransmitters in neurophysiology of sleep	Vol II · P7 · Q13
§Short Q38	What are neuropsychiatric categories of memory and possible location	Vol II · P7 · Q1
§Short Q39	Ross syndrome	Vol I · P1 · Q17 · p. 112
§Short Q40	Fast eye movement	Vol I · P1 · Q6 · p. 47
§Short Q41	Diagnostic criteria of brain death	Vol II · P7 · Q12
§Short Q42	Thyroid related orbitopathy	Vol I · P2 · Q12 · p. 194
§Short Q43	Neurological complications of hemodialysis	Vol I · P2 · Q34 · p. 259
§Short Q45	Referred pain	Vol I · P2 · Q24 · p. 231
§Short Q46	Detrusor sphincter dyssynergia	Vol I · P1 · Q18 · p. 118
§Short Q47	Cortical blindness	Vol I · P1 · Q5 · p. 43
§Short Q48	Neurobiology of memory	Vol II · P7 · Q1
§Short Q49	Sensory receptors and their functions	Vol I · P2 · Q23 · p. 228
§Short Q50	Discuss anatomical model for praxis and apraxia	Vol I · P1 · Q1 · p. 26
§Short Q51	Anatomical aspect of gait	Vol I · P1 · Q13 · p. 85
§Short Q52	Anatomical course of III cranial nerve and its clinical correlates	Vol I · P2 · Q10 · p. 187
§Short Q53	Central and peripheral vertigo	Vol I · P2 · Q17 · p. 208
§Short Q54	Assessment of functional blindness	Vol I · P2 · Q7 · p. 176

Autoimmune

No.	Question	Answered at
§Long Q1	Paraneoplastic syndromes significant in neurological practice with short note on their Mx.	Vol III · P9 · Q17
§Long Q2	Role of antibodies and their targets in the diagnosis and Mx of paraneoplastic neurological diseases.	Vol III · P9 · Q17
§Inter Q1	Diagnosis of sarcoidosis	Vol III · P9 · Q20
§Inter Q2	Autoimmune encephalitis	Vol III · P9 · Q15
§Short Q1	NMDAR encephalitis	Vol III · P9 · Q15
§Short Q2	Ant AMPA encephalitis	Vol III · P9 · Q15
§Short Q3	Opsoclonus myoclonus syndrome	Vol III · P9 · Q19
§Short Q4	Immunological evaluation of autoimmune encephalitis	Vol III · P9 · Q16
§Short Q5	Autoimmune limbic encephalitis	Vol III · P9 · Q15
§Short Q6	Autoimmune encephalitis	Vol III · P9 · Q15

Cerebellar

No.	Question	Answered at
§Long Q1	Approach to chronic progressive ataxic disorder.	Vol III · P9 · Q24
§Long Q2	Approach to a case of subacute ataxia. Discuss specific Mx of common causes.	Vol III · P9 · Q24
§Short Q1	SUSAC syndrome	Vol III · P9 · Q14
§Short Q2	Episodic ataxia	Vol III · P9 · Q25

AHC

No.	Question	Answered at
§Short Q1	SMA	Vol III · P10 · Q38
§Short Q2	Electrophysiological assessment of MND	Vol III · P10 · Q39
§Short Q3	Pseudobulbar palsy	Vol III · P10 · Q41
§Short Q4	Floppy infant syndrome	Vol III · P10 · Q5

Dementia

No.	Question	Answered at
§Long Q1	Approach towards a patient with dementia.	Vol II · P7 · Q2
§Long Q2	What do you mean by cognition? How you study cognition in real life? What are different types of cognitive dysfunction? Write	Vol II · P7 · Q2
§Long Q3	How would you like to approach a 63 years old man with urinary incontinence and progressive gait disorder?	Vol II · P7 · Q8

No.	Question	Answered at
§Long Q4	Discuss rapidly progressive neurodegenerative dementia.	Vol II · P7 · Q7
§Long Q5	Critically evaluate the medical treatment of Alzheimer's dementia.	Vol II · P7 · Q5
§Inter Q1	What are the newer therapeutic options for AD?	Vol II · P7 · Q5
§Short Q1	Vascular dementia	Vol II · P7 · Q2
§Short Q2	Genetics of AD	Vol II · P7 · Q6
§Short Q3	Autism	Vol II · P7 · Q9
§Short Q4	MCI	Vol II · P7 · Q2
§Short Q5	Recent advances in drug therapy of AD	Vol II · P7 · Q5

Demyelinating disorders

No.	Question	Answered at
§Long Q1	Approach and Mx of NMO spectrum disorder.	Vol III · P9 · Q3
§Long Q2	Diagnostic criteria of MS and role of MRI in its diagnosis.	Vol III · P9 · Q1
§Inter Q1	How will you manage the young female presenting with relapsing remitting MS?	Vol III · P9 · Q2
§Short Q1	INO and underlying mechanism	Vol III · P9 · Q8
§Short Q2	MOG antibody associated disorder	Vol III · P9 · Q4
§Short Q3	Causes and Mx of sequential vision loss in both eyes	Vol III · P9 · Q7
§Short Q4	One and half syndrome	Vol III · P9 · Q8
§Short Q5	Central pontine myelinolysis	Vol III · P9 · Q9
§Short Q6	Rhombencephalitis	Vol II · P8 · Q7
§Short Q7	Revised McDonald criteria in MS	Vol III · P9 · Q1
§Short Q8	Critically evaluate and discuss the Mx of MS	Vol III · P9 · Q2
§Short Q9	Post leukoencephalopathy	Vol III · P9 · Q10
§Short Q10	Benign megalocephalic leukodystrophy	Vol III · P9 · Q11
§Short Q11	Leukoaraiosis	Vol III · P9 · Q12

Infections

No.	Question	Answered at
§Long Q1	Types of COVID-19 vaccine, their mechanism and associated neurological complications.	Vol II · P8 · Q2
§Long Q2	COVID-19 associated encephalopathy with focus on its pathogenesis, diagnosis and neuroimaging.	Vol II · P8 · Q1

No.	Question	Answered at
§Long Q3	COVID-19 and management of neuro immunological disorder.	Vol II · P8 · Q2
§Long Q4	Discuss toll like receptor 3 and viral infections of nervous system.	Vol II · P8 · Q6
§Long Q5	Approach to a case of acute febrile encephalopathy.	Vol II · P8 · Q1
§Long Q6	Approach towards management of a patient with chronic meningitis.	Vol II · P8 · Q5
§Long Q7	Discuss lymphocytic predominant meningitis.	Vol II · P8 · Q5
§Short Q1	Toxoplasmosis	Vol II · P8 · Q16
§Short Q2	Focal lesion of brain in HIV infected patient	Vol II · P8 · Q16
§Short Q3	Serological test of NCC	Vol II · P8 · Q19
§Short Q4	Diagnosis of CJD	Vol II · P8 · Q22
§Short Q5	Neurological complications of herpes zoster	Vol II · P8 · Q9
§Short Q6	Serological diagnosis of SSPE	Vol II · P8 · Q10
§Short Q7	Microbiological test in TBM	Vol II · P8 · Q13
§Short Q8	Immune restoration syndrome in AIDS	Vol II · P8 · Q3
§Short Q9	Role of corticosteroids in bacterial meningitis	Vol II · P8 · Q14
§Short Q10	Single enhancing lesion in HIV patient	Vol II · P8 · Q16
§Short Q11	New variant CJD	Vol II · P8 · Q22
§Short Q12	Guidelines in management of TBM in HIV	Vol II · P8 · Q13
§Short Q13	Treatment of cerebral malaria	Vol II · P8 · Q20
§Short Q14	Cerebral malaria	Vol II · P8 · Q20
§Short Q15	Role of steroids in TBM	Vol II · P8 · Q13
§Short Q16	Neurological complications of dengue fever	Vol II · P8 · Q7
§Short Q17	Life cycle of Taenia Solium	Vol II · P8 · Q19
§Short Q18	CJD	Vol II · P8 · Q22
§Short Q19	Septic encephalopathy	Vol II · P8 · Q5
§Short Q20	Post COVID 19 neurological complications	Vol II · P8 · Q1

NMJ

No.	Question	Answered at
§Inter Q1	Anatomy and physiology of NMJ	Vol III · P10 · Q18
§Inter Q2	Discuss approach to a patient of NMJ disorder	Vol III · P10 · Q20
§Short Q1	LEMS	Vol III · P10 · Q24

No.	Question	Answered at
§Short Q2	NMJ	Vol III · P10 · Q18
§Short Q3	Antibody and role of thymectomy in MG	Vol III · P10 · Q21
§Short Q4	Myasthenic crisis	Vol III · P10 · Q22
§Short Q5	Mechanism of autoimmunity in MG	Vol III · P10 · Q21

STROKE

No.	Question	Answered at
§Long Q1	Recent advances in endovascular therapy in stroke.	Vol II · P4 · Q4
§Long Q2	Pathogenesis of perihematoma edema, Mx, prognostic implications in ICH based on recent advances.	Vol II · P4 · Q12
§Long Q3	Long term Mx of stroke with special reference to secondary prevention.	Vol II · P4 · Q15
§Long Q4	Current trends in Mx of ICH.	Vol II · P4 · Q11
§Long Q5	Discuss pathogenesis and Mx of acute thromboembolic infarction in a 45 years old female patient.	Vol II · P4 · Q1
§Long Q6	Discuss the different intravascular options available for the patient presented with acute stroke within 24 hours.	Vol II · P4 · Q4
§Inter Q1	Controversies in stroke treatment and prevention.	Vol II · P4 · Q7
§Inter Q2	Sonothrombolysis	Vol II · P4 · Q5
§Inter Q3	Barriers for standard of care in acute ischemic stroke.	Vol II · P4 · Q6
§Short Q1	Bulbar watershed ischemic stroke.	Vol II · P4 · Q9
§Short Q2	Newer recommendation in 2018 on Mx of AIS.	Vol II · P4 · Q1
§Short Q3	Diffuse – 3 trial.	Vol II · P4 · Q3
§Short Q4	RCVS	Vol II · P4 · Q14
§Short Q5	Wallenberg syndrome	Vol II · P4 · Q8
§Short Q6	Anton's syndrome	Vol II · P4 · Q10
§Short Q7	Surgical treatment of ICH	Vol II · P4 · Q11
§Short Q8	Cerebral microbleeds	Vol II · P4 · Q13
§Short Q9	Cerebral amyloid angiopathy	Vol II · P4 · Q13
§Short Q10	Anticoagulant in stroke	Vol II · P4 · Q16
§Short Q11	Secondary prevention of stroke	Vol II · P4 · Q15
§Short Q12	Draw a diagram to explain clinical manifestation of Wallenberg syndrome.	Vol II · P4 · Q8
§Short Q13	Time window in acute stroke : current concepts	Vol II · P4 · Q3

No.	Question	Answered at
§Short Q14	Posterior reversible leukoencephalopathy	Vol II · P4 · Q14

Imaging

No.	Question	Answered at
§Inter Q1	Functional neuroimaging in stroke	Vol II · P4 · Q2
§Inter Q2	Neuroimaging in eclampsia	Vol I · P3 · Q3 · p. 280
§Inter Q3	Discuss neuroimaging in acute necrotizing encephalopathy	Vol I · P3 · Q4 · p. 283
§Short Q1	MRS	Vol I · P3 · Q1 · p. 268
§Short Q2	MR evaluation in large brain abscess	Vol II · P8 · Q21
§Short Q3	Calcification of brain- Differential diagnosis	Vol II · P8 · Q19
§Short Q4	Imaging features of JE	Vol II · P8 · Q8
§Short Q5	Spinal cord MR changes in SCD	Vol I · P3 · Q7 · p. 293
§Short Q6	Myelographic changes in spinal cord compression	Vol I · P3 · Q8 · p. 295
§Short Q7	Advanced neuroimaging technique in NCC	Vol II · P8 · Q19
§Short Q8	Bilateral T2 hyperintensity in basal ganglia, possible causes and mechanism	Vol II · P8 · Q7
§Short Q9	Role of functional imaging in neurological disorders	Vol I · P3 · Q1 · p. 268
§Short Q10	Functional neuroimaging in diagnosis of degenerative dementias.	Vol I · P3 · Q1 · p. 268
§Short Q11	Imaging difference between ADEM and MS	Vol III · P9 · Q5
§Short Q12	Multiple enhancing lesions of the brain	Vol II · P8 · Q16
§Short Q13	Amyloid PET scan	Vol I · P3 · Q1 · p. 268
§Short Q14	DD of Neuro imaging finding of single and multiple enhancing Lesions	Vol II · P8 · Q16

Muscles

No.	Question	Answered at
§Long Q1	What are channelopathies? What are the roles of channelopathies in nervous system? How you are going to manage them?	Vol III · P10 · Q34
§Long Q2	What are the internal errors of metabolism in nervous system? What are their phenotypic manifestations? How are you going to	Vol III · P10 · Q36
§Long Q3	Structure and function of mitochondria and their relevance in mitochondrial cytopathies.	Vol III · P10 · Q37
§Long Q4	Discuss the genetic basis of DMD and promising therapies in the Mx of DMD.	Vol III · P10 · Q31

No.	Question	Answered at
§Short Q1	Congenital myopathies	Vol III · P10 · Q32
§Short Q2	Inclusion body myositis	Vol III · P10 · Q26
§Short Q3	Critical illness myopathy	Vol III · P10 · Q6
§Short Q4	Distal myopathies	Vol III · P10 · Q33
§Short Q5	Inflammatory myopathies	Vol III · P10 · Q25
§Short Q6	Genetics of DMD	Vol III · P10 · Q31
§Short Q7	Drug induced myopathies	Vol III · P10 · Q29
§Short Q8	Overlap syndrome	Vol III · P10 · Q28
§Short Q9	What do you mean by channelopathies? Just name the phenotypic manifestation of the different affected system in Neurology.	Vol III · P10 · Q34

MOVEMENT DISORDER

No.	Question	Answered at
§Long Q1	IPD and Parkinsonian syndrome	Vol II · P6 · Q5
§Long Q2	Early Mx of Parkinson's disease. When to start, what to start and why?	Vol II · P6 · Q7
§Long Q3	Discuss actions of antiparkinsonian drugs in relation of mechanism of parkinsonism.	Vol II · P6 · Q7
§Long Q4	Parkinson's plus syndrome. How they differ from IPD? Discuss non-motor complications of Parkinson's disease and their Mx.	Vol II · P6 · Q5
§Long Q5	Recent advances in Mx of Parkinson's disease.	Vol II · P6 · Q7
§Long Q6	Discuss evaluation, Mx and long term outcome of NPH.	Vol II · P6 · Q22
§Inter Q1	What are the subtypes of PSP, describe the salient features of each subtype.	Vol II · P6 · Q5
§Short Q1	Mx of Wilsons disease	Vol II · P6 · Q14
§Short Q2	Biomarkers in Parkinson's disease	Vol II · P6 · Q6
§Short Q3	Tardive dyskinesias	Vol II · P6 · Q18
§Short Q4	Ocular signs of PSP	Vol II · P6 · Q5
§Short Q5	DBS in Parkinson's disease	Vol II · P6 · Q10
§Short Q6	Palatal myoclonus	Vol II · P6 · Q15
§Short Q7	DBS	Vol II · P6 · Q10
§Short Q8	Substantia nigra	Vol II · P6 · Q2
§Short Q9	Hyperekplexia	Vol II · P6 · Q16
§Short Q10	PNKD	Vol II · P6 · Q17

No.	Question	Answered at
§Short Q11	Alpha synuclein and Parkinson's disease	Vol II · P6 · Q4
§Short Q12	Spinal myoclonus	Vol II · P6 · Q15
§Short Q13	Mx of tremors	Vol II · P6 · Q11
§Short Q14	RLS	Vol II · P6 · Q20
§Short Q15	Role of Parkin gene in etiology of Parkinson's disease	Vol II · P6 · Q4
§Short Q16	Benign ET	Vol II · P6 · Q11
§Short Q17	Different causes of Chorea	Vol II · P6 · Q12
§Short Q18	NMS	Vol II · P6 · Q19
§Short Q19	Sleep related movement disorders	Vol II · P6 · Q21
§Short Q20	Sleep abnormalities in parkinson's disease	Vol II · P6 · Q8

Nutritional

No.	Question	Answered at
§Inter Q1	Mechanism of neurological manifestations of B12 deficiency.	Vol III · P11 · Q20
§Short Q1	Copper deficiency myelopathy	Vol III · P11 · Q21
§Short Q2	Neurology of B12 deficiency	Vol III · P11 · Q20

Nerves

No.	Question	Answered at
§Long Q1	Important causes of neuropathy with emphasis on demyelinating neuropathies. How GBS in India differs from other parts of the	Vol III · P10 · Q1
§Long Q2	Discuss in detail about dysimmune neuropathies.	Vol III · P10 · Q1
§Long Q3	Give recent review of pathogenesis, classification, diagnostic method and treatment of leprosy neuropathy.	Vol III · P10 · Q9
§Long Q4	Discuss autoimmune neuropathies and their Mx.	Vol III · P10 · Q1
§Long Q5	How would you like to approach to a case of lumbosacral radiculo-plexus neuropathy? Discuss the pathological mechanism and th	Vol III · P10 · Q15
§Long Q6	Discuss the anatomy of lumbosacral plexus. Discuss approach to a patient with suspected lumbosacral plexopathy.	Vol III · P10 · Q15
§Long Q7	Discuss an approach to a case of acute neuropathies.	Vol III · P10 · Q1
§Inter Q1	Electrophysiological evaluation of AIDP.	Vol III · P10 · Q2
§Short Q1	CIDP variants	Vol III · P10 · Q3
§Short Q2	Diagnosis of CIDP	Vol III · P10 · Q3

No.	Question	Answered at
§Short Q3	Critical care neuropathy	Vol III · P10 · Q6
§Short Q4	Ulnar nerve entrapment	Vol III · P10 · Q11
§Short Q5	Diagnostic criteria of CTS	Vol III · P10 · Q12
§Short Q6	Pathogenesis of leprosy	Vol III · P10 · Q9
§Short Q7	Approach to a case of multiple cranial nerve palsies	Vol III · P10 · Q17
§Short Q8	Diagnosis of Porphyria	Vol III · P10 · Q8
§Short Q9	Myeloradiculopathy	Vol III · P10 · Q16
§Short Q10	Non compressive myelopathy	Vol III · P10 · Q16
§Short Q11	Leprous neuropathy	Vol III · P10 · Q9
§Short Q12	Treatment of leprosy neuropathy	Vol III · P10 · Q9
§Short Q13	Para malignant neuropathies	Vol III · P10 · Q7
§Short Q14	Difference between compressive and non compressive myelopathy	Vol III · P10 · Q16
§Short Q15	Cauda equina syndrome	Vol III · P10 · Q16
§Short Q16	Infective myelopathy	Vol III · P10 · Q16
§Short Q17	Nerve biopsy in leprosy	Vol III · P10 · Q9

Headache

No.	Question	Answered at
§Long Q1	Approach and Mx of thunderclap headache.	Vol II · P7 · Q18
§Long Q2	Formation and circulation of CSF and pathogenesis of IIH.	Vol II · P7 · Q20
§Long Q3	Describe pathophysiological mechanism of migraine and their therapeutic implications.	Vol II · P7 · Q15
§Long Q4	Discuss what predicts the change from episodic to chronic migraine and its Mx.	Vol II · P7 · Q16
§Short Q1	Unusual headache	Vol II · P7 · Q23
§Short Q2	TAC	Vol II · P7 · Q21
§Short Q3	Vitamin D and headache	Vol II · P7 · Q25
§Short Q4	Ophthalmoplegic migraine	Vol II · P7 · Q24
§Short Q5	Treatment of trigeminal neuralgia	Vol II · P7 · Q22
§Short Q6	Medication overuse headache	Vol II · P7 · Q17
§Short Q7	Role of vasoactive peptides in migraine	Vol II · P7 · Q15

Epilepsy

No.	Question	Answered at
§Long Q1	Impact of newer antiepileptic drugs in the management of intractable epilepsy.	Vol II · P5 · Q14
§Long Q2	Discuss mechanism, use, side effects of new antiepileptic drugs with a focus on drug combination of refractory epilepsy.	Vol II · P5 · Q14
§Long Q3	Describe recent advances in pathobiology of status epilepticus and role of new generation anti-seizures medications.	Vol II · P5 · Q14
§Inter Q1	Artifacts in EEG	Vol II · P5 · Q1
§Inter Q2	Neuroimaging in refractory epilepsy	Vol II · P5 · Q19
§Short Q1	EEG in SSPE	Vol II · P5 · Q4
§Short Q2	Lennox gastaut syndrome	Vol II · P5 · Q8
§Short Q3	EEG in metabolic encephalopathy	Vol II · P5 · Q5
§Short Q4	Myoclonic epilepsy in pediatric population	Vol II · P5 · Q11
§Short Q5	Rasmussen's encephalitis	Vol II · P5 · Q12
§Short Q6	Super refractory status epilepticus	Vol II · P5 · Q18
§Short Q7	Role of steroids in epilepsy	Vol II · P5 · Q17
§Short Q8	West syndrome	Vol II · P5 · Q7
§Short Q9	Indications of epilepsy surgery	Vol II · P5 · Q19
§Short Q10	Reflex epilepsies	Vol II · P5 · Q10
§Short Q11	Pre-hospital management of status epilepticus	Vol II · P5 · Q18
§Short Q12	Absence seizure	Vol II · P5 · Q6
§Short Q13	Lacosamide	Vol II · P5 · Q15
§Short Q14	Dravet syndrome	Vol II · P5 · Q9
§Short Q15	EEG abnormality in primary epilepsies	Vol II · P5 · Q3
§Short Q16	Levetiracetam	Vol II · P5 · Q15
§Short Q17	Ketogenic diet	Vol II · P5 · Q16
§Short Q18	Focal cortical dysplasia	Vol II · P5 · Q13
§Short Q19	Causes of surgically treatable epilepsy and long term prognosis	Vol II · P5 · Q19
§Short Q20	Inherited partial epilepsies	Vol II · P5 · Q10
§Short Q21	Hereditary epilepsies	Vol II · P5 · Q10
§Short Q22	Closed loop stimulation devices in epilepsy Mx	Vol II · P5 · Q20

Electrophysiology

No.	Question	Answered at
§Long Q1	Electrophysiological evaluation of LMN disorders.	Vol III · P10 · Q43
§Long Q2	Role of video EEG in pre-surgical evaluation of intractable epilepsy.	Vol II · P5 · Q19
§Inter Q1	Electrophysiological evaluation of cardiac arrest	Vol I · P3 · Q11 · p. 309
§Inter Q2	Electrophysiological evaluation of AIDP	Vol III · P10
§Short Q1	Electrophysiological evaluation in leprous neuropathy.	Vol I · P3 · Q18 · p. 346
§Short Q2	Blink reflex in Bell's palsy	Vol I · P3 · Q13 · p. 324
§Short Q3	Late reflex	Vol I · P3 · Q12 · p. 317
§Short Q4	H reflex	Vol I · P3 · Q12 · p. 317
§Short Q5	F wave	Vol I · P3 · Q12 · p. 317
§Short Q6	SSEP	Vol I · P3 · Q11 · p. 309
§Short Q7	Electrophysiology of CTS	Vol I · P3 · Q15 · p. 336
§Short Q8	Electrophysiological changes in root lesion	Vol I · P3 · Q16 · p. 339
§Short Q9	Neurophysiological evaluation of respiratory muscles.	Vol I · P3 · Q19 · p. 348
§Short Q10	Electrophysiological evaluation of plexopathies	Vol I · P3 · Q17 · p. 342
§Short Q11	Electrophysiological criteria for diagnosing GBS	Vol III · P10 · Q2
§Short Q12	Periodic complexes	Vol II · P5 · Q4
§Short Q13	Application of electrophysiology in movement Disorders	Vol I · P3 · Q21 · p. 354
§Short Q14	Electrodiagnostic characteristics suggestive of muscle specific kinase MG.	Vol III · P10 · Q19

Drugs and Miscellaneous

No.	Question	Answered at
§Long Q1	How would you like to approach a 59 years old man with progressive proximal and distal weakness of arm and legs of 2 years du	Vol III · P11 · Q17
§Long Q2	Current status of stem cell therapy in neurological diseases.	Vol III · P11 · Q27
§Long Q3	How will you approach a young patient presenting with behaviour abnormality, memory impairment and seizures.	Vol III · P11 · Q18
§Inter Q1	Genetic testing and next generation sequencing.	Vol III · P11 · Q1
§Inter Q2	Newer monoclonal antibodies in neurological practice and their specific indications for use.	Vol III · P11 · Q8
§Inter Q3	Diagnostic approach for the patient presenting with bilateral wasting and weakness of small muscles of hands.	Vol III · P11 · Q19
§Inter Q4	Discuss evaluation of brain death.	Vol II · P7 · Q12

No.	Question	Answered at
§Short Q1	Newer anticoagulant	Vol III · P11 · Q13
§Short Q2	Pregabalin	Vol III · P11 · Q14
§Short Q3	Natalizumab	Vol III · P11 · Q9
§Short Q4	Galantamine	Vol II · P7 · Q5
§Short Q5	Memantine	Vol II · P7
§Short Q6	Cenobamate	Vol II · P5 · Q15
§Short Q7	Aducanumab	Vol II · P7
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§Short Q12	Perampanel : current status	Vol II · P5 · Q15
§Short Q13	Use of IVIg in neurology	Vol III · P11 · Q12
§Short Q14	Polysomnographic evaluation in sleep disorders	Vol II · P7 · Q14
§Short Q15	Role of tilt table test in evaluation of syncope	Vol II · P7 · Q10
§Short Q16	Nerve biopsy	Vol III · P11 · Q22
§Short Q17	Role of nerve and muscle biopsy in neurology	Vol III · P11 · Q22
§Short Q18	Whole genome sequencing	Vol III · P11 · Q1
§Short Q19	Antisense oligonucleotide	Vol III · P11 · Q4
§Short Q20	RTPCR	Vol III · P11 · Q5
§Short Q21	Randomization	Vol III · P11 · Q24
§Short Q22	Peer review	Vol III · P11 · Q25
§Short Q23	Meta analysis	Vol III · P11 · Q26
§Short Q24	Gene therapy	Vol III · P11 · Q3
§Short Q25	Transcranial magnetic stimulation	Vol III · P11 · Q23
§Short Q26	What are neuro-genetic diseases which attenuate with age? Describe one of them.	Vol III · P11 · Q6
§Short Q27	SINO syndrome	Vol III · P11 · Q7
§Short Q28	Genetic polymorphism	Vol III · P11 · Q2
§Short Q29	Visual snow syndrome	Vol III · P11 · Q29

PAPER I: Basic Sciences (Neuroanatomy & Physiology) — March 2025

No.	Question	Answered at
Q1	Discuss in brief frontal lobe and its connections. (4+6)	Vol I · P1 · Q2 · p. 30
Q2	Neuroanatomy of trigeminal nerve.	Vol I · P1 · Q8 · p. 58
Q3	Neurogenic bladder.	Vol I · P1 · Q18 · p. 118
Q4	Discuss Brachial plexus and its major lesions.	Vol III · P10 · Q14
Q5	Discuss the major areas of brain involved in language production and clinical characteristics of different types of aphasia.	Vol I · P1 · Q1 · p. 26
Q6	Discuss in brief cerebellum and its connections.	Vol III · P9 · Q23
Q7	Discuss briefly neuroanatomy of spinal cord and different spinal cord syndromes.	Vol I · P1 · Q10 · p. 69
Q8	Discuss in brief "Brainstem syndromes."	Vol I · P1 · Q6 · p. 47
Q9	Discuss the pathophysiology of "Migraine."	Vol II · P7 · Q15
Q10	Discuss brainstem centres for horizontal and vertical saccadic eye movements.	Vol I · P1 · Q6 · p. 47

PAPER I: Basic Sciences (Neuroanatomy & Physiology) — December 2025

No.	Question	Answered at
Q1	Explain the basis of decremental response on repetitive nerve stimulation.	Vol III · P10 · Q19
Q2	Draw well labelled diagram of thalamus and discuss various clinical syndromes due to thalamic lesions.	Vol I · P1 · Q4 · p. 38
Q3	Explain Pathophysiology of Parkinson's disease.	Vol II · P6 · Q4
Q4	Discuss pathways of memory and explain various amnesic syndromes.	Vol II · P7 · Q1
Q5	Discuss mechanism of Creutzfeldt Jacob disease.	Vol II · P8 · Q22
Q6	Draw and well labelled section of spinal cord and explain various clinical syndromes due to cord lesions.	Vol I · P1 · Q10 · p. 69
Q7	Explain anatomy of sympathetic pathways and discuss clinical localization of Horner's syndrome.	Vol II · P4 · Q8
Q8	Write a note on anatomy of 7th cranial nerve and explain anatomical localization.	Vol I · P1 · Q9 · p. 63
Q9	Explain pathophysiological basis of autoimmune encephalitis.	Vol III · P9 · Q15
Q10	Write a note on anatomy of radial nerve and explain anatomical localization of lesions affecting radial nerve.	Vol III · P10 · Q10

PAPER II: Clinical Neurology & Methodology — March 2025

No.	Question	Answered at
Q1	Discuss CSF formation, circulation, flow dynamics in normal state and discuss intracranial hypotension.	Vol I · P1 · Q15 · p. 100

No.	Question	Answered at
Q2	Describe gate control theory of pain.	Vol I · P1 · Q14 · p. 91
Q3	Wilson's disease.	Vol II · P6 · Q14
Q4	Discuss Neuropsychiatric manifestation of systemic lupus erythematosus (SLE).	Vol III · P9 · Q21
Q5	Discuss approach to progressive myoclonic epilepsy.	Vol II · P5 · Q11
Q6	Discuss various channelopathies of skeletal muscle.	Vol III · P10 · Q35
Q7	Briefly describe approach to floppy infant.	Vol III · P10 · Q42
Q8	Pathophysiology of spasticity and brief note on post stroke spasticity.	Vol I · P1 · Q12 · p. 79
Q9	Discuss late responses in nerve conduction studies.	Vol I · P3 · Q12 · p. 317
Q10	Discuss neurological manifestations of dengue fever.	Vol II · P8 · Q7

PAPER II: Clinical Neurology & Methodology — December 2025

No.	Question	Answered at
Q1	Enumerate the causes of acute flaccid quadriplegia and discuss its clinical approach.	Vol III · P10 · Q5
Q2	Discuss clinical approach to a patient with painful ophthalmoplegia.	Vol I · P2 · Q9 · p. 184
Q3	Management of Immune mediated necrotizing myopathy.	Vol III · P10 · Q27
Q4	Discuss clinical approach to a patient with fever and altered sensorium of one-week duration.	Vol II · P8 · Q5
Q5	Discuss clinical approach to a patient with language disorder.	Vol I · P1 · Q1 · p. 26
Q6	Discuss clinical approach to patient with chorea.	Vol II · P6 · Q12
Q7	Describe mini mental status examination and discuss its advantages/ fallacies.	Vol II · P7 · Q3
Q8	Describe clinical approach to a 40-year-old gentleman who presents with new onset headache of one-month duration.	Vol II · P7 · Q19
Q9	Discuss autonomic function tests in detail.	Vol I · P1 · Q17 · p. 112
Q10	Discuss approach to bladder dysfunction with focus on differentiation between upper motor versus lower motor neuron type of b	Vol I · P1 · Q18 · p. 118

PAPER III: Diagnostic & Investigative Neurology — March 2025

No.	Question	Answered at
Q1	Discuss the differential diagnosis and management of Thunderclap Headaches.	Vol II · P7 · Q18
Q2	Diagnosing neurological diseases in the era of Artificial Intelligence and Machine Learning.	Vol I · P3 · Q10 · p. 303

No.	Question	Answered at
Q3	Restless leg Syndrome.	Vol II · P6 · Q20
Q4	Discuss the types & management of Spinal Muscle Atrophy (SMA) in adult.	Vol III · P10 · Q38
Q5	Discuss approach to visual loss.	Vol I · P2 · Q8 · p. 178
Q6	Discuss the determination of brain death by latest guidelines.	Vol II · P7 · Q12
Q7	Autoimmune encephalitis with antibodies to cell surface antigens.	Vol III · P9 · Q15
Q8	Randomization.	Vol III · P11 · Q24
Q9	List the causes, approach to diagnosis and discuss the management of Inflammatory Myopathies.	Vol III · P10 · Q25
Q10	Discuss the differentiating features of axonal vs demyelinating neuropathy on Nerve Conduction Study and their pitfall.	Vol III · P10 · Q43

PAPER III: Diagnostic & Investigative Neurology — December 2025

No.	Question	Answered at
Q1	Transcranial Magnetic Stimulation: principle and evidence in headache management.	Vol II · P7 · Q26
Q2	High Intensity Focused Ultrasound (HIFU) in management of Parkinson's disease.	Vol II · P6 · Q10
Q3	Musculoskeletal ultrasound guided median nerve hydrodissection for carpal tunnel syndrome: steps of the procedure and known c	Vol III · P10 · Q13
Q4	Lumbar puncture: Procedure details specific to the diagnosis of suspected Normal Pressure Hydrocephalus.	Vol II · P7 · Q8
Q5	Role of CT Perfusion imaging in the management of acute ischemic stroke in extended window, with special emphasis to large ve	Vol II · P4 · Q3
Q6	Activation procedures in routine electroencephalogram (EEG).	Vol II · P5 · Q2
Q7	Non-invasive monitoring of intracranial pressure.	Vol I · P3 · Q9 · p. 299
Q8	Cognitive evoked potentials: current role in research and practice.	Vol II · P7 · Q4
Q9	Describe the past and currently available stent retrievers available for the management of stroke.	Vol II · P4 · Q4
Q10	Single fibre electromyography: describe the procedure, normal and abnormal findings.	Vol I · P3 · Q20 · p. 351

PAPER IV: Recent Advances in Neurology — March 2025

No.	Question	Answered at
Q1	Tofersen in the management of Motor Neuron Disease.	Vol III · P10 · Q40
Q2	Seed Amplification Assay in Parkinson's Disease.	Vol II · P6 · Q6
Q3	Nodopathies and paranodopathies: clinico-electrophysiological characteristics.	Vol III · P10 · Q4

No.	Question	Answered at
Q4	Interferonopathies.	Vol III · P9 · Q22
Q5	Stent retriever techniques versus aspiration catheter for management of Acute Ischemic Stroke with Large Vessel Occlusion.	Vol II · P4 · Q4
Q6	Gepants for management of migraine.	Vol II · P7 · Q16
Q7	Magnetic Resonance Imaging guided focussed ultrasound for treatment of tremor: mechanism and evidence.	Vol II · P6 · Q10
Q8	Role of Ocrelizumab in the management of Multiple Sclerosis: mechanism, dose and monitoring.	Vol III · P9 · Q2
Q9	Newer monoclonal antibodies in the management of Myasthenia Gravis.	Vol III · P10 · Q23
Q10	Arterial Spin Labelling MRI: Applications in Neurology.	Vol I · P3 · Q2 · p. 276

PAPER IV: Recent Advances in Neurology — December 2025

No.	Question	Answered at
Q1	Asymptomatic carotid stenosis management: Current evidence.	Vol II · P4 · Q17
Q2	Non-invasive neuromodulation in the management of neuropathic pain.	Vol III · P11 · Q23
Q3	Evidence of endovascular treatment in management of medium or distal vessel occlusion (MeVO).	Vol II · P4 · Q4
Q4	Diagnosis and management of cerebral amyloid associated related inflammation (CAARI).	Vol III · P11 · Q28
Q5	Responsive neurostimulation in the management of drug refractory epilepsy.	Vol II · P5 · Q20
Q6	Enzyme replacement therapies for metabolic storage disorders-current recommendations.	Vol III · P11 · Q16
Q7	Sensors and wearables in Movement Disorders.	Vol II · P6 · Q9
Q8	Seronegative primary demyelinating disorders: approach and management.	Vol III · P9 · Q6
Q9	Symptomatic treatments and emerging Disease-Modifying Therapies in Huntington's disease.	Vol II · P6 · Q13
Q10	Emerging therapeutic options in management of Myasthenia Gravis.	Vol III · P10 · Q23



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Part 1

Neuroanatomy and Localisation — Systems and Pathways

1 · CEREBRAL CORTEX — LANGUAGE, FRONTAL LOBE AND CORPUS CALLOSUM

Q1. Discuss the major areas of brain involved in language production and the clinical characteristics of different types of aphasias.

LONG

Paper I · March 2025 · Q5

10 marks

Also asked as: Anatomy §Long Q8 — "Discuss organisation of speech and various aphasias" · Paper II, Dec 2025, Q5 — "Clinical approach to a patient with language disorder" · Anatomy §Short Q50 (praxis/apraxia overlap)

Source: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 13 *Aphasia and Aphasic Syndromes*, §Anatomy of Language and §Differential Diagnosis of Aphasic Syndromes, pp. 133–143 (Fig. 13.1, p. 134; Box 13.1, p. 135; Tables 13.1–13.8, pp. 136–143). Supplementary: Dejong's *The Neurologic Examination*, 8th ed. — Ch. 9 *Disorders of Speech and Language*.

1. Definitions — fix these first

- **Aphasia** = acquired loss/impairment of language (comprehension + expression) due to brain damage — not a disorder of articulation, voice or thought.
- **Dysarthria** = disorder of articulation only; **aphemia** = transient muteness with normal writing (may not qualify as a language disorder at all).
- Two bedside rules of thumb from the text:
 - If the patient **can write or type normally**, the disorder is probably **not** aphasic.
 - If the patient's effortful utterances **can be transcribed into normal language**, the patient is **not** aphasic.

2. Anatomical substrate of language (Fig. 13.1)

- **Cortical centres**
 - **Broca area** — posterior part of inferior frontal gyrus, **Brodmann areas 44 and 45**; "programs" the adjacent motor cortex for mouth and larynx.
 - **Wernicke area** — posterior superior temporal gyrus, **Brodmann area 22**; sensory association cortex just posterior to primary auditory cortex (areas 41, 42).
 - **Supramarginal gyrus** (area 40) — encoding of speech sounds for production; **angular gyrus** (area 39) — reading/writing interface.
- **Connecting pathway**
 - **Arcuate fasciculus** — deep subcortical white matter bundle joining Wernicke to Broca; not drawn in Fig. 13.1 but explicitly named in its legend. Its interruption = conduction aphasia.
 - Auditory information travels by **direct and indirect dorsal pathways** to Broca area for both repetition and spontaneous speech.
- **Output and input loops**
 - **Speech output:** Broca area → adjacent motor cortex → corticobulbar tract → brainstem cranial nerve nuclei (Fig. 13.2).
 - **Reading:** visual language stimuli perceived by occipital cortex → converted to auditory language information.
 - **Writing:** activation of motor neurons projecting to arm and hand.
- **Subcortical contributions** (increasingly recognised)

- **Thalamus** — relay for the reticular activating system; "alerts" language cortex. Dominant thalamic lesions frequently produce a **fluent aphasia**.
- **Caudate nucleus and putamen** — participate in expressive speech.
- **Hemispheric dominance**
 - Aphasia follows **left hemisphere** lesions in almost all right-handers and in a majority of left-handers.
 - **Crossed aphasia** = aphasia from a right hemisphere lesion in a right-handed patient (rare).
 - A French series of 107 stroke patients confirmed ~150 years of clinical work: **frontal lesions → non-fluent aphasia; posterior temporal lesions → impaired comprehension**.

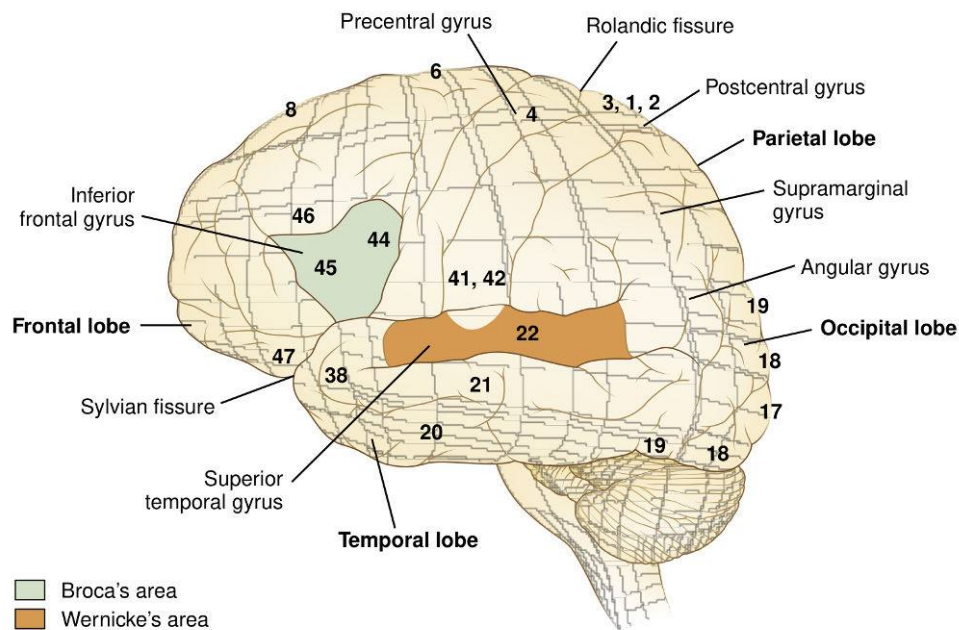


Fig. 13.1 The lateral surface of the left hemisphere, showing a simplified gyral anatomy and the relationships between Wernicke area and Broca area. Not shown is the arcuate fasciculus, which connects the two cortical speech centers via the deep, subcortical white matter.

Reproduced from Bradley & Daroff 8e, **Fig. 13.1**, p. 134 — the diagram to draw in the exam. Label: Broca area (44, 45), Wernicke area (22), primary auditory cortex (41, 42), supramarginal and angular gyri, Sylvian and Rolandic fissures, Brodmann numbers.

3. Bedside language examination — six parts (Box 13.1)

- **Spontaneous speech** — informal interview, structured task, automatic sequences. Most important variable = **fluency**.
- **Naming** — objects, object parts, pictures, colours, body parts (anomia may be word-class specific; proper names often worst affected).
- **Auditory comprehension** — one-, two- and three-step commands; prefer **yes/no and pointing** responses and **nonsense questions** ("Do you vomit every day?") because apraxia confounds command-following.
- **Repetition** — "no ifs, ands, or buts" (aphasics fail grammatically complex phrases); "Methodist Episcopal" separates out dysarthria.
- **Reading** — aloud *and* for comprehension.
- **Writing** — spontaneous sentence, dictation, copying. The **most sensitive** indicator of mild aphasia and the part most often omitted; it also permits analysis of spelling.

4. Classifying the aphasias — the three-step bedside algorithm

- **Step 1 — Is speech fluent or non-fluent?** (fluent → posterior/post-Rolandic lesion; non-fluent → anterior/pre-Rolandic lesion).
- **Step 2 — Is comprehension intact or impaired?**
- **Step 3 — Is repetition intact or impaired?** Intact repetition ⇒ the perisylvian language circuit is spared ⇒ a **transcortical** syndrome (typically a watershed lesion: ACA-MCA anterior border zone, or MCA-PCA parietal border zone).

Syndrome	Speech	Naming	Compre- hension	Repe- tition
Broca	Non-fluent, mute or telegraphic, sometimes dysarthric	Impaired	Intact (mild difficulty with complex grammar)	Impaired
Wernicke	Fluent with paraphasic errors; not dysarthric; sometimes logorrhoic	Impaired (often bizarre paraphasic misnaming)	Impaired	Impaired
Global	Mute or non-fluent	Impaired	Impaired	Impaired
Conduction	Fluent, hesitant, literal paraphasic errors	Moderately impaired	Intact	Impaired
Anomic	Fluent, word-finding pauses, circumlocution	Impaired	Intact	Intact
Transcortical motor	Non-fluent	Impaired	Intact	Intact
Transcortical sensory	Fluent, echolalic	Impaired	Impaired	Intact
Mixed transcortical (isolation of the speech area)	Non-fluent, echolalic	Impaired	Impaired	Intact
Pure alexia without agraphia	Intact	± impaired, especially colours	Intact	Intact

Syndrome	Reading / writing	Associated signs
Broca	Reading often impaired ("third alexia"); writing impaired — dysmorphic, dysgrammatical	Right hemiparesis; right hemisensory loss; ± apraxia of left limbs
Wernicke	Reading usually impaired (occasionally spared); writing impaired, with spelling errors	Usually none; ± right homonymous hemianopia
Global	Both impaired	Right hemiparesis, hemisensory loss, hemianopia
Conduction	Reading aloud moderately impaired, comprehension largely intact; writing variable	± apraxia of left limbs; ± mild right hemiparesis / hemisensory loss / hemianopia
Anomic	Both intact, except for anomia in writing	Variable or none

Syndrome	Reading / writing	Associated signs
Transcortical motor	Both ± intact	Watershed (ACA-MCA) lesion
Transcortical sensory	Both impaired	Watershed (MCA-PCA) lesion
Mixed transcortical (isolation of the speech area)	Both impaired	Large/bilateral watershed infarction sparing perisylvian cortex; advanced dementia
Pure alexia without agraphia	Reading impaired (some sparing of single letters); writing intact	Right hemianopia or superior quadrantanopia; short-term memory loss; motor/sensory signs usually absent

Table 1 · Bedside features of the aphasic syndromes — compiled verbatim from Bradley & Daroff 8e, Tables 13.1–13.7, pp. 136–143.

5. Lesion localisation — what to write for each syndrome

Syndrome	Lesion site	Vascular territory / notes
Broca	Posterior inferior frontal gyrus (areas 44, 45) plus adjacent cortex and subcortical white matter	Upper division of left MCA. Lesions confined to lower precentral gyrus → only dysarthria and mild expressive disturbance. Permanent non-fluency requires damage to two subcortical sites : rostral subcallosal fasciculus deep to Broca area and periventricular white matter beside the body of the left lateral ventricle
Wernicke	Posterior superior temporal gyrus (area 22)	Lower division of left MCA; hemianopia if optic radiation involved
Global	Whole perisylvian language zone	Left ICA / proximal MCA occlusion; large lesions evolve from global → Broca over weeks to months
Conduction	Arcuate fasciculus / supramarginal gyrus	Disconnection of Wernicke from Broca
Transcortical syndromes	Outside the perisylvian circuit — anterior frontal or parietal cortex	Border-zone (watershed) infarction; also advanced dementia and hypoxic injury
Subcortical aphasia	Dominant thalamus, caudate, putamen	Thalamic lesions → fluent aphasia

Table 2 · Anatomical correlation (Bradley & Daroff 8e, Ch. 13, pp. 136–141).

6. Points that earn extra marks

- **Paraphasias**: *literal/phonemic* = wrong sound ("shoon" for spoon); *verbal/semantic* = wrong word ("fork" for spoon). **Neologism** = non-existent word form. **Jargon** = speech so contaminated that meaning cannot be discerned.
- **Broca aphasia is frequently associated with depression** — patients are aware of and frustrated by the deficit; this may limit rehabilitation. Wernicke patients are typically **unaware/unconcerned**.

- **Differential diagnosis of fluent paraphasic speech:** aphasia vs psychosis vs delirium vs dementia. Sudden-onset fluent paraphasic speech in a middle-aged or elderly patient = left hemisphere lesion until proved otherwise.
- **Primary progressive aphasia** — language impairment as the presenting and dominant feature of a neurodegenerative process (Ch. 13, §Language in Dementing Diseases, p. 145).

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Repetition is the single most discriminating bedside test** — it separates the perisylvian (repetition impaired) from the transcortical (repetition intact) syndromes in one question.
- Fluent + impaired comprehension + **no hemiparesis** in an elderly patient = Wernicke aphasia; it is the aphasia most often misdiagnosed as an acute confusional state or psychosis.
- Non-fluent + intact comprehension + **intact** repetition = transcortical motor (watershed); look for hypotension/carotid stenosis, not embolism.
- Pure alexia without agraphia = left occipital infarct + splenium of corpus callosum (PCA territory); the patient **can write but cannot read what he has just written**, and colour naming is impaired.
- Always test **writing** — it is the most sensitive screen for mild aphasia and the part candidates forget in the practical exam.
- A mute patient who writes normally is **not** aphasic — think dysarthria, akinetic mutism, extrapyramidal disease, laryngeal disease or catatonia.

Q2. Discuss in brief the frontal lobe and its connections.

LONG

Paper I · March 2025 · Q1

4 + 6 marks

Also asked as: Anatomy §Long Q11 (frontal contribution to episodic loss of consciousness — answered elsewhere) · overlaps Paper I · March 2025 · Q5 (Broca area) and Anatomy §Intermediate Q8 (callosal connections)

Source: DeJong's *The Neurologic Examination*, 8th ed. — Ch. 7 *Functions of the Cerebral Cortex and Regional Cerebral Diagnosis*, §The Frontal Lobes, §The Prefrontal Area and §Frontal Motor Areas (Figs. 7.1, 7.2; Boxes 7.1, 7.2) and Ch. 6 *Gross and Microscopic Anatomy of the Cerebral Hemispheres* (Figs. 6.1–6.3, 6.9, 6.10). Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 9 *Behavior and Personality Disturbances*, §Frontosubcortical Circuitry, pp. 76–78 (Box 9.1, p. 78; Figs. 9.3 and 9.4, pp. 78–79). Also Ch. 18, p. 202 (frontal eye fields) and Ch. 45, p. 636 (frontal lobe incontinence).

1. Anatomical subdivisions — the "4 marks" half of the answer

• Motor areas

- **Primary motor cortex** — area 4, precentral gyrus; contains the giant **Betz cells** that give rise to the corticospinal and corticobulbar tracts.
- **Premotor cortex** — area 6, immediately anterior to area 4, between the precentral gyrus and the prefrontal area; plans and executes **sequences** of movement (the basis of Luria's fist-edge-palm test); receives from sensory cortex, projects to motor cortex and motor thalamus.
- **Supplementary motor area (SMA)** — medial area 6, just anterior to primary motor cortex; plans movements from memory, gives **temporal organisation to multiple movements** and coordinates movement between the two hands.
- **Frontal eye fields** — middle frontal gyrus; drive conjugate gaze to the **opposite** side.
- **Broca (motor speech) area** — inferior frontal gyrus, areas 44 and 45, anterior to the motor strip.

- **Prefrontal cortex** — everything anterior to area 6, area 8 and the speech areas: areas 9–12, 32, 45, 47. Thin, granular cortex with small, sparse layer-5 pyramidal cells. Three clinical divisions:
 - **Dorsolateral prefrontal cortex (DLPFC).**
 - **Medial prefrontal cortex (MPC).**
 - **Orbitofrontal cortex (OFC).**
- The **anterior cingulate gyrus** is sometimes counted with the frontal lobe, although its connections are primarily with limbic structures.

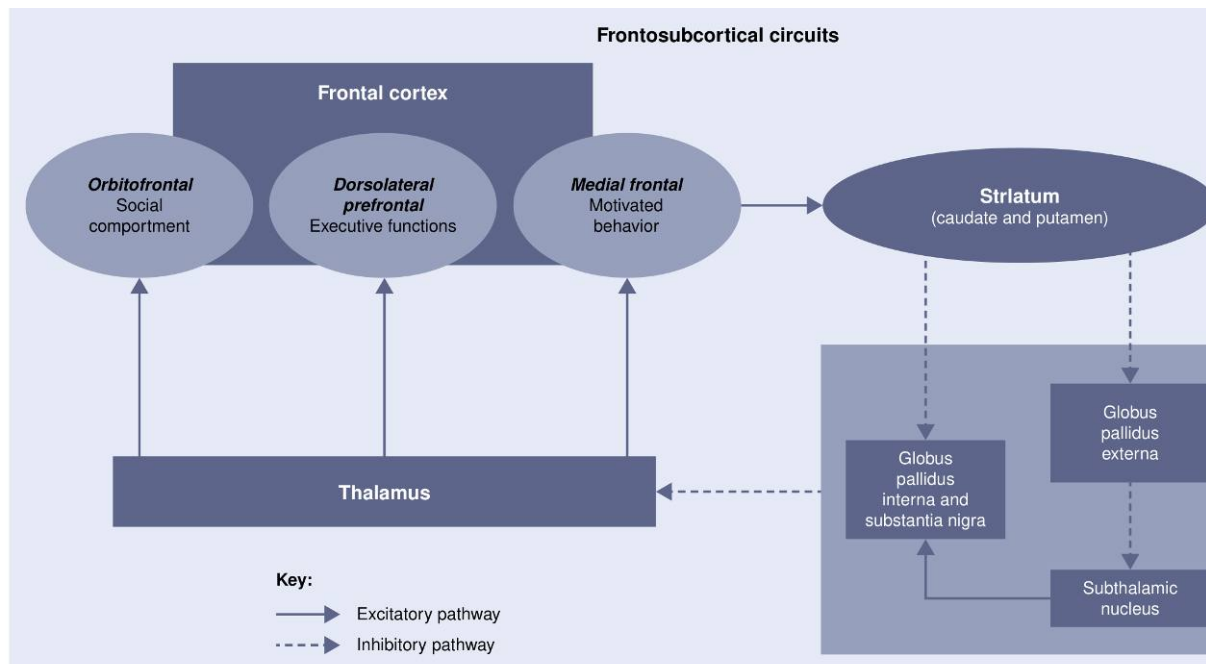


Fig. 9.4 Outline of frontal subcortical circuits relevant to common neurobehavioral sequelae of traumatic brain injury. (Adapted from Arciniegas, D.B., Beresford, T.P., 2001. *Neuropsychiatry: An Introductory Approach*. Cambridge University Press, Cambridge, UK, p. 58. Copyright © Cambridge University Press, 2001.)

Reproduced from Bradley & Daroff 8e, **Fig. 9.4**, p. 79 — the frontosubcortical circuits. Label: orbitofrontal (social comportment), dorsolateral prefrontal (executive function), medial frontal (motivated behaviour) → striatum → GPi/SNr (direct) or GPe → STN → GPi (indirect) → thalamus → back to frontal cortex; mark excitatory (solid) and inhibitory (dashed) limbs.

2. Connections — four systems to name and draw

System	Fibres	What it connects	Clinical note
Projection (efferent)	Corticospinal, corticobulbar, corticopontine (frontopontine), corticostriate, corticothalamic, corticoreticular	Arise from infragranular layer 5 → internal capsule (anterior limb and genu carry frontopontine and anterior thalamic radiation) → basal ganglia, thalamus, brainstem nuclei, cord	Lesion → contralateral hemiparesis; frontal projections to pontomedullary reticular formation modulate axial posture and stepping (Ch. 25, p. 335)
Projection (afferent)	Thalamocortical fibres, chiefly from the dorsomedial nucleus ; mesocortical dopaminergic fibres from the midbrain	Prefrontal cortex is the main projection site of the DM thalamic nucleus	Dopaminergic input subserves reward, attention, short-term memory, planning and drive

System	Fibres	What it connects	Clinical note
Long association	Superior longitudinal (arcuate) fasciculus, uncinate fasciculus, cingulum, occipitofrontal fasciculus	Frontal lobe to parietal, temporal, occipital and limbic cortex of the same hemisphere	Interruption produces disconnection syndromes (Ch. 6, p. 126); arcuate lesion → conduction aphasia
Commissural	Genu and rostrum (forceps minor) of the corpus callosum; anterior commissure	Frontal cortex of one side to mirror-image cortex of the other	Anterior callosal lesion → alien/anarchic hand, unilateral (left) apraxia, unilateral agraphia

Table 3 · Connections of the frontal lobe — DeJong's 8e, Ch. 6 §Commissural Fibers and §The Internal Capsule, and Ch. 7 §The Prefrontal Area.

3. Frontosubcortical circuits (Bradley, Ch. 9, pp. 76-78)

- Alexander and colleagues described **five discrete parallel circuits** linking regions of frontal cortex → **striatum** → **globus pallidus and substantia nigra** → **thalamus** → back to the same frontal region: **motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate**.
- The last three are the **behavioural** circuits. **Disruption at any point in the circuit** — frontal cortex, corpus striatum, globus pallidus — produces the same behavioural syndrome; this is why subcortical disease produces "frontal" signs.

Circuit	Function	Syndrome when disrupted (Box 9.1)
Dorsolateral prefrontal	Executive function — planning, organisation, set-shifting, working memory, decision-making about voluntary saccades	Poor organisational and memory-search strategies; stimulus-bound behaviour ; environmental dependency; impaired set-shifting and set maintenance ("dysexecutive syndrome")
Lateral orbitofrontal	Social comportment; inhibition; connections with amygdala and limbic system	Disinhibition syndrome — emotional incontinence, tactlessness, irritability, undue familiarity, antisocial behaviour, mood disorders (depression, lability, mania), obsessive-compulsive disorder
Anterior cingulate / medial frontal	Motivated behaviour, drive, initiation	Apathetic-akinetic syndrome — impaired motivation, apathy, poverty of speech, psychic emptiness, poor response inhibition; at its extreme akinetic mutism

Table 4 · The three behavioural frontosubcortical circuits — Bradley & Daroff 8e, Box 9.1, p. 78 and Figs. 9.3-9.4, pp. 78-79.

4. Clinical features of frontal lobe disease — the "6 marks" half

• Prefrontal / behavioural

- Earliest change is often **loss of recent memory**, retention and immediate recall, then impaired judgement, especially in social and ethical situations.
- Loss of socially acquired inhibition → inappropriate behaviour, carelessness of dress and hygiene, sexual promiscuity, inability to manage business or personal finance.

- Impaired abstraction; difficulty with any task requiring deviation from routine; distractibility; slowed problem-solving; rapid fatigue.
- **Witzelsucht** (facetiousness, senseless joking and punning) or **moria** (silliness) and euphoria at one extreme; **abulia** (difficulty initiating and sustaining spontaneous movement, reduced emotional responsiveness, speech and social interaction) and apathy at the other.
- Extensive **bilateral** prefrontal lesions → **akinetic mutism** or persistent unresponsiveness.
- Massive **unilateral** frontal lesions, especially non-dominant, may cause few symptoms — a classic pitfall.
- **Motor**
 - Contralateral spastic hemiparesis (area 4); lesions of the **anterior and medial** motor cortex cause **less paralysis and more spasticity** and release **primitive reflexes** (grasping, groping).
 - **SMA syndrome** — reduced spontaneous movement and difficulty performing volitional acts to command in the contralateral limbs, while the limbs work normally in automatic activity such as dressing; may be mistaken for corticospinal weakness. Hemineglect and apraxia may coexist, from a frontal rather than a parietal lesion. SMA lesions may cause the **alien hand syndrome**.
 - Unilateral prefrontal lesions → **imitation behaviour and utilisation behaviour**.
- **Gaze** — destructive frontal eye field lesion deviates the eyes **ipsilaterally**; an epileptic discharge deviates them **contralaterally**.
- **Language** — dominant inferior frontal gyrus → Broca (non-fluent) aphasia.
- **Sphincter and gait**
 - Incontinence, particularly with involvement of the **paracentral lobule**; the classic picture of **frontal lobe incontinence** is severe urgency, frequency and urge incontinence in a patient who is **socially aware and embarrassed**, with normally coordinated micturition (Bradley Ch. 45, p. 636).
 - Frontal (higher-level) gait disorder — wide base, start hesitation, freezing, very slow shuffling steps, impaired postural responses, frequent falls (Ch. 25, Table 25.1, p. 337).
- **Seizures**
 - Motor cortex → focal **Jacksonian** seizures of the contralateral limbs.
 - SMA → tonic posturing, unilateral or asymmetrical, with grimacing, automatisms, laughing or speech arrest.
 - Orbitofrontal / frontopolar → pedalling, thrashing movements easily mistaken for pseudoseizures.
 - DLPFC → adverse seizures with head and eye turning, usually contralateral.

5. Two case histories worth quoting

- **Phineas Gage (1848)** — a tamping rod through the left cheek and out near the vertex; he survived but became "irreverent, profane, impatient and unable to hold a job", "a child in his intellectual capacities, with the general passions of a strong man". The case established the frontal lobe's role in personality and laid the groundwork for frontal leucotomy (DeJong, Box 7.1).
- **Patient "EVR" (Eslinger and Damasio)** — after removal of an orbitofrontal meningioma he had a **verbal IQ of 120 and normal neuropsychological testing**, yet lost his savings in a bad venture, was sacked repeatedly for lateness, took two hours to get ready each morning and hoarded useless objects. The point for the exam: **bedside cognitive testing can be entirely normal in orbitofrontal disease** (DeJong, Box 7.2).

6. Causes

- **Degenerative** — frontotemporal dementia (apathy in up to 95%; Bradley Table 9.1, p. 78), Alzheimer disease, progressive supranuclear palsy, Huntington disease.
- **Neoplastic** — meningioma (olfactory groove, sphenoid wing), glioma, butterfly glioma of the corpus callosum; witzelsucht or apathy may precede memory loss and impaired judgement, with anosmia, seizures, forced grasping, frontal ataxia and visual field defects.
- **Vascular** — anterior cerebral artery infarction, anterior communicating artery aneurysm rupture.
- **Traumatic** — orbitofrontal contusion; Bradley Ch. 9 discusses the frontosubcortical circuits specifically as the framework for the neurobehavioural sequelae of traumatic brain injury.
- **Other** — multiple sclerosis, normal-pressure hydrocephalus, neurosyphilis, alcohol-related and nutritional disease.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- The examiner wants **three circuits and three syndromes**: dorsolateral → dysexecutive; orbitofrontal → disinhibited; anterior cingulate → apathetic/akinetic. Write them as a table.
- A lesion **anywhere in the circuit** — cortex, caudate, putamen or pallidum — reproduces the frontal syndrome; that is why "frontal" signs occur in Huntington and Parkinson disease.
- **Normal MMSE does not exclude frontal disease**. Test set-shifting (Luria fist-edge-palm, alternating sequences), go/no-go, verbal fluency, proverb interpretation and look for primitive reflexes.
- A destructive frontal eye field lesion makes the patient **look at the lesion**; a seizure makes the patient **look away from it**.
- Frontal lobe incontinence = urgency and urge incontinence in a socially embarrassed, non-demented patient with normally coordinated voiding — quite different from the frontal patient with dementia.
- Bilateral medial frontal (anterior cingulate / SMA) lesions give **akinetic mutism** — always in the differential of the "unresponsive but awake" patient alongside persistent vegetative state and locked-in syndrome.

Q3. Describe the corpus callosum and discuss the clinical features of lesions involving the corpus callosum.

INTERMEDIATE

Anatomy §Intermediate Q8

6-8 marks

Source: DeJong's *The Neurologic Examination*, 8th ed. — Ch. 6 *Gross and Microscopic Anatomy of the Cerebral Hemispheres*, §Commissural Fibers (Figs. 6.9, 6.10) and Ch. 10 *Agnosia, Apraxia and Related Disorders of Higher Cortical Function*, §Disconnection Syndromes and §Alien Hand Syndrome. Supplementary: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 11 *Limb Apraxias and Related Disorders* and Ch. 13, p. 144 (alexia without agraphia).

1. Gross anatomy

- The **largest commissural system** of the brain — a broad band of fibres at the floor of the interhemispheric fissure connecting the **neocortical** areas of the two hemispheres.
- **Four named parts** (anterior to posterior)
 - **Rostrum** — lies just below the frontal horn; continuous with the lamina terminalis, which forms the anterior wall of the third ventricle. The subcallosal and paraterminal gyri (limbic) lie beneath it.
 - **Genu** — the anterior bend; its fibres sweeping round the front of the interhemispheric fissure form the **forceps minor (frontalis)**.

- **Body (trunk)** — the major portion.
- **Splenium** — the thickened posterior termination; its fibres form the **forceps major (occipitalis)**.
- **Topography of the fibres** — the single most examinable fact
 - **Anterior third** — anterior frontal lobes, **including the speech areas**.
 - **Body** — posterior frontal and parietal lobes.
 - **Splenium** — temporal and occipital lobes.
- The corpus callosum contains **no crossing fibres from the striate cortex or from the hand area** of motor or sensory cortex — these regions communicate through the transcallosal connections of their **association** cortex.
- The **tapetum** is a thin sheet of radiating callosal fibres forming the roof of the temporal horn and the roof and lateral wall of the occipital horn.
- The other commissures: **anterior commissure** (in the lamina terminalis, above the optic chiasm, behind and below the rostrum; connects olfactory bulbs, amygdalae, basal forebrain and — in primates mainly — the two temporal neocortices) and the **hippocampal commissure (psalterium)** between the crura of the fornix beneath the body of the callosum.

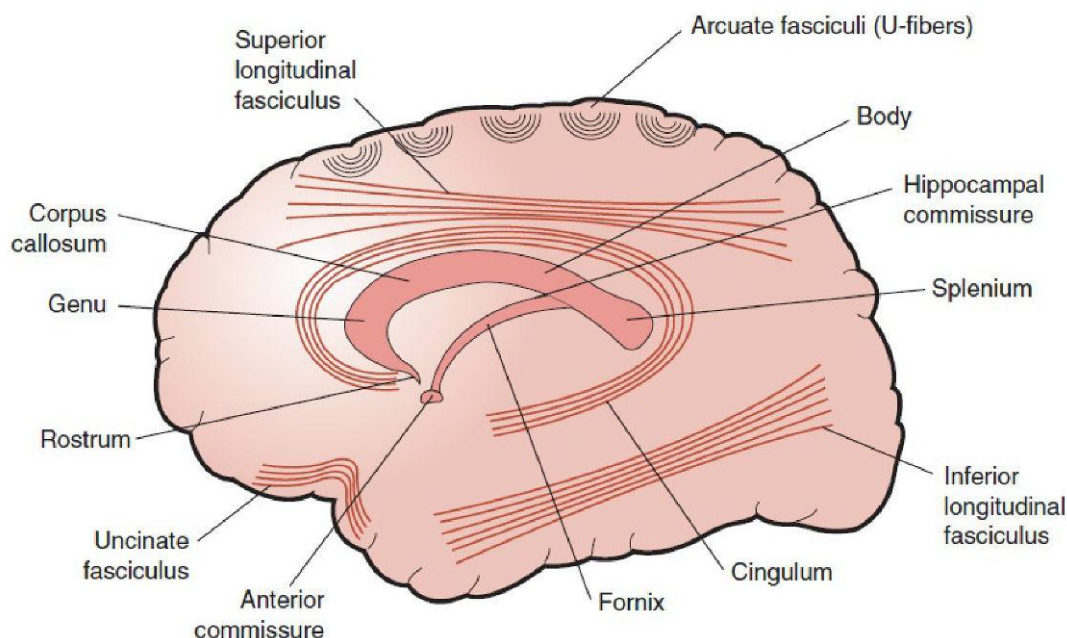


FIGURE 6.9 Sagittal view demonstrating short association fibers (arcuate or U-fibers), long association bundles, and major commissures.

Reproduced from DeJong's The Neurologic Examination 8e, Fig. 6.9 — the diagram to reproduce. Label: rostrum, genu, body and splenium of the corpus callosum; anterior commissure; hippocampal commissure; fornix; cingulum; superior longitudinal, inferior longitudinal and uncinate fasciculi; arcuate (U) fibres.

2. Blood supply and imaging correlates

- Chiefly the **anterior cerebral artery** (pericallosal and callosomarginal branches); the splenium also receives posterior circulation supply. **Anterior cerebral artery thrombosis may soften a large part of the corpus callosum**, and mental symptoms then dominate: apathy, drowsiness, memory loss, poor concentration, personality change — the picture of a frontal lesion.

3. Callosal syndromes — by site of lesion

Site	Clinical features	Mechanism / notes
Anterior callosum (genu, rostrum, anterior body)	Unilateral (left) tactile anomia; unilateral left agraphia; unilateral left ideomotor apraxia (callosal apraxia); difficulty copying drawings with the right hand; dyscalculia; impaired somaesthetic transfer; alien (anarchic) hand with intermanual conflict	Right hemisphere motor and sensory cortex disconnected from the left (language-dominant) hemisphere. Callosal apraxia = inability to pantomime to command, imitate or use objects with the left hand, with the right hand normal
Posterior callosum (splenium)	Left tactile anomia, left visual anomia, agraphia of the left hand; with a coexisting left occipital infarct, pure alexia without agraphia and impaired colour naming	Visual information reaching only the right occipital cortex cannot reach the left angular gyrus
Whole length	A reported case had unilateral verbal anosmia, hemialexia, unilateral ideomotor apraxia, unilateral agraphia, unilateral tactile anomia, unilateral constructional apraxia, absent somaesthetic transfer and dissociative phenomena	The complete "split brain"
Medial frontal lobe / SMA (for contrast)	Frontal variant of alien hand — uncooperative but not contentious hand, reflex grasping and other autonomous behaviour, little or no intermanual conflict ; non-fluent aphasia and a prominent grasp reflex	Distinguish from the callosal variant, where intermanual conflict is typical and nearly always affects the left hand
Parietal lobe (for contrast)	Sensory/posterior alien hand — parietal sensory deficits, left hemineglect resembling anosognosia; the left arm may involuntarily attack the right side of the body	Ideomotor apraxia of the non-dominant hand points to the callosal form; a hemisensory deficit points to the sensory form

Table 5 · Callosal disconnection syndromes — Dejong's 8e, Ch. 10, §Disconnection Syndromes and §Alien Hand Syndrome.

4. Diseases of the corpus callosum

- **Agenesis** — a common developmental defect, complete or incomplete. Commissural fibres, instead of crossing, cluster along the ventricular wall as the **bundle of Probst**. Usually found incidentally; when there are severe deficits (intellectual disability, seizures, motor signs) these are attributable to accompanying malformations or migration/organisation defects rather than to the agenesis itself. Three callosal abnormalities are recognised — **hypoplasia, agenesis and dysgenesis**.
- **Marchiafava-Bignami disease** — rare, related to **chronic alcoholism and undernutrition**; necrosis and degeneration of the **middle two-thirds** of the corpus callosum. Presentation ranges from dementia, apraxia, gait disorder, spasticity, seizures, incontinence and psychiatric disturbance to stupor and coma.
- **Tumours** — particularly glioma, crossing as a **butterfly glioma**; also lymphoma.
- **Vascular** — anterior cerebral artery infarction; also callosal haemorrhage.
- **Demyelination** — multiple sclerosis (callosal-septal interface lesions; "Dawson fingers" arise from the callosal veins).
- **Surgical** — **commissurotomy (corpus callosotomy)**, now rarely performed, for intractable epilepsy (particularly drop attacks). Split-brain patients have been the basis of research into hemispheric lateralisation because stimuli can be presented selectively to one hemisphere.

- **Others reported to produce callosal disconnection** — infarction, haemorrhage, Marchiafava-Bignami disease, multiple sclerosis and **Alzheimer disease**. Alien hand is also described in corticobasal syndrome, Creutzfeldt-Jakob disease, hypoglycaemic encephalopathy, hyperosmolar states, migraine and PRES.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- The examinable topographic rule: **anterior third = frontal (speech); body = posterior frontal and parietal; splenium = temporal and occipital**.
- **Callosal apraxia and callosal agraphia are LEFT-sided**, because it is the right hemisphere that has been disconnected from the language-dominant left.
- Two alien hands: **callosal** (anterior callosum, intermanual conflict, left hand, ideomotor apraxia) versus **frontal** (medial frontal/SMA, grasp reflex, non-fluent aphasia, no conflict).
- **Pure alexia without agraphia** requires two lesions — left occipital cortex **and** splenium — and is the classic PCA-territory disconnection syndrome.
- Callosal agenesis is usually asymptomatic; **Marchiafava-Bignami disease is the acquired callosal disease to name** in an alcoholic with dementia and gait failure.

Part 3

Neuroimaging and Clinical Neurophysiology

1 · FUNCTIONAL, MOLECULAR AND ADVANCED NEUROIMAGING

Q1. Role of functional imaging in neurological disorders.

LONG

Imaging §Short Q9

10 marks (grouped answer)

Also asked as: Imaging §Short Q1 — "MRS" · Imaging §Short Q10 — "Functional neuroimaging in the diagnosis of degenerative dementias" · Imaging §Short Q13 — "Amyloid PET scan"

Source: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 42 *Functional and Molecular Neuroimaging*, §Functional Neuroimaging Modalities and §Clinical Applications, pp. 576–600 (Table 42.1, p. 578; Figs. 42.1–42.9, pp. 579–588; Figs. 42.18–42.22, pp. 593–596). MRS: Ch. 42, p. 592 and Ch. 68 *Stroke in Children*, p. 1052 (Fig. 68.6); Ch. 100 *Epilepsies*, §Magnetic Resonance Spectroscopy, p. 1647. Ch. 35 *Electroencephalography and Evoked Potentials*, §Aging and Dementia, p. 441 (event-related potentials).

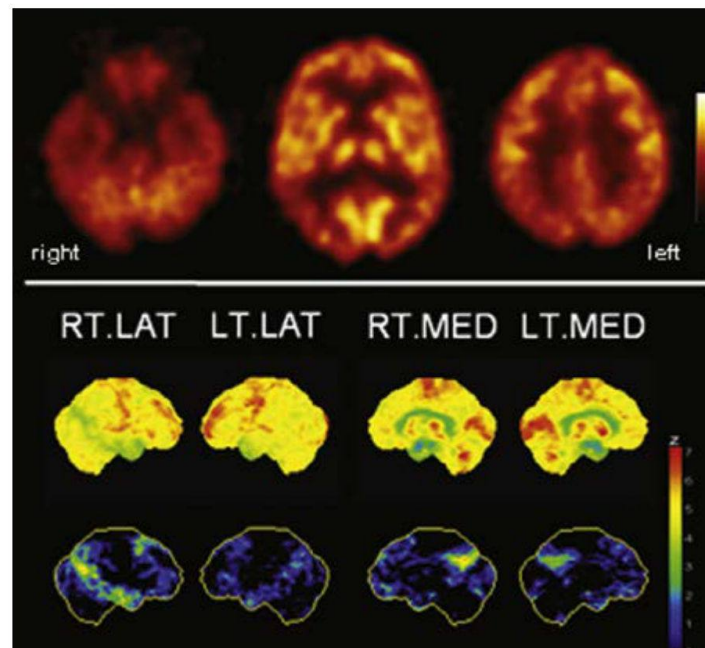
1. What "functional" imaging means, and the four modalities

- Structural imaging (CT, MRI) gives superb anatomical resolution. **Functional and molecular imaging visualise brain functions that are not necessarily related to brain structure** — cerebral blood flow (CBF), metabolism, receptor binding and pathological protein deposits.
- Their value is in **mapping brain function** and in **detecting disease-related molecular change that occurs independently of, or before, structural change**.
- The four techniques to name (Ch. 42, pp. 576–579)
 - **fMRI** — blood oxygen level-dependent (BOLD) effect. A transient local excess of **oxygenated** blood follows regional CBF and neuronal activity; oxyhaemoglobin acts as an **intrinsic contrast agent** and a surrogate marker of neuronal oxygen consumption.
 - **Arterial spin labelling (ASL) MRI** — magnetically labelled arterial water as an **endogenous** tracer; gives quantitative CBF maps without contrast (see Q2).
 - **PET** — positron-emitting tracer; the positron travels < 1 mm, annihilates with an electron and yields two 511-keV photons detected in coincidence. Spatial resolution **3–5 mm**. Tracers are given in **non-pharmacological (microgram) doses**, so they neither perturb the system nor have pharmacological effects.
 - **SPECT** — gamma-emitting radionuclide (^{99m}Tc , ^{123}I), lead collimators instead of coincidence detection. Lower sensitivity than PET; acquisition takes **20–30 minutes**; spatial resolution only **7–10 mm** and it deteriorates with depth (better for cortical than subcortical structures).
- **Radionuclides:** ^{11}C ($t_{1/2}$ 20.4 min), ^{15}O ($t_{1/2}$ 2.03 min) and ^{18}F ($t_{1/2}$ 109.7 min), all cyclotron-produced. Only **the long half-life of ^{18}F allows shipping** from a cyclotron to a distant PET site — which is why only ^{18}F -labelled radiopharmaceuticals are widely available clinically. ^{99m}Tc $t_{1/2}$ 6.02 h, ^{123}I $t_{1/2}$ 13.2 h.
- **Hybrid systems:** PET/CT (low-dose CT for attenuation correction) and, more recently, PET/MRI, which allows synchronous morphological, functional and molecular imaging in one session.

2. [^{18}F]FDG — the workhorse tracer

- Glucose analogue [^{18}F]2-deoxy-2-fluoro-d-glucose. Taken up by glucose transporters, phosphorylated by hexokinase; **FDG-6-P cannot be transported out or metabolised further, so it is irreversibly trapped** — its distribution therefore mirrors regional cerebral glucose metabolism.
- Glucose metabolic rate is **closely related to maintenance of ion gradients and transmitter turnover (especially glutamate)**, making FDG an ideal marker of neuronal function.

- **Technique:** scan started **30–60 min** after injection; scan duration **5–20 min**. Maintain **normal plasma glucose** and standard resting conditions (low noise, low ambient light) during uptake, or regional activation distorts the metabolic pattern.
- **Normal distribution:** highest in neocortex, basal ganglia and thalamus; intermediate in hippocampus, amygdala, brainstem and cerebellum; **lowest in white matter**. There is an age-related decline, most marked in **frontal cortex**.
- **Interpretation** is by qualitative visual reading, which **should be supported by voxel-based statistical analysis** against age-matched normal controls (e.g. Neurostat/3D-SSP z-score maps), and always with parallel inspection of a recent CT/MRI to exclude a structural cause of regional hypometabolism.



Reproduced from Bradley & Daroff 8e, **Fig. 42.1**, p. 579 — ^{18}F FDG PET in early Alzheimer disease. Upper panel: transaxial FDG uptake. Lower panel: Neurostat/3D-SSP surface projections (upper row) and z-score deviation from age-matched controls (lower row); RT.LAT, LT.LAT, RT.MED, LT.MED. Label when reproducing: temporoparietal + posterior cingulate/precuneus hypometabolism, asymmetry, sparing of sensorimotor and occipital cortex.

3. Functional imaging in the degenerative dementias — the core of this question

- Dementia is **diagnosed clinically**, but the diagnosis of the **specific disease** causing it increasingly relies on imaging. Current research criteria define Alzheimer disease (AD) by **biomarkers — amyloid and tau in CSF or on PET** — so AD no longer implies dementia at the time of diagnosis but a process that will lead to it (preclinical AD; prodromal AD = MCI).
- **^{18}F FDG PET is the most firmly established functional technique**; CBF imaging (SPECT, PET, ASL MRI) is the alternative. Hypoperfusion patterns on CBF SPECT are similar to FDG metabolic deficits but **accuracy is inferior** on meta-analysis and direct comparison.

Disease	Characteristic [¹⁸ F]FDG PET pattern	Discriminating value / other tracers
Alzheimer disease	Bilateral, often asymmetrical hypometabolism of temporal and parietal association cortex with the temporoparietal junction at the centre; posterior cingulate gyrus and precuneus affected early (voxel-based analysis). Frontal association cortex as disease progresses. Relative sparing of primary motor and visual cortex, basal ganglia and cerebellum (used as reference regions)	Meta-analysis: sensitivity 96%, specificity 90% . Autopsy-confirmed series with visual reading alone: sensitivity 84%–94%, specificity 73%–74%. When FDG PET disagreed with the initial clinical diagnosis, PET was considerably more likely to match the pathology
Dementia with Lewy bodies	AD-like pattern plus hypometabolism of primary visual and occipital association cortex (linked to visual hallucinations); relative preservation of hippocampus and of the mid- to posterior cingulate — the " cingulate island sign "	Occipital hypometabolism: sensitivity 83%–92%, specificity 91%–93% (autopsy-confirmed 90%/80%). [¹²³I]FP-CIT DAT SPECT is superior — pooled sensitivity 87%, specificity 94%; striatal DAT loss is an indicative biomarker in the DLB criteria whereas occipital hypometabolism is only supportive
Behavioural variant FTD	Bilateral, often asymmetrical frontal hypometabolism, most marked in mesial (polar) frontal cortex; striatum, thalamus, temporal and parietal cortex less affected	Voxel-based analysis separated FTD from AD with 90% accuracy (sens 98%, spec 86%) in an autopsy-confirmed study — better than clinical diagnosis alone. Frontal/anterior temporal hypometabolism is a criterion for probable bvFTD. Amyloid scans are typically negative
Semantic variant PPA	Predominant rostral temporal hypometabolism, usually asymmetric leftward	Distinguishes svPPA from lvPPA
Logopenic variant PPA	Strongly leftward-asymmetric temporoparietal hypometabolism	Commonly caused by AD — a non-amnesic AD presentation
Non-fluent variant PPA	Left frontal hypometabolism, inferior frontal or posterior frontoinsula emphasis	FTLD spectrum
Posterior cortical atrophy	Rightward-asymmetric temporoparietal hypometabolism with pronounced lateral occipital association cortex involvement	Another non-amnesic AD presentation
Vascular dementia	Defects of FDG uptake corresponding to infarcts, not sparing regions usually preserved in AD	Defects in basal ganglia, thalamus and cerebellum are important diagnostic clues
Parkinson disease dementia	Very similar, if not identical, to DLB	Separated from DLB only by the clinical 1-year rule . PD-MCI shows decreased temporoparietal, occipital, precuneus and frontal metabolism; posterior cingulate, BA18/19 and caudate hypometabolism predict conversion to PDD

Table 1 · [¹⁸F]FDG PET patterns in the degenerative dementias — Bradley & Daroff 8e, Ch. 42, §Clinical Applications, pp. 579–586 (Figs. 42.1–42.8).

4. Amyloid PET — the molecular imaging answer

- **Tracers** (Table 42.1, p. 578)
 - [^{11}C]PIB (Pittsburgh compound B) — the first; short half-life restricts it to cyclotron sites.
 - [^{18}F]flutemetamol (GE-067, Vizamyl) — chemically related to PIB; [^{18}F]florbetapir (AV-45, Amyvid) and [^{18}F]florbetaben (BAY-949172, NeuraCeq) — stilbene derivatives. All licensed after formal trials comparing in-vivo imaging in terminally ill patients with **post-mortem beta-amyloid**.
 - [^{18}F]FDDNP was the first ^{18}F amyloid marker but did not match the specificity of [^{11}C]PIB.
- **Imaging times after injection:** $\approx$ **60 min** for florbetapir; **90-120 min** for flutemetamol and florbetaben.
- **How the scan is read**
 - All amyloid tracers show **high non-specific binding to white matter**, more so with the ^{18}F compounds than with PIB.
 - **Negative scan** = activity in **white matter surrounded by low grey-matter activity** (grey-white contrast preserved).
 - **Positive scan** = high uptake in **cortical** areas as well, so the grey-white distinction is lost.
 - Visual reading is **binary**. **Formal reader training is required**, and colour scales and rules for partial cortical uptake differ slightly between tracers.
- **Quantification**
 - **SUVr** (standardised uptake value ratio) against a reference region devoid of fibrillary amyloid — pons, cerebral white matter, cerebellar cortex, or (for convenience) whole cerebellum.
 - Reference-region caveats: cerebellar cortex may contain diffuse and vascular amyloid; the pons is small with low counts; white matter has high non-specific binding but is **very stable in AD even with progression**, hence favoured for longitudinal studies.
 - Because thresholds differ between tracers and reference regions, the **centiloid** scale was introduced to standardise uptake measures.
- **Early-uptake (R1) maps** from simple kinetic analysis are very similar to FDG scans, so a single amyloid study can also give perfusion-like diagnostic information.

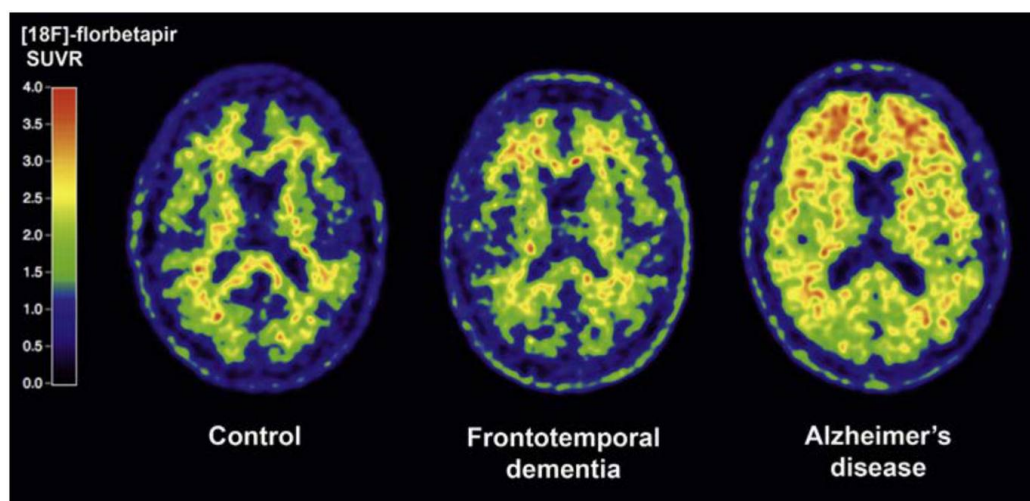


Fig. 42.5 [^{18}F]florbetapir positron emission tomography (PET) demonstrating nonspecific white-matter uptake in a normal control subject (*left*) and patient with frontotemporal dementia (FTD) (*middle*) as well as cortical binding to amyloid in a patient with Alzheimer disease (AD) (*right*). *SUVr*. Standardized uptake value ratio.

Reproduced from Bradley & Daroff 8e, **Fig. 42.5**, p. 582 — [^{18}F]florbetapir PET. Non-specific **white-matter** uptake in a normal control (*left*) and in frontotemporal dementia (*middle*) — grey-white contrast preserved = **negative**. Cortical binding in Alzheimer disease (*right*) — grey-white contrast lost = **positive**. Label when reproducing: *SUVr* colour scale, white-matter uptake, cortical uptake.

Question	Answer from Bradley Ch. 42
Does a positive scan mean AD?	No. Positivity in normal controls and in other diseases rises steeply with age, reaching 40% in cognitively normal 80-year-olds. Amyloid deposition may be incidental in elderly patients with other neurodegenerative or cerebrovascular disease. About two-thirds of DLB (but only one-third of PDD) patients have a positive amyloid scan. Cerebral amyloid angiopathy without AD is rare but also gives a positive scan
Does a negative scan exclude Alzheimer dementia?	Largely, yes — but up to 30% of patients clinically diagnosed with Alzheimer dementia have a negative amyloid scan , and the few with pathology suggest they did not have AD at all
Does the intensity correlate with severity?	No. There is no close correlation between amyloid load and cognition in normals or in demented patients. Only the laterality may match the clinical picture (left-sided in IvPPA, right-sided in PCA). Do not use intensity as a marker of clinical impairment
What does it add in MCI?	> 50% of MCI patients with a positive amyloid scan plus neuronal dysfunction on FDG or severe hippocampal atrophy progress to dementia in 2–3 years (40%–50% within 2 years when both amyloid and FDG are abnormal). ~90% of MCI patients with normal amyloid AND normal FDG do not progress in that period. Discordant results give an intermediate prognosis. In a real-life memory-clinic population, amyloid PET predicted conversion better than FDG PET
How does it compare with CSF?	Brain amyloid deposition is inversely related to CSF amyloid concentration ; as diagnostic markers, CSF amyloid and amyloid PET give similar information
What is missed?	Current tracers detect fibrillary amyloid only. Initial deposition as oligomers , which may be the neurotoxic species, is not detected; tracer development is ongoing

Table 2 · Amyloid PET — the six caveats that earn the marks (Bradley & Daroff 8e, Ch. 42, pp. 580–582).

5. Tau, transmitter and inflammation PET

- **Tau PET** — deposits are of much lower density than amyloid and are primarily **intracellular**, yet imageable. [¹⁸F]flortaucipir (**AV-1451**) is the most used first-generation ligand; it relates to symptoms and severity and can be used for **staging and monitoring progression**. In amyloid-positive patients, tau **spreads from mesial temporal areas to the rest of the temporal lobe and then other cortex, following Braak stages** (Fig. 42.6, p. 583). Elderly normals show hippocampal uptake even without amyloid. First-generation tracers show **off-target binding** (e.g. [¹⁸F]THK5351 to MAO-B); second-generation tracers should reduce this.
- **Cholinergic imaging** — the most prominent transmitter deficit in AD is loss of cholinergic fibres from the **nucleus basalis of Meynert**. Nicotinic receptor ligands are under development; past ligands had very slow kinetics. PDD is associated with cholinergic reductions **greater than in AD**.
- **Dopaminergic imaging** (Fig. 42.9, p. 588) — [¹⁸F]FDOPA (dopamine synthesis), [¹¹C]DTBZ (VMAT2) and [¹²³I]FP-CIT (dopamine transporter). Used to separate degenerative parkinsonism from essential tremor, drug-induced and psychogenic parkinsonism, and to separate DLB from AD. Note that nigrostriatal projections may also be damaged in FTD and in PSP/CBD.
- **Microglial (neuroinflammation) imaging** — ligands to the mitochondrial translocator protein 18 kDa (**TSPO**) expressed by activated microglia. Binding is moderately increased in

manifest and prodromal AD and shows activated microglia in the substantia nigra in PD, but **low or non-specific binding and a TSPO polymorphism prevent routine clinical use.**

- **Synaptic imaging** — tracers for the synaptic vesicle protein **SV2A** provide a molecular marker of synaptic function complementary to FDG and fMRI.

6. fMRI and resting-state networks

- **Task-based fMRI designs**
 - **Block design** — series of stimuli for 20–30 s alternating with rest blocks of similar length over several minutes.
 - **Event-related design** — $\approx$ 30–40 stimuli of each type in counterbalanced order, each followed by a baseline period.
 - Multi-subject studies need **stereotactic normalisation**; time series are analysed by univariate **general linear model** (local effect size) or by multivariate methods (partial least squares) for network-level connectivity; graph theory and dynamic causal modelling/Granger causality for effective connectivity.
- **Resting-state fMRI (Rs-fMRI)** — analysis of spontaneous BOLD fluctuations reveals consistent intrinsic connectivity networks: motor, language, attention, and the **default mode network (DMN)** (medial temporal lobe, superior parietal and prefrontal areas), which **deactivates** during task performance. Analysed by seed-region correlation or independent component analysis.
- **Rs-fMRI needs much less patient cooperation** than task fMRI, which is why it is used in prodromal dementia research — but **high inter-scanner and longitudinal variability limits its use for individual diagnosis or prognosis.**
- **Findings:** reduced DMN connectivity in AD dementia and (less so) amnesic MCI; salience network alteration (dorsal anterior cingulate, anterior insula) in bvFTD; reduced DMN and frontoparietal connectivity in PD/DLB with cognitive decline. Single-centre accuracy reaches 80%, but **falls below 80% on multicentre data with cross-validation — so Rs-fMRI is not sufficiently validated as a diagnostic test.**
- **Non-linear course:** hippocampal **hyperactivity** during memory tasks predicts later cognitive decline; hyperactivation may be compensatory early and a marker of network pathology later.
- **Established clinical fMRI use — presurgical brain mapping** (pp. 594–596)
 - Localises eloquent motor, language and memory cortex before resection of tumours or epileptic foci; for anterior temporal lobe resection, fMRI language lateralisation has a positive predictive value of **60%–81%** for post-operative language deficit.

7. Magnetic resonance spectroscopy (MRS)

- MRS provides **quantitative histochemical information in vivo** without ionising radiation; it is acquired as an add-on to a standard MRI and displayed as a **spectrum of metabolite peaks against chemical shift (ppm).**
- **Principal metabolites and what they mean**
 - **N-acetylaspartate (NAA)** — present in almost all neurons; **a decrease corresponds to neuronal loss or dysfunction** (Ch. 42, p. 592). It is the neuronal marker.
 - **Choline (Cho)** — membrane turnover; **increased with high cellularity / proliferation**, e.g. a markedly increased choline peak in a high-grade tumour (Ch. 75).
 - **Creatine (Cr)** — energy metabolism; used as the internal reference for ratios (NAA/Cr, Cho/Cr). Proton MRS shows **absent or markedly decreased creatine** in the cerebral creatine deficiency syndromes (Ch. 91, p. 1405).
 - **Lactate** — a **doublet** peak; marks anaerobic glycolysis. A lactate peak in brain parenchyma or ventricular CSF is the signature of **mitochondrial disease (MELAS)** (Ch. 68, p. 1052) and is

also described in acute demyelinating and ischaemic lesions.

- **Glutamine** — elevated in **hepatic encephalopathy** (Ch. 59, p. 893).
- **Lipid peak** — abnormal lipid peak with periventricular white-matter lesions and a thin corpus callosum (Ch. 97, p. 1541).

• Clinical uses named in Bradley

- **Brain tumours** — MRS "has been suggested in addition to MRI to help in the characterisation" of tumours (Ch. 42, p. 592); depressed NAA with elevated choline in a glioma; helps in the **tumour vs radiation necrosis** problem.
- **Epilepsy surgery** — MRS provides quantitative histochemical information in the presurgical work-up (Ch. 100, p. 1647).
- **Mitochondrial disease** — lactate doublet (Fig. 68.6).
- **Motor neuron disease** — ^1H -MRS is a **non-invasive marker of upper motor neuron involvement** (Ch. 97, p. 1537); reduced NAA in motor cortex.
- **Neurodegeneration and movement disorders** — reduced NAA relative to total creatine in cerebellar cortex supports a degenerative cerebellar disorder (Ch. 96, p. 1519); MRS holds promise for differentiating neurodegenerative causes of chorea/parkinsonism (Ch. 23, p. 332).
- **Inborn errors of metabolism** — MRS and DWI "provide additional insights" (Ch. 91, p. 1391).
- **Concussion/TBI** — MRS and PET demonstrate altered cerebral metabolism after concussion (Ch. 61, p. 910).

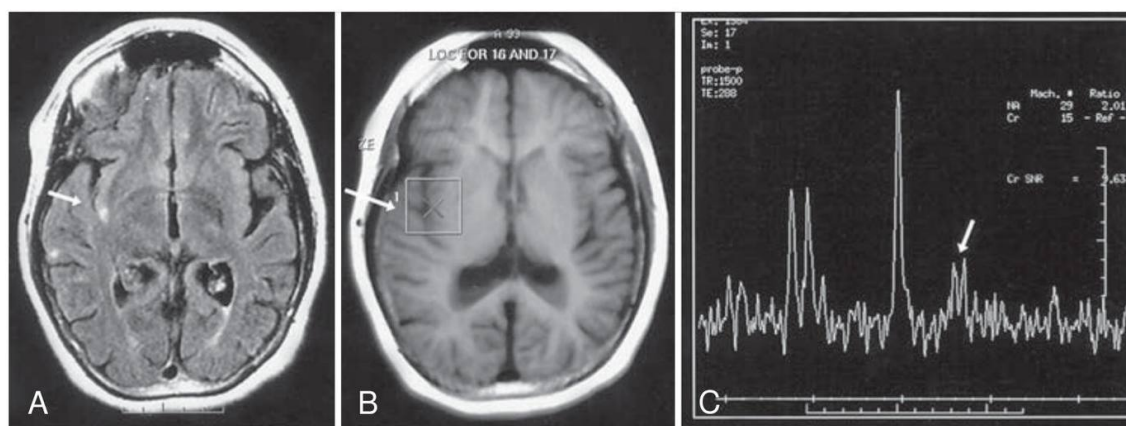


Fig. 68.6 Magnetic resonance imaging (MRI) of an 18-year-old girl who presented at age 12 with headaches and went on to develop bilateral incoordination, decreased attention span, decline in school performance, and fatigability. **A**, Fluid spin echo inversion recovery MRI demonstrates multiple bilateral lesions in nonvascular territories. **B**, A section of the involved area is selected for evaluation using MR spectroscopy (MRS). **C**, MRS demonstrates a lactate doublet peak consistent with mitochondrial disease in an area of signal abnormality (arrows).

Reproduced from Bradley & Daroff 8e, **Fig. 68.6**, p. 1052 — MRS in mitochondrial disease. **A**, FLAIR MRI: multiple bilateral lesions in **non-vascular** territories. **B**, the voxel is placed within the abnormal area. **C**, the spectrum shows a **lactate doublet** (arrow). Label when reproducing a spectrum: x-axis in ppm, NAA $\approx$ 2.0, Cr $\approx$ 3.0, Cho $\approx$ 3.2, lactate doublet $\approx$ 1.3 (inverted at TE 135 ms).

8. Other clinical applications to list quickly

Setting	Functional/molecular imaging contribution (Bradley Ch. 42)
Brain tumours	^{18}F FDG and amino-acid tracers (^{18}F FET, ^{11}C MET, ^{18}F FDOPA) and the proliferation tracer ^{18}F FLT for grading, biopsy and radiotherapy target definition, and for separating recurrence from treatment effect (Figs. 42.14–42.17, pp. 591–592)

Setting	Functional/molecular imaging contribution (Bradley Ch. 42)
Epilepsy	Interictal FDG PET shows a hypometabolic zone (typically larger than the epileptogenic zone); ictal CBF SPECT shows hyperperfusion at seizure onset. Both are used in presurgical evaluation of MRI-negative or discordant cases (Figs. 42.18–42.20, pp. 593–595)
Presurgical mapping	fMRI for motor, language and memory localisation; combined with PET/MEG (Figs. 42.21, 42.22)
Autoimmune / paraneoplastic disease	Cerebral FDG PET as an adjunct in questionable autoimmune limbic encephalitis; whole-body FDG PET/CT is the method of choice for occult tumour screening — sensitivity/specificity $\approx$ 89%/83% in paraneoplastic syndromes, higher than conventional imaging; repeat for up to 4 years if negative. Paraneoplastic cerebellar degeneration may show early cerebellar hypermetabolism before hypometabolism
Ischaemic stroke	[¹⁵ O]water PET is the most accurate measure of CBF but is rarely feasible acutely. Practice is structural imaging first, with diffusion/perfusion MRI reserved for anterior-circulation large-vessel occlusion 6–24 h from last known well. Functional imaging demonstrates diaschisis and the dynamics of language recovery (Fig. 42.24, p. 599)
Coma and disorders of consciousness	Coma is associated with a 30%–60% fall in global glucose metabolism ; the most severe reductions occur in persistent vegetative state. Rs-fMRI and activation fMRI are used to detect covert awareness / minimally conscious state

Table 3 · Functional and molecular imaging outside dementia — Bradley & Daroff 8e, Ch. 42, pp. 589–600.

GUIDELINE UPDATE — BEYOND THE TEXTBOOK

- **Beyond the prescribed textbook.** Two developments that post-date Bradley 8e are worth one line each if the examiner asks for "recent advances": (i) the **2018 NIA-AA ATN framework** has been operationalised by **blood-based biomarkers** — plasma p-tau217, p-tau181 and A β 42/40 — which are approaching amyloid-PET accuracy and will change who gets a PET scan; and (ii) **anti-amyloid monoclonal antibodies (lecanemab, donanemab)** require **amyloid confirmation before treatment** and serial MRI (not PET) for **ARIA** surveillance, so amyloid PET has shifted from a research tool to a treatment gateway. **Appropriate-use criteria** restrict amyloid PET to patients with objective cognitive impairment in whom the cause is uncertain and knowing it will change management — it is **not** a screening test for the worried well. This paragraph is outside the prescribed sources and is flagged as such.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Read the pattern, not the picture.** Temporoparietal + posterior cingulate/precuneus = AD; add occipital = DLB; frontal/anterior temporal = bvFTD; defects in basal ganglia, thalamus and cerebellum = vascular.
- **Cingulate island sign** (preserved posterior cingulate with occipital hypometabolism) is the high-specificity DLB sign; **DAT SPECT beats FDG PET** for DLB vs AD (87%/94%).
- Amyloid PET: a **negative scan is more useful than a positive one**. Positivity reaches 40% in cognitively normal 80-year-olds and occurs in two-thirds of DLB.
- **MRS one-liner:** NAA = neurons (down in almost everything neuronal), choline = cellularity (up in tumour), lactate = anaerobic metabolism (mitochondrial disease, abscess, necrosis), creatine = internal reference (absent in creatine deficiency syndromes).
- Quote resolution when asked about limitations: **PET 3-5 mm, SPECT 7-10 mm**; PET is susceptible to **partial volume effect** when the lesion is less than twice the scanner resolution — which is exactly why hippocampal hypometabolism looks less impressive than the pathology predicts.
- Resting-state fMRI is a **research tool**: single-centre accuracy 80%, multicentre < 80%. Say so — examiners reward knowing what is *not* yet clinical.

Q2. Arterial Spin Labelling MRI: applications in neurology.**INTERMEDIATE****Paper IV · March 2025 · Q10****6-8 marks**

Source: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 42 *Functional and Molecular Neuroimaging*, §Arterial Spin Labeling, p. 577, and §Clinical Applications (dementia, p. 580; stroke, p. 598). Supplementary: Ch. 40 *Structural Imaging*, §Ischemic stroke, pp. 514-516 (Fig. 40.37, p. 516) and Ch. 53 *Neurointensive Care*, §Regional CBF monitoring, p. 782.

1. Definition and principle

- ASL is an **MRI technique that estimates cerebral perfusion at tissue level, non-invasively and without any contrast medium**. The main physiological parameter measured is **CBF**.
- It uses the **water molecules of blood as an endogenous contrast agent**: protons in arterial blood are **magnetically labelled (inverted) below the imaging slab** before they flow into the tissue of interest; a label image and a control image are subtracted, and the difference is proportional to perfusion.
- Output is a **quantitative parametric CBF map** suitable for visual and region-of-interest analysis. This contrasts with dynamic contrast-enhanced MRI (DCE-MRI) and CT perfusion, which require an exogenous bolus.
- First described in the **early 1990s** (Detre 1992; Williams 1992).

2. Types and technical parameters — the details that earn marks

Parameter	Detail (Bradley Ch. 42, p. 577)
Labelling method	Three types: pulsed ASL (PASL) , pseudo-continuous ASL (pCASL) and continuous ASL (CASL) . pCASL and PASL are the most used currently
Labelling plane	Positioned below the brain

Parameter	Detail (Bradley Ch. 42, p. 577)
Post-labelling delay (PLD)	Time between the end of labelling and the start of imaging — i.e. the time allowed for labelled blood to reach the tissue. It depends on blood velocity, which falls with age . Recommended: 1500 ms in children; 1800 ms in healthy adults < 70 years; 2000 ms above 70 years; 2000 ms for adult patients
Signal-to-noise ratio	The main drawback is inherently low SNR . ASL is possible at 1.5 T but low SNR lengthens scan time and therefore makes it sensitive to motion artefact . Higher field strength and better coils are what have made ASL clinically practical
Background suppression	Needed, along with prevention of patient motion, to reduce noise and artefact that would otherwise mask the small label-control signal difference
Readout	Traditionally fast echo-planar imaging (EPI) . Newer 3D readouts — 3D GRASE (gradient and spin echo) and 3D RARE (rapid acquisition relaxation enhanced) — have superior SNR, acquire the whole volume in one shot and remove the slice-dependent variation of the perfusion signal seen with 2D

Table 4 · ASL acquisition parameters — Bradley & Daroff 8e, Ch. 42, p. 577.

3. Applications in neurology

- **Dementia** (Ch. 42, p. 580)
 - Patterns of **hypoperfusion** in AD mirror the metabolic deficits on [^{18}F]FDG PET. ASL is explicitly named among the "increasing number of techniques to provide CBF mapping **as replacement of FDG PET**".
 - Studies in selected series suggest **similar accuracy to FDG PET**, but the text is careful: **larger studies are still needed to confirm robustness**.
 - Attraction in practice: no radiation, no cyclotron, no tracer, and it can be added to the structural MRI the patient is already having.
- **Acute ischaemic stroke** (Ch. 40, pp. 514–516; Ch. 42, p. 598)
 - Perfusion imaging defines the **ischaemic penumbra** as the mismatch between a small diffusion lesion and a larger perfusion deficit (Fig. 40.37). ASL is the contrast-free way of generating that perfusion map.
 - Current recommendations put the priority on **essential structural imaging to avoid loss of time**, reserving diffusion- and perfusion-weighted MRI for **large anterior circulation vessel occlusion between 6 and 24 hours** from last known well.
 - Useful reference numbers for the answer: normal CBF **45–60 mL/100 g/min** (Ch. 53, p. 781); values below **10 mL/100 g/min** indicate ischaemia.
- **Other named uses of regional CBF measurement** (for which ASL is the MRI option)
 - Neurocritical care — ASL/PWI-MRI is listed among the regional CBF techniques (with Xe-133, xenon-CT, SPECT, PET and CT perfusion); MRI has the advantage of **greater anatomical information and simultaneous diffusion imaging**, but requires transport out of the ICU (Ch. 53, p. 782).
 - Brain tumours and epilepsy — perfusion is one of the physiological parameters that hybrid and multiparametric imaging combines with metabolism and receptor binding.

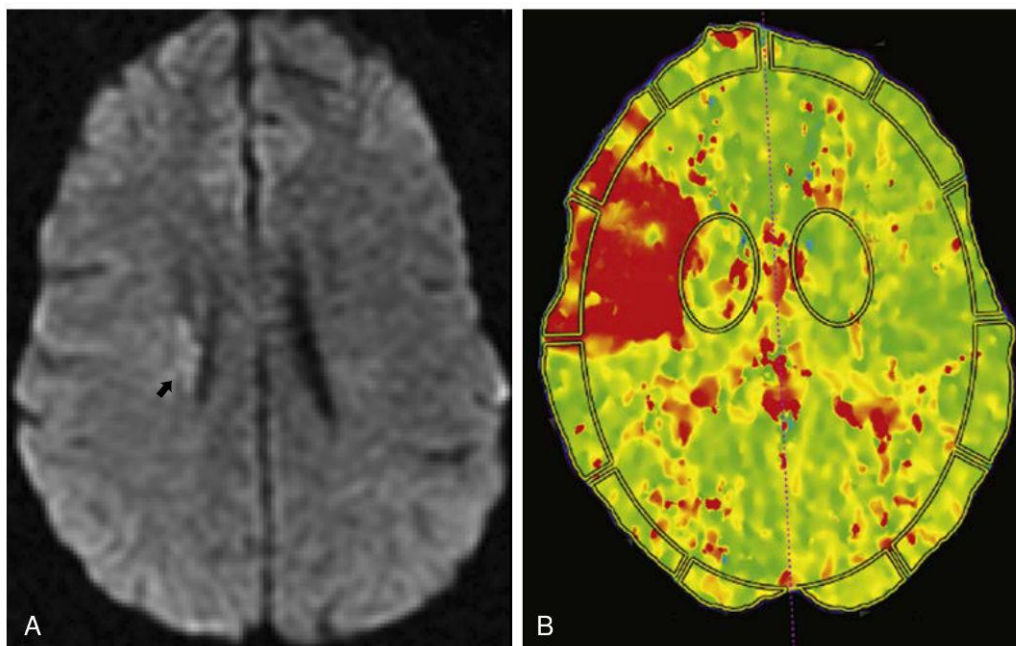


Fig. 40.37 Ischemic Penumbra in Acute Right Middle Cerebral Artery Stroke. **A**, Diffusion-weighted image reveals a small, circumscribed area of restricted diffusion in the paraventricular region of the right centrum semiovale (arrow). **B**, Magnetic resonance perfusion-weighted image demonstrates a much larger perfusion deficit, as revealed by increased mean transit time, indicated in red. The perfusion deficit (red) outside the small area of restricted diffusion (arrow, **A**) represents the ischemic penumbra.

Reproduced from Bradley & Daroff 8e, **Fig. 40.37**, p. 516 — the diffusion-perfusion mismatch that a perfusion map (including ASL) is used to show. **A**, DWI: small area of restricted diffusion in the right centrum semiovale (arrow) = core. **B**, MR perfusion: a much larger deficit shown by increased mean transit time (red). The red territory outside the diffusion lesion is the ischaemic penumbra.

4. Advantages and limitations — the balanced close

Advantages	Limitations
No gadolinium — usable in renal impairment (no nephrogenic systemic fibrosis risk), in pregnancy where gadolinium is contraindicated, and in children	Low intrinsic SNR — the dominant technical problem
Fully quantitative CBF in mL/100 g/min, not a relative index	Motion sensitivity , because long acquisitions are needed to recover SNR
Repeatable — no tracer dose limit, so it can be used serially and for longitudinal studies	Choice of post-labelling delay is critical; a PLD that is too short in an elderly patient or in slow collateral flow produces arterial transit artefact and apparent hypoperfusion
No ionising radiation, unlike PET, SPECT, xenon-CT and CT perfusion	Not yet validated against FDG PET in large dementia cohorts
Adds only minutes to an MRI the patient is already undergoing	Still requires MRI access and patient cooperation; unsuitable for the unstable ICU patient who cannot be transported

Table 5 · ASL — balance sheet, compiled from Bradley & Daroff 8e, Ch. 40 pp. 500–501, Ch. 42 pp. 577–580 and Ch. 53 p. 782.

GUIDELINE UPDATE — BEYOND THE TEXTBOOK

- **Outside the prescribed textbook, flagged as such.** The **2015 ISMRM/European consensus statement on ASL perfusion MRI for clinical applications** recommends **pCASL with background-suppressed 3D readout** as the default implementation, with the PLDs Bradley quotes. Applications that have matured since Bradley 8e and are reasonable to name in a 2025–26 answer: **arterial transit artefact as a marker of collateral flow** in large-vessel occlusion; **post-ictal hypoperfusion and ictal hyperperfusion** in seizure localisation; **hyperperfusion in status epilepticus and in MELAS stroke-like episodes**; ASL in **moyamoya and after revascularisation**; and ASL as a non-contrast alternative for detecting arteriovenous shunting. None of these is in the prescribed sources.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **One-line definition:** ASL labels arterial blood water magnetically below the imaging slab and subtracts label from control to give a quantitative CBF map with no contrast and no radiation.
- Numbers to quote: three types (**PASL, pCASL, CASL**); **pCASL and PASL** are used; PLD **1500 ms paediatric, 1800 ms adult < 70 y, 2000 ms > 70 y and for adult patients**.
- The examiner is testing whether you know the **weakness**: low SNR → long scans → motion sensitivity. Say it first, then say 3D GRASE/RARE readout is the fix.
- In dementia, position ASL as **a candidate replacement for FDG PET** whose accuracy looks similar in selected series but is **not yet confirmed in large studies** — that exact caveat is in the textbook.
- In stroke, remember Bradley's priority order: **structural imaging first; perfusion only to select large-vessel occlusion in the 6–24 h window**. Never let a perfusion sequence delay thrombolysis.



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Part 6

Movement Disorders

1 · BASAL GANGLIA — ANATOMY, CIRCUITRY AND PATHOPHYSIOLOGY

Q1. Anatomy and connections of the basal ganglia; describe their involvement in the pathogenesis of different movement disorders.

LONG

Anatomy §Long Q2

10 marks

Also asked as: Anatomy §Long Q7 — "Anatomy and physiological pathway of basal ganglia along with clinical implication" · Anatomy §Short Q5 — "Basal ganglia"

Source: DeJong's *The Neurologic Examination*, 8th ed. — Ch. 26 *The Extrapyramidal Level*, §Anatomy and Physiology, §Basal Ganglia Physiology and §Basal Ganglia Pathophysiology (Figs. 26.1–26.4, Box 26.1, Table 26.1); Ch. 2 *Overview of the Nervous System*, §Basal Ganglia. Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 96 *Parkinson Disease and Other Movement Disorders*, §Movement Disorders and the Basal Ganglia, §Basal Ganglia Anatomy, §Functional Organization of the Basal Ganglia and Other Pathways and §Biochemistry, pp. 1498–1502 (Figs. 96.1–96.3, Tables 96.1 and 96.2).

1. What counts as "basal ganglia" — settle the nomenclature first

- Bradley (p. 1499): there is **no clear consensus**. For the purposes of movement disorders the basal ganglia are the structures of the **striatopallidal circuits that modulate the thalamocortical projection — caudate nucleus, putamen, GPe, GPi, plus SNc, SNr and the subthalamic nucleus (STN)**.
- **DeJong's terminology (Ch. 2 and Ch. 26)** — the words examiners like to hear
 - **Striatum (neostriatum)** = caudate + putamen. The streaming fibres of the anterior limb of the internal capsule between them give the striped ("striated") look; the finely myelinated bundles crossing toward the pallidum are **Wilson's pencils**.
 - **Pallidum (paleo-/archistriatum)** = globus pallidus; pale because it is traversed by myelinated fibres. **External medullary lamina** separates GP from putamen; the **internal medullary lamina** divides GP into **GPe** and **GPi**.
 - **Corpus striatum** = caudate + putamen + GP. **Lenticular (lentiform) nucleus** = putamen + GP (lens-shaped).
 - **Dorsal striatum** = caudate + putamen (motor/cognitive); **ventral striatum** = nucleus accumbens + anterior perforated substance + olfactory tubercle (limbic).
 - **Clastrum**, **amygdala** and **substantia innominata** lie at the base of the hemisphere but are **not functionally part of the motor basal ganglia** — do not include them.
- **Key anatomical relations to draw**
 - The **internal capsule thrusts straight through the region**: putamen and GP lie **lateral** to it; caudate, thalamus, STN and SN lie **medial**.
 - Caudate = head (bulges into frontal horn), body, tail (curves into roof of temporal horn, abutting the amygdala). **Sulcus terminalis**, containing the stria terminalis and thalamostriate vein, separates caudate from thalamus.
 - Putamen is separated from the insula by external capsule, claustrum and extreme capsule.
 - **SN** lies in the midbrain between crus cerebri and tegmentum at the level of the superior colliculi; **SNr is functionally a midbrain extension of GPi**.
 - **STN (corpus Luysii)** — small lens-shaped mass in the ventral thalamic region, just dorsomedial to the cerebral peduncle.

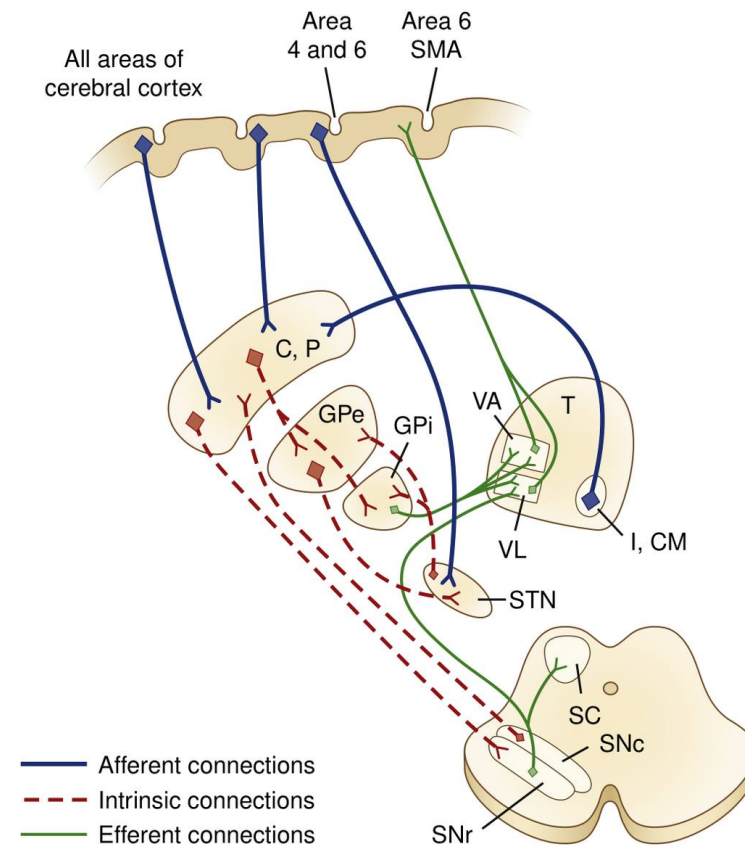


Fig. 96.1 Schematic drawing of interconnections between the basal ganglia and its afferent and efferent connections. CM, Centromedian nucleus of thalamus; C,P, caudate, putamen (striatum); GPe, lateral (external) globus pallidus; GPi, medial (internal) globus pallidus; SC, superior colliculus; SMA, supplementary motor area; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; T, thalamus; VA, ventral anterior; VL, ventrolateral.

Reproduced from Bradley & Daroff 8e, **Fig. 96.1**, p. 1499 — the overview diagram to draw first. Label: all areas of cerebral cortex, areas 4 and 6, SMA; C,P (caudate, putamen = striatum); GPe; GPi; STN; SNc; SNr; SC; thalamus with VA, VL and I,CM. Use three line styles — **afferent**, **intrinsic** and **efferent** connections.

2. Microstructure and cell types (worth two marks on their own)

- The SN normally contains about **500,000 dopaminergic neurons**; their development and maintenance depend on the transcriptional regulators **Nurr1, Lmx1a, Lmx1b, Msx1 and Pitx3** (Bradley, p. 1499).
- Striatal neurons: small cells outnumber large by **20:1**. The commonest cell is the **small spiny GABAergic medium spiny neuron**, co-localising **enkephalin, dynorphin or substance P** — this is the striatal output cell. The **small aspiny interneurons are cholinergic**.
- **Striosome-matrix organisation**: patches (striosomes) rich in substance P and enkephalin lie in an acetylcholine-staining matrix. **Enkephalinergic neurons carry D₂ receptors; substance-P neurons carry D₁ receptors**.
- GP contains only ~5% as many cells as the striatum and all are large; transmitter is mainly GABA, with **substance P in GPi and enkephalin in GPe**.
- SNc neurons contain **neuromelanin**, a by-product of dopamine synthesis — hence the pigmentation, and hence the pallor of the SN in Parkinson disease.

3. Afferents, efferents and the pallidal outflow bundles

Connection	Origin	Termination	Transmitter
Corticostriate	Whole ipsilateral neocortex (layers V-VI pyramidal cells)	Striatum (head of caudate ← frontal; body ← parietal/occipital; tail ← temporal; putamen ← areas 4 and 6)	Glutamate
Corticosubthalamic ("hyperdirect")	Cerebral cortex	STN directly	Glutamate
Thalamostriate	Intralaminar nuclei, DM and VA	Striatum	Acetylcholine (?)
Nigrostriatal	SNc	Striatum	Dopamine (+ cholecystokinin)
Coeruleostriatal / raphe-striatal	Locus coeruleus / raphe nuclei	Striatum and SN	Noradrenaline / serotonin
Striatopallidal	Striatum	GPe and GPi	GABA (+ substance P to GPe)
Striatonigral (comb bundle)	Striatum	SNr	GABA + substance P or enkephalin
Pallidosubthalamic	GPe only	STN (via subthalamic fasciculus)	GABA
Subthalamopallidal	STN	GPi, SNr, GPe	Glutamate
Pallidothalamic	GPi (via ansa lenticularis and fasciculus lenticularis → thalamic fasciculus)	VA, VL, centromedian	GABA
Nigrothalamic / nigrotectal	SNr	VA and DM thalamus / superior colliculus	GABA
Thalamocortical	VA, VL	Motor, premotor cortex and SMA	Glutamate
Descending pallidal	GPi, SNr	Pedunculopontine nucleus (PPN) , zona incerta	GABA

Table 1 · Major basal ganglia pathways — DeJong's 8e, Ch. 26, Table 26.1 and §Striatal/Pallidal Afferents and Efferents; Bradley & Daroff 8e, Table 96.2, p. 1502.

- **Fields of Forel** — the classic viva question on pallidal outflow
 - **Field H (prerubral/tegmental field)** — just rostral to the red nucleus; carries dentatothalamic and rubrothalamic fibres. Pallidofugal fibres stream in and turn upward.
 - **Field H₂ = lenticular fasciculus** (dorsal division) — emerges from the **dorsal** surface of GPi and **pierces** the internal capsule.
 - **Field H₁ = thalamic fasciculus** (ventral division), lying just dorsal to the **zona incerta**; ansa + fasciculus lenticularis + dentatothalamic and rubrothalamic fibres all converge here and enter VL/VA.
 - **Ansa lenticularis** emerges from the **ventral** surface of GPi and **loops around** the posterior limb of the internal capsule.

- DeJong: “the point where the thalamic fasciculus converges on VL is of singular strategic importance in the function of the motor system” — this is the anatomical basis of the **VIM target** for tremor surgery.

4. The five parallel loops and the three functional divisions

- Five parallel, largely closed circuits pass through the basal ganglia: **motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal and limbic** (Bradley, p. 1499).
- These are now grouped into **three divisions — sensorimotor, associative and limbic** — subserving motor, cognitive and emotional function respectively (Table 96.1).
- The basic loop in every case is: **cortex → striatum → GPi/SNr → thalamus → cortex**. Projections from cortex→striatum, STN→GPi and thalamus→cortex are **excitatory (glutamate)**; striatal and pallidal outputs are **inhibitory (GABA)**.

Division	Cortical afferents	Striatal nucleus	Termination of BG efferents	Function
Sensorimotor	Motor cortex, primary motor cortex	Putamen	Premotor cortex, supplementary motor area	Movement
Associative	Frontal, parietal, temporal, occipital cortex	Dorsal caudate	Prefrontal cortex	Cognition
Limbic	Hippocampus, amygdala, cingulate, temporal, orbitofrontal cortex	Ventral striatum (nucleus accumbens)	Anterior cingulate cortex, medial orbitofrontal cortex	Emotion, motivation

Table 2 · Divisions of the striatum — Bradley & Daroff 8e, Table 96.1, p. 1500.

5. Direct and indirect pathways — the core of the answer

- **Direct pathway** (D_1 -mediated, *facilitates* movement)
 - Cortex →(**glu, +**)→ putamen (D_1) →(**GABA, -**)→ GPi/SNr →(**GABA, -**)→ VA/VL thalamus →(**glu, +**)→ motor cortex.
 - At rest GPi/SNr **tonically inhibit** the thalamus. Direct-pathway activity inhibits that inhibition — i.e. **disinhibits** the thalamus → **net cortical excitation**.
 - It is part of an excitatory cortico-cortical circuit that **initiates and maintains ongoing movement**.
- **Indirect pathway** (D_2 -mediated, *inhibits* movement)
 - Cortex →(**glu, +**)→ putamen (D_2) →(**GABA, -**)→ GPe →(**GABA, -**)→ STN →(**glu, +**)→ GPi/SNr →(**GABA, -**)→ thalamus.
 - Net effect: GPe is inhibited → STN is **disinhibited** → STN drives GPi harder → more thalamic inhibition → **net cortical inhibition**.
 - It **suppresses extraneous, competing movement** so that the movement selected by the direct pathway can be executed cleanly.
- **Hyperdirect pathway**
 - Direct cortex → STN projection, increasingly emphasised (Bradley, p. 1500; Coude et al., 2018); it gives the fastest, most global “brake”.
- **Dopaminergic modulation from SNc — one sentence that earns the mark**
 - Dopamine **facilitates the direct pathway via D_1** and **inhibits the indirect pathway via D_2** . Both actions increase thalamocortical excitation, i.e. both are pro-kinetic.

• The "brake" metaphor (DeJong)

- GPi/SNr output is a brake on thalamic and brainstem motor pattern generators. **Striatum releases the brake focally** (specific, focused disinhibition to select the wanted movement); **STN applies the brake globally** (to suppress competing movements).

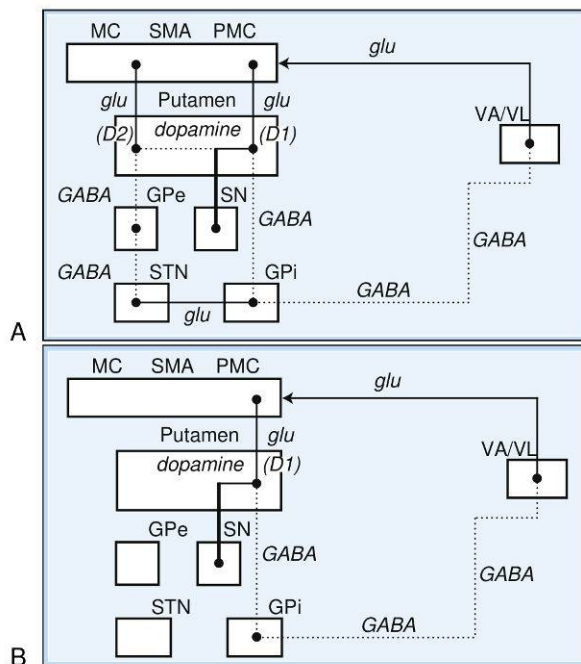
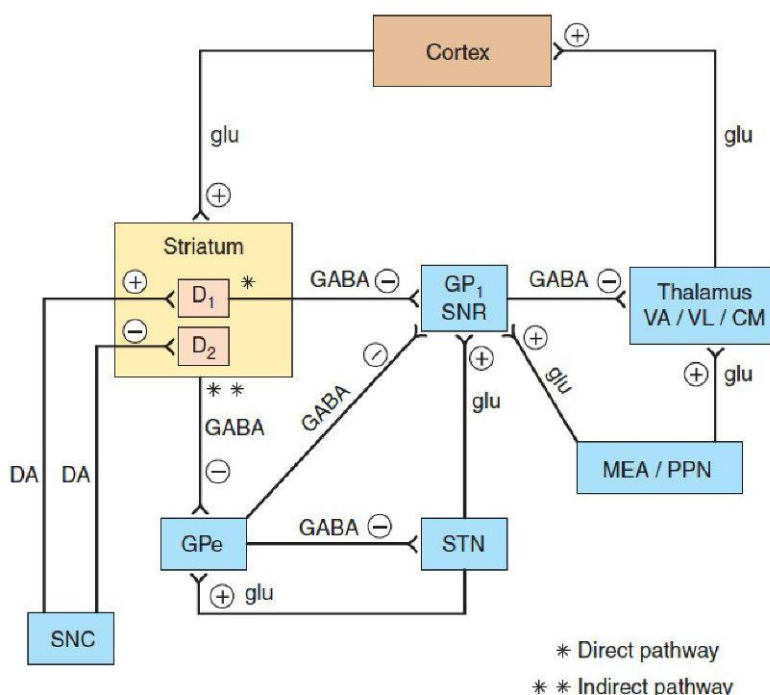


Fig. 96.2 Schematic drawing of internuclear connections of basal ganglia, including (A) direct and indirect pathways and (B) direct pathway. (See Fig. 96.3 for depiction of indirect pathway.) Excitatory pathways in solid lines, inhibitory pathways in dotted lines. D_1 , Dopamine D_1 receptor; D_2 , dopamine D_2 receptor; GABA, γ -aminobutyric acid; glu, glutamate; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; MC, motor cortex; PMC, premotor cortex; SMA, supplementary motor area; SN, substantia nigra; STN, subthalamic nucleus; VA/VL, ventral anterior/ventrolateral thalamic nuclei.

Reproduced from Bradley & Daroff 8e, **Fig. 96.2**, p. 1501 — **A**, direct and indirect pathways; **B**, direct pathway alone. Label when reproducing: MC, SMA, PMC; putamen with D_1 and D_2 ; GPe, GPi, STN, SN, VA/VL. Mark every limb with its transmitter (glu / GABA / dopamine) and use **solid lines for excitatory, dotted for inhibitory**.



Reproduced from DeJong's *The Neurologic Examination 8e*, **Fig. 26.4** — the direct and indirect basal ganglia loops, drawn with explicit + and – signs. Original legend: “the indirect loop includes the GPe and subthalamic nucleus; the direct loop results in excitation of the thalamus and cortex, the indirect loop in inhibition. +, excitatory; –, inhibitory; CM, centromedian thalamic nucleus; D1/D2, dopamine receptors; DA, dopamine; GABA, γ-aminobutyric acid; glu, glutamic acid; GPe/GPi, globus pallidus externa/interna; MEA, midbrain extrapyramidal area; PPN, pedunculopontine nucleus; SNc/SNr, substantia nigra compacta/reticulata; STN, subthalamic nucleus; VA/VL, ventral anterior/ventral lateral thalamic nuclei.” Mark * = direct pathway, ** = indirect pathway.

6. Pathogenesis of movement disorders — applying the model

- **Hypokinetic disorders = increased basal ganglia output** (Bradley p. 1500; DeJong Ch. 26)
 - **Parkinson disease:** death of SNc dopaminergic neurons → **reduced facilitation of the direct pathway** (D_1) and **reduced inhibition of the indirect pathway** (D_2) → STN released from GPe control → **increased firing of STN and GPi** → excessive inhibition of thalamocortical pathways → **bradykinesia** (Fig. 96.3, A). This is the “**GPi rate theory**”.
 - Intraoperative microelectrode recording **confirms** STN and GPi overactivity in PD, and firing rates return toward normal with effective pharmacotherapy.
- **Hyperkinetic disorders = reduced basal ganglia output**
 - **Huntington disease:** early, preferential loss of **enkephalin-containing medium spiny neurons of the indirect pathway** → GPe disinhibited → STN profoundly inhibited → GPi/SNr output falls → thalamus disinhibited → **chorea** (Fig. 96.3, B). With progression **all** medium spiny neurons die, including direct-pathway cells — which is why **parkinsonism and dystonia emerge late**, and why **juvenile HD is akinetic-rigid from the outset**.
 - **Hemiballism:** a lesion of the contralateral STN (classically lacunar infarction) removes STN excitation of GPi → loss of inhibitory drive to the thalamus → violent proximal flinging. Only ~20% of cases have a demonstrable STN lesion on MRI; in others the lesion lies in STN afferents or efferents.
 - Experimentally, chorea can be produced by lesioning STN, by disinhibiting GPe, or by giving dopaminergic agents.
- **Dystonia — where the model breaks down**
 - Overactivity of **both** direct and indirect pathways has been proposed, yet intraoperative recordings in dystonia show **low firing rates with an abnormal pattern** in GPi.
 - Therefore **a simple change in firing rate is insufficient**. Disordered **patterns and synchrony** of pallidal firing, abnormal **sensorimotor integration** and altered control of spinal/brainstem reflexes are invoked.
- **Other named limitations of the rate model (state these to score)**
 - Bradykinesia and chorea **coexist** in HD and in levodopa-treated PD.
 - Thalamic lesions should worsen parkinsonism — **they do not**.
 - Pallidal lesions should worsen chorea — instead **pallidotomy dramatically relieves chorea**.
 - The model does not explain tremor (a hyperkinetic sign in a hypokinetic disease), the effects of DBS, or the efficacy of anticholinergics. Proposed refinements: bursting neuron, synchronisation, prokinetic/antikinetic oscillator and systems oscillator theories.
- **Movement disorders whose generator lies OUTSIDE the basal ganglia** (Bradley, p. 1499)
 - **Essential tremor, restless legs syndrome, stiff person syndrome, hemifacial spasm, spinal myoclonus and painful legs-moving toes** — brainstem, cerebellum, spinal cord or even peripheral nerve.
 - **Guillain-Mollaret triangle** (red nucleus–inferior olive–dentate) → **palatal myoclonus/tremor and myorhythmia. Propriospinal pathways and segmental spinospinal loops** → propriospinal and segmental spinal myoclonus. A **corticolemniscal-thalamocortical** and a **spinobulbar-spinal** circuit subserve other myoclonus.

- **Zona incerta** — GABAergic, an extension of the thalamic reticular nucleus between thalamus and fields of Forel, carrying pallidal output; may synchronise basal ganglia and cerebellar activity and is of interest in ET.
- **Lateral habenula** has an inhibitory influence on SNc; role in movement disorders unknown.

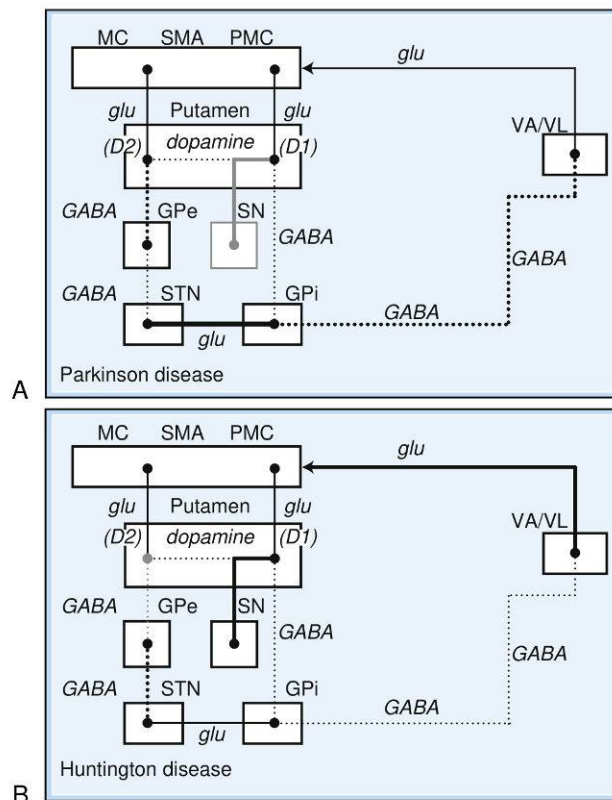


Fig. 96.3 Schematic drawing of functional activities in the direct and indirect pathways in Parkinson disease (PD) and Huntington disease (HD). **A**, In PD, reduced dopaminergic facilitation of direct pathway and inhibition of indirect pathway due to death of dopaminergic neurons causes increased firing and increased inhibition of thalamocortical pathways, producing bradykinesia. **B**, In HD, loss of striatal neurons leads to reduced activity in indirect pathway, causing reduced inhibition of thalamocortical pathways, with production of excessive or involuntary movements. (See Fig. 96.2 for explanations to abbreviations.) D_1 , Dopamine D_1 receptor; D_2 , dopamine D_2 receptor; GABA, γ -aminobutyric acid; glu, glutamate; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; MC, motor cortex; PMC, premotor cortex; SMA, supplementary motor area; SN, substantia nigra; STN, subthalamic nucleus; VA/VL, ventral anterior/ventrolateral thalamic nuclei.

Reproduced from Bradley & Daroff 8e, **Fig. 96.3**, p. 1501 — the single most examinable diagram in this volume. **A**, Parkinson disease; **B**, Huntington disease. Label: thickened lines = overactive pathways, thin/grey = underactive; D_1/D_2 , GPe, GPi, STN, SN, VA/VL, MC/SMA/PMC.

7. Neurotransmitters and receptors of the basal ganglia

- **Glutamate** — all the major excitatory synapses (cortex→striatum, cortex→STN, STN→GPi, thalamocortical). Receptors: ionotropic **NMDA**, **AMPA**, **kainate** (NMDA implicated in excitotoxic injury) and metabotropic.
- **GABA** — main inhibitory transmitter, synthesised by **glutamic acid decarboxylase**. Three receptor classes GABA_A (ligand-gated chloride channel, benzodiazepine sensitive), GABA_B (metabotropic) and GABA_C.
- **Dopamine** — five receptors in two families: **D_1 family (D_1 , D_5)**, adenylate-cyclase dependent, **direct pathway**; **D_2 family (D_2 , D_3 , D_4)**, **indirect pathway**, also cortex, limbic system and pituitary.

- **Acetylcholine** — large aspiny striatal interneurons and the PPN; striatal cholinergic receptors are mainly **muscarinic (M1-M5)**. This is why anticholinergics work in PD and why cholinergic PPN loss is invoked for gait failure.
- **Adenosine A_{2A}** receptors are **co-localised with D₂ receptors** on indirect-pathway medium spiny neurons — the rationale for **istradefylline**.
- Peptide co-transmitters: **substance P and dynorphin in the direct pathway; enkephalin in the indirect pathway**. Also noradrenaline (locus coeruleus), serotonin (dorsal raphe) and the cannabinoid system (**CB1** receptor is abundant in the basal ganglia; ligands anandamide and 2-arachidonoylglycerol).

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Learn one diagram, not three.** Draw Fig. 96.2, A; then thicken/thin the arrows to make Fig. 96.3 (PD) and (HD). Everything else in this answer hangs off that drawing.
- **Dopamine is pro-kinetic twice over** — D₁ excites the direct pathway and D₂ inhibits the indirect pathway; *both* increase thalamocortical drive. Losing it therefore produces a double hit.
- **Direct pathway disease → hypokinesia (PD); indirect pathway disease → hyperkinesia (chorea, ballism).** Say this sentence explicitly — it is the examiner's checkpoint.
- **GPe is the only pallidal segment that projects to the STN;** every other pallidal efferent arises from GPi. This single fact explains hemiballism and early HD chorea.
- Quote the model's failures (dystonia, tremor, thalamic and pallidal lesions, coexistence of bradykinesia with chorea) — a candidate who only recites the rate model looks dated.
- Remember the **extra-basal-ganglia** movement disorders — ET, RLS, hemifacial spasm, palatal and spinal myoclonus, stiff person syndrome. Naming them shows you understand the limits of the circuit.

Q2. Substantia nigra.

SHORT

Movement Disorder §Short Q8

5 marks

Source: DeJong's *The Neurologic Examination*, 8th ed. — Ch. 26 *The Extrapyramidal Level*, §Substantia Nigra; Ch. 2 §Basal Ganglia. Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 96 *Parkinson Disease and Other Movement Disorders*, §Basal Ganglia Anatomy and §Pathology, pp. 1499–1506 (Figs. 96.1–96.3, 96.6).

1. Anatomy

- A **melanin-containing (pigmented) nucleus** of the midbrain, lying in the cerebral peduncle **between the crus cerebri and the tegmentum**, at the level of the superior colliculi; it extends the length of the midbrain **ventral to the red nucleus and dorsal to the cerebral peduncles**.
- The SNc of one side is **continuous across the midline** with that of the other.
- **Two parts**
 - **Pars compacta (SNc)** — deep; large **melanin-containing dopaminergic** neurons (neuromelanin is a by-product of dopamine synthesis). Normally about **500,000** dopaminergic neurons.
 - **Pars reticulata (SNr)** — superficial; large multipolar, **non-pigmented GABAergic** neurons resembling those of the globus pallidus. **SNr is structurally and functionally homologous with GPi**, separated from it only by the internal capsule and crus cerebri.

- Development and maintenance of the midbrain dopaminergic neurons depend on the transcriptional regulators **Nurr1, Lmx1a, Lmx1b, Msx1 and Pitx3**.

2. Connections and function

Tract	Origin → termination	Transmitter	Function
Nigrostriatal	SNc → striatum (caudate + putamen)	Dopamine	Facilitates direct pathway (D ₁), inhibits indirect pathway (D ₂) — i.e. pro-kinetic
Striatonigral (comb bundle)	Striatum → SNr	GABA + substance P / enkephalin	Striatal control of basal ganglia output
Nigrothalamic	SNr → VA and mediodorsal thalamus	GABA	Tonic inhibition of thalamocortical drive (with GPi)
Nigrotectal	SNr → superior colliculus	GABA	Saccadic eye movement control (oculomotor loop)
Nigro-PPN / reticular	SN ↔ PPN and reticular formation	GABA / acetylcholine	Locomotion, muscle tone, akinesia

Table 3 · Connections of the substantia nigra — DeJong's 8e, Ch. 26, Table 26.1 and §Substantia Nigra; Bradley & Daroff 8e, p. 1502, Table 96.2.

3. Clinical correlates — why the SN matters

- **Parkinson disease** — the most striking pathological changes occur in the SNc. The SN **appears pale to the naked eye**; microscopy shows neuronal loss, gliosis and **extracellular pigment**, with **Lewy bodies** (eosinophilic cytoplasmic inclusions with a dense core and pale halo, containing hyperphosphorylated neurofilament protein, lipids, iron, ubiquitin and **α-synuclein**) in surviving neurons.
- **Progressive supranuclear palsy** — the SN is **depigmented, orange and shrunken**; the locus coeruleus is less affected than in PD.
- **MPTP / MPP⁺ toxicity** — severe SN neuronal loss **without** Lewy body formation; active neurodegeneration with extracellular melanin and neuronophagia was still present 10 years after exposure.
- **Manganism** — F-dopa PET shows **normal presynaptic dopaminergic function**, indicating post-synaptic (striatal/pallidal) pathology, not nigral.
- **Wilson disease** — increased T2 signal in the **lateral SNr** with midbrain tegmental hyperintensity gives the "**face of the giant panda**" sign.
- **Neurodegeneration with brain iron accumulation** — brown discoloration of GPi and SNr.
- **Imaging the nigrostriatal terminal: DaTscan** (SPECT dopamine transporter ligand) and F-dopa PET show reduced striatal uptake proportional to ipsilateral SN degeneration; DaTscan separates PD from ET, drug-induced and functional parkinsonism, but **not** from atypical parkinsonism.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **SNc = dopaminergic, an input modulator of the striatum. SNr = GABAergic, an output nucleus, the twin of GPI.** Getting this pair right is most of the answer.
- Lewy bodies are **eosinophilic with a halo in the brainstem** but **lack the halo in cortical neurons** — a favourite one-liner.
- SN pallor is visible to the naked eye at autopsy in PD; in PSP the SN is orange and shrunken.
- The **nigrotectal** projection to the superior colliculus explains why saccadic abnormalities occur in basal ganglia disease.
- Normal presynaptic F-dopa PET in the face of parkinsonism points to **manganism, vascular parkinsonism, drug-induced parkinsonism or a functional disorder**.

Q3. Dopaminergic pathways in the CNS.**SHORT****Anatomy §Short Q19****5 marks**

Source: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 96 *Parkinson Disease and Other Movement Disorders*, §Basal Ganglia Anatomy, §Functional Organization and §Biochemistry, pp. 1499–1502 (Fig. 96.2, Table 96.2). Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 50 *Neuroendocrinology*, Table 50.1, p. 731 and p. 740; Ch. 10 *Depression and Psychosis in Neurological Practice*, pp. 102 and 116; Ch. 101 *Sleep and Its Disorders*, p. 1670. DeJong's *The Neurologic Examination*, 8th ed. — Ch. 7 *Functions of the Cerebral Cortex*, §The Prefrontal Area; Ch. 26 §Substantia Nigra and §Basal Ganglia Physiology.

1. Where dopamine is made

- Dopamine is synthesised from tyrosine; the **rate-limiting enzyme is tyrosine hydroxylase**, for which **iron is an essential cofactor** (Bradley Ch. 101, p. 1710 — the basis of the iron-dopamine hypothesis of RLS).
- The cell bodies lie in the **midbrain dopaminergic system (cell groups A8-A10): substantia nigra pars compacta (A9), ventral tegmental area (A10), retrorubral field (A8) and the ventral periaqueductal grey**; plus the **hypothalamic (tuberal/arcuate) dopaminergic neurons**.
- Neuromelanin, the pigment of the SNc, is a by-product of dopamine synthesis.

2. The pathways

Pathway	Origin → target	Normal function	Clinical correlate
Nigrostriatal	SNc (A9) → caudate and putamen	Facilitates direct pathway via D₁ , inhibits indirect pathway via D₂ ; net increase in thalamocortical drive	Parkinson disease ; drug-induced parkinsonism; the pathway imaged by DaTscan and F-dopa PET
Mesolimbic	Ventral tegmental area (A10) → ventral striatum / nucleus accumbens, amygdala, hippocampus	Motivation, reward, emotional aspects of movement (the limbic loop)	Positive symptoms of psychosis (the "dopamine hypothesis"); impulse-control disorders and dopamine dysregulation syndrome on dopamine agonists; target of addiction
Mesocortical	Midbrain (A10) → prefrontal cortex	Reward, attention, short-term memory, planning and drive (DeJong, Ch. 7)	Executive dysfunction and apathy in PD; negative symptoms of schizophrenia

Pathway	Origin → target	Normal function	Clinical correlate
Hypothalamic → pituitary (the tuberoinfundibular projection)	Hypothalamus → anterior pituitary lactotrophs	Tonic dopaminergic inhibition of prolactin release (Bradley, Ch. 50, p. 740)	Hyperprolactinaemia and galactorrhoea with D ₂ -blocking antipsychotics/antiemetics; postictal prolactin rise after generalised and complex partial seizures
Ascending arousal (vPA G/A8-A10)	Ventral periaqueductal grey and midbrain dopaminergic neurons → widespread	Maintenance of wakefulness , with reciprocal connections to sleep-wake regulatory neurons; tyrosine hydroxylase levels fall before waking and rise with motor activity	Excessive daytime sleepiness and sleep attacks in PD and on dopaminergic drugs; the circadian patterning of RLS

Table 4 · Central dopaminergic pathways — compiled from Bradley & Daroff 8e, Ch. 96 pp. 1499–1502, Ch. 50 Table 50.1 p. 731 and p. 740, Ch. 10 p. 102, Ch. 101 p. 1670, and DeJong's 8e Ch. 7 and Ch. 26.

3. Receptors and pharmacology — the marks are here

- **Five receptors, two families. D₁ family (D1, D5)** — adenylylate-cyclase dependent, **excitatory**, sited in the **direct pathway**, cortex and limbic system. **D₂ family (D2, D3, D4)** — **inhibitory**, sited in the **indirect pathway**, cortex, limbic system and **pituitary**.
- Adenosine **A_{2A}** receptors are co-localised with striatal D₂ receptors on indirect-pathway medium spiny neurons → rationale for **istradefylline**.
- Neurotensin is described as an "**endogenous neuroleptic**" and regulates mesolimbic, mesocortical and nigrostriatal dopamine neurons (Table 50.1, p. 731).
- **Antipsychotics share striatal D₂ blockade** (Ch. 10, p. 116); the propensity to cause drug-induced parkinsonism follows D₂ affinity: **risperidone = ziprasidone > olanzapine > quetiapine > clozapine** (Ch. 96, p. 1517).
- **VMAT2 inhibitors** (tetrabenazine, deutetabenazine, valbenazine) deplete presynaptic dopamine and therefore cause parkinsonism and depression but, unlike receptor blockers, **do not cause tardive dyskinesia**.

GUIDELINE UPDATE — BEYOND THE TEXTBOOK

- **One terminological note, flagged as outside the prescribed texts.** The eponym "**tuberoinfundibular**" for the hypothalamo-pituitary dopaminergic projection does not appear anywhere in Bradley & Daroff 8e, DeJong 8e or Preston & Shapiro 4e — the books describe the pathway by its function ("hypothalamic dopaminergic inhibition of prolactin release") rather than by name. The classical teaching list of **four** pathways (nigrostriatal, mesolimbic, mesocortical, tuberoinfundibular) is standard pharmacology nomenclature and is safe to write in the exam; the first three are named explicitly in Bradley (Table 50.1, p. 731).

4. Applying the pathways at the bedside

- **Nigrostriatal.** Its degeneration produces PD; its pharmacological blockade produces drug-induced parkinsonism, and chronic blockade produces tardive dyskinesia through postulated **denervation supersensitivity of post-synaptic D₂ receptors**. Its integrity is what DaTscan measures — normal in drug-induced, vascular and functional parkinsonism, abnormal in PD and in every atypical parkinsonism.

- **Mesolimbic.** Excess activity is the basis of the dopamine hypothesis of psychosis; excess pharmacological stimulation in PD produces **impulse-control disorders and the dopamine dysregulation syndrome**, and these are agonist-driven, not levodopa-driven. Ask the patient *and* the spouse at every visit.
- **Mesocortical.** Its failure underlies the **executive dysfunction, bradyphrenia and apathy** of PD and the negative symptoms of schizophrenia — neither of which improves with more dopamine at the receptor.
- **Hypothalamo-pituitary.** Blockade raises prolactin; conversely dopamine agonists are used to suppress prolactin in prolactinoma. A **postictal prolactin rise** after generalised or complex partial seizures reflects transient loss of hypothalamic dopaminergic inhibition (Ch. 50, p. 740) — useful in separating epileptic from functional seizures.
- **The therapeutic dilemma in one sentence:** every drug that helps one pathway harms another, which is why the ideal antipsychotic (mesolimbic blockade without nigrostriatal or tuberoinfundibular blockade) does not exist, and why **quetiapine, clozapine and pimavanserin** — the three agents with the least nigrostriatal effect — are the only acceptable choices in a parkinsonian patient with psychosis.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Four pathways, four clinical consequences of blocking them:** nigrostriatal → parkinsonism/tardive dyskinesia; mesolimbic → antipsychotic efficacy; mesocortical → negative symptoms and apathy; tuberoinfundibular → hyperprolactinaemia.
- **D₁ = direct = excitatory; D₂ = indirect = inhibitory.** Both are pro-kinetic because the second is an inhibition of an inhibitory loop.
- **Iron is the cofactor for tyrosine hydroxylase** — the single sentence that links iron deficiency, dopaminergic dysfunction and restless legs syndrome.
- Antipsychotic parkinsonism ranking (risperidone ≥ ziprasidone > olanzapine > quetiapine > clozapine) mirrors D₂ affinity — quote it when asked which antipsychotic to use in a PD patient with psychosis.
- A drug that **depletes** dopamine (VMAT2 inhibitor) causes parkinsonism but never tardive dyskinesia; a drug that **blocks the receptor** causes both.



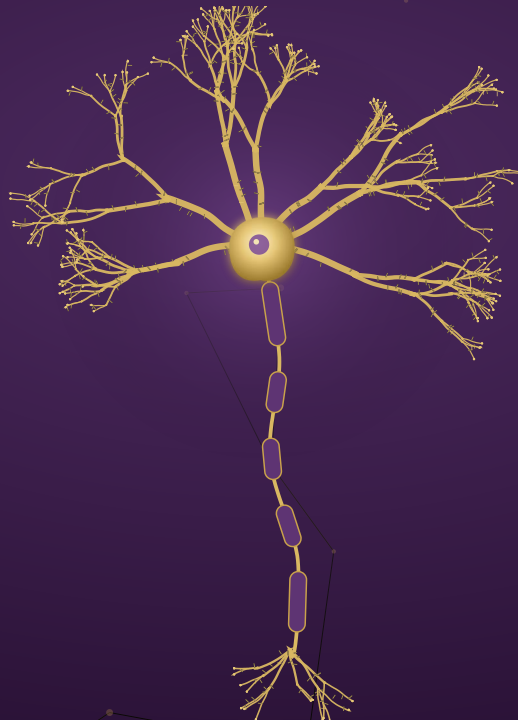
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Part 9

Demyelinating, Autoimmune and Cerebellar Disorders

1 · MULTIPLE SCLEROSIS AND THE INFLAMMATORY DEMYELINATING DISEASES

Q1. Diagnostic criteria of multiple sclerosis and the role of MRI in its diagnosis.

LONG

Demyelinating §Long Q2

10 marks

Also asked as: Demyelinating §Short Q7 — "Revised McDonald criteria in MS"

Source: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 80 *Multiple Sclerosis and Other Inflammatory Demyelinating Diseases of the Central Nervous System*, §Diagnosis (§Diagnostic Criteria, §Diagnostic Studies, §Differential Diagnosis) and §Clinical Course and Prognosis, pp. 1233–1240 (Table 80.1, p. 1234; Tables 80.2 and 80.3, p. 1237; Box 80.2, p. 1238; Figs. 80.8–80.12, pp. 1234–1237). Supplementary: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 40 *Structural Imaging Using Magnetic Resonance Imaging and Computed Tomography*, §Multiple Sclerosis and Other White Matter Diseases, pp. 524–526.

1. The principle behind every set of MS criteria

- MS is diagnosed **clinically with MRI support** — biopsy proof is rare and undesirable, so accurate criteria are of crucial importance.
- The **common thread of all MS criteria** is the demonstration of lesions:
 - **Dissemination in space (DIS)** — more than one area of the CNS involved.
 - **Dissemination in time (DIT)** — more than one episode, separated in time.
- Diagnosis **also requires elimination of more likely alternative diagnoses** — this is written into the criteria themselves, not an afterthought.
- Historical evolution:
 - **Poser criteria (1983–2001)** — required **two clinical attacks with objective examination evidence** for clinically definite MS (CDMS); CSF, evoked potentials and imaging were only supportive.
 - **McDonald 2001** — the modern era: activity on follow-up MRI was allowed to **substitute for a second clinical attack**, so DIS/DIT could be met radiologically. Sensitivity and specificity were preserved and diagnosis could be made **sooner**.
 - **Revised 2010, then 2017 (Thompson et al.)** — the currently used version.

2. The 2017 revised McDonald criteria — what actually changed

- **At least one characteristic demyelinating episode is still required** to diagnose relapsing-remitting MS (RRMS).
- **DIS** is satisfied if MRI shows **≥ 1 lesion in two of four typical locations**:
 - **Periventricular**
 - **Cortical or juxtacortical**
 - **Infratentorial**
 - **Spinal cord**
 - **Change 1: cortical lesions were added** as a typical location, interchangeable with juxtacortical.
- **DIT** is satisfied by either:
 - **Simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time** (a single scan can prove DIT), **or**

– A **new T2 or new gadolinium-enhancing lesion on a follow-up scan**.

- **Change 2 — symptomatic lesions now count.** The 2010 criteria forbade using symptomatic brainstem or spinal cord lesions for DIS/DIT; the 2017 revision removed that restriction.
- **Change 3 — CSF oligoclonal bands (OCBs) can substitute for DIT.** In a patient with one clinical event who fulfils DIS, **CSF-specific OCBs** now satisfy DIT, because positive bands are an **independent risk factor for further clinical activity**.
- **Change 4 —** the panel directed that the clinician should **ascertain the disease phenotype at diagnosis and periodically reassess it**.

Clinical attacks	Objective lesions	Additional data needed for diagnosis
2 or more	Objective clinical evidence of ≥ 2 lesions, or of 1 lesion with reasonable historical evidence of a prior attack	None — clinical evidence alone suffices; additional evidence is desirable but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	DIS ; OR await a further clinical attack implicating a different CNS site
1	Objective clinical evidence of ≥ 2 lesions	DIT ; OR await a second clinical attack; OR demonstration of CSF-specific oligoclonal bands
1	Objective clinical evidence of 1 lesion (CIS)	DIS (or await an attack at a different site) AND DIT (or CSF-specific oligoclonal bands, or await a second attack)
0 — progression from onset (PPMS)	—	One year of disease progression (retrospective or prospective) AND at least two of: DIS in brain (≥ 1 T2 lesion periventricular, cortical/juxtacortical or infratentorial); DIS in cord (≥ 2 T2 lesions); positive CSF

Table 1 · The 2017 revised McDonald criteria — reproduced from Bradley & Daroff 8e, **Table 80.1**, p. 1234. Diagnosis in every row also requires **elimination of more likely diagnoses**.

3. Role of MRI — why it is the preferred modality

- MRI is the preferred modality **both for diagnosis and for longitudinal follow-up**. Virtually **all** MS patients have T2/FLAIR abnormalities, and **new lesions occur 9-10 times more often than new clinical attacks** in RRMS — MRI therefore detects the subclinical disease that the history cannot.
- **Characteristic lesion morphology and site**
 - Focal, discrete, **ovoid**, oriented **perpendicular to the plane of the lateral ventricles** = **Dawson fingers**, representing perivenular inflammation.
 - Deep white matter and **centrum semiovale**; cortical and deep grey structures (deep grey lesions are commonest in the **thalami**).
 - **Juxtacortical** lesions involving the U-fibres (crescentic; favour MS).
 - **Corpus callosum** — punctate hyperintensities along the **septocallosal margin** (undersurface); relatively specific for MS.
 - **Posterior fossa** — cerebellum, middle cerebellar peduncles, areas adjacent to the fourth ventricle; also posterior optic radiations.
 - Lesions adjacent to the **temporal horns** favour MS.
- **Ageing the lesion with MRI**

- **Acute (< 12 weeks)** — gadolinium enhancement on T1 (BBB disruption); larger, less well-defined margins; may be DWI-bright; may be T1-dark acutely from oedema.
 - Enhancement patterns: **incomplete (open) ring** — the pattern that is **specific for demyelination**; less commonly a complete ring; or patchy/homogeneous. **Ring enhancement indicates significant tissue destruction.**
 - **Subacute** — enhancement gone, DWI may still be bright.
 - **Chronic** — T2/FLAIR hyperintense, smaller, sharp margins; persistent profound T1 hypointensity = **"black hole"** = irreversible axonal loss and permanent demyelination.
- **Spinal cord imaging**
 - **Over 90%** of MS patients have cord lesions at some point; **30%** of patients presenting with a non-myelitic CIS already have asymptomatic cord disease.
 - MS cord lesions typically involve **fewer than two contiguous vertebral segments** and are **asymmetric** (contrast with the longitudinally extensive lesion of NMOSD).
 - T1 hypointensity is uncommon in the cord; **cord atrophy correlates strongly with disability**, and cord lesions produce symptoms more often than brain lesions.
 - **Field strength and atrophy**
 - **3 T and 7 T** greatly improve detection of T2 and enhancing lesions and of cortical lesions; **more patients fulfil the criteria** at higher field strength.
 - Brain atrophy rate in MS is **0.6%–1.35% per year**; **brain parenchymal fraction** is the standard whole-brain measure. **Grey matter atrophies more than white matter**, deep grey nuclei most of all. Atrophy measurement remains suboptimal in clinical practice (confounded by ageing, osmotic agents, anti-inflammatory drugs).

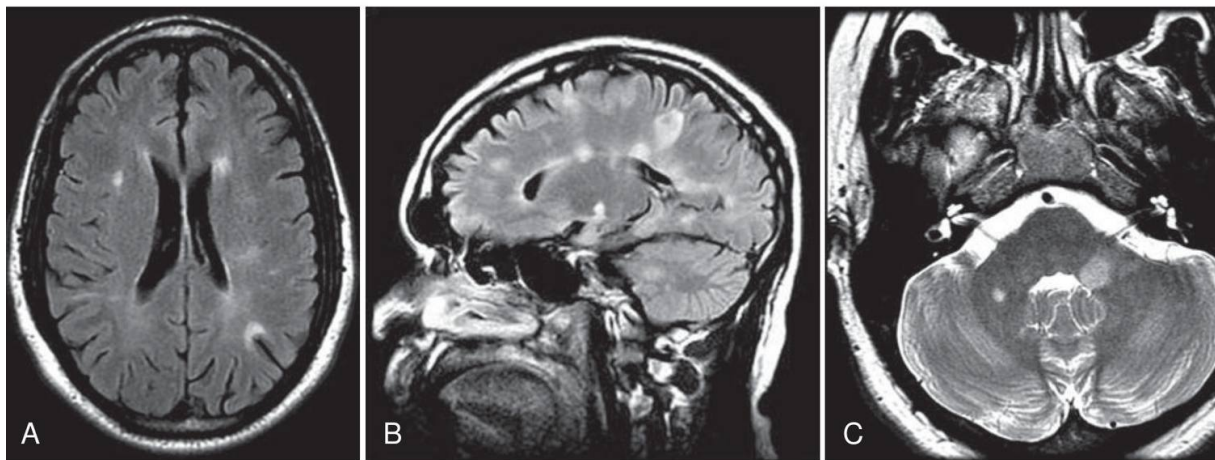


Fig. 80.8 Typical Magnetic Resonance Imaging Appearance of Multiple Sclerosis Lesions in Brain. **A**, Axial view with presence of both periventricular (PV) and juxtacortical lesions. **B**, Sagittal view with classic Dawson's finger appearance of PV lesions. Also present are juxtacortical and posterior fossa lesions. **C**, Axial view of posterior fossa lesions. T2 images are often best for viewing infratentorial lesions.

*Reproduced from Bradley & Daroff 8e, **Fig. 80.8**, p. 1234 — typical MRI appearance of MS. **A** axial: periventricular and juxtacortical lesions. **B** sagittal: classic **Dawson fingers**, plus juxtacortical and posterior fossa lesions. **C** axial posterior fossa lesions (T2 is best for infratentorial disease). Label when reproducing: periventricular lesion perpendicular to ventricle, juxtacortical U-fibre lesion, infratentorial lesion, lateral ventricle, fourth ventricle.*

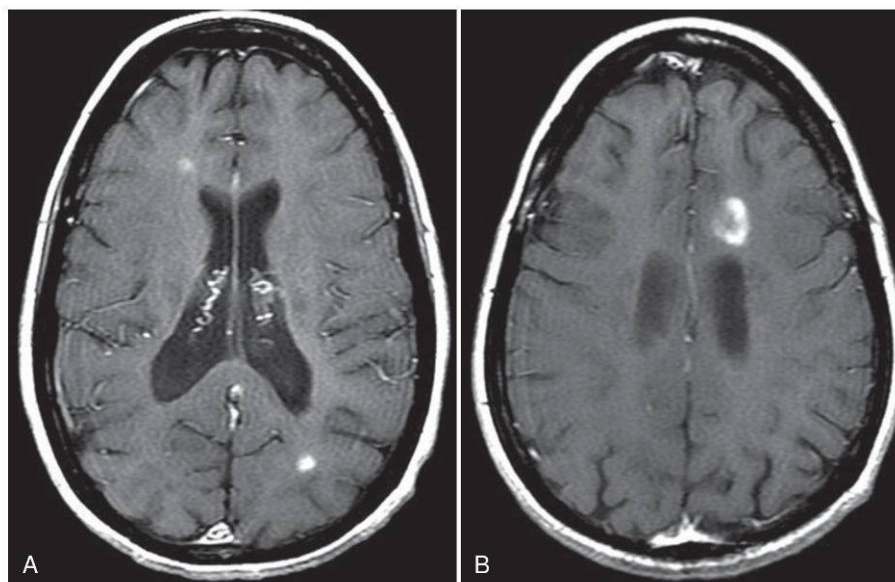


Fig. 80.9 Common Enhancement Patterns in the Brain. A, Homogeneous uptake of contrast. B, Open-ring pattern, specific for demyelinating lesions.

Reproduced from Bradley & Daroff 8e, **Fig. 80.9**, p. 1235 — common enhancement patterns. **A** homogeneous uptake of contrast. **B** the **open-ring** pattern, **specific for a demyelinating lesion** and classically open towards the grey matter. Label when reproducing: incomplete ring open toward cortex, enhancing rim, non-enhancing core.

4. Supporting laboratory studies (and their limits)

- **CSF** — never makes or excludes the diagnosis alone, but is important in atypical syndromes, atypical/non-diagnostic MRI and progressive courses without relapses.
 - Clear, colourless, **normal opening pressure**; cell count normal, mildly raised in **15%-20%**; predominant cell is the **T lymphocyte**.
 - **Pleocytosis > 50 WBC** should raise suspicion of another aetiology.
 - **OCBs are the most important diagnostic test** — excess antibody from one or more plasma-cell clones; the banding pattern is stable through the illness; **10%-20% of confirmed CDMS patients have no OCBs** at a given time.
 - Raised **IgG index** (or IgG as a fraction of protein/albumin) in **> 90%**.
 - **Myelin basic protein** is a marker of tissue damage but its specificity is unknown — **not recommended for diagnosis**.
- **Evoked potentials**
 - Value = detecting a **clinically silent second lesion**, supporting multifocality.
 - Only **VEPs** were judged useful for determining increased risk of MS. **P100 prolongation** in **> 90%** of patients with a history of optic neuritis, **even after complete visual recovery**.
 - EPs are **not part of the McDonald criteria**, and MRI has supplanted them — they are not routine.
- **Optical coherence tomography** quantifies retinal nerve fibre layer thinning after optic neuritis (the RNFL is unmyelinated) and correlates with optic nerve atrophy, but is **not used in diagnosis at present**.

Test	Sensitivity in clinically definite MS
MRI	90%-97%
CSF oligoclonal bands	85%-95%
Visual evoked response	80%-85%

Test	Sensitivity in clinically definite MS
Somatosensory evoked potential	65%–80%
Brainstem auditory evoked response	50%–65%
CSF IgG index	70%–90% (normal controls 3%)
CSF IgG/total protein	67%
CSF albumin	23% (normal controls 3%)

Table 2 · Relative yield of investigations — Bradley & Daroff 8e, **Tables 80.2 and 80.3**, p. 1237. Oligoclonal bands occur in ~7% of patients with other neurological disease.

5. Clinical phenotype must be stated with the diagnosis (2013 classification)

- **RRMS** — clearly defined relapses with full or partial recovery; **no progression between relapses**. 80%–90% of MS begins this way.
- **SPMS** — initial relapsing course followed by progression, with or without occasional relapses, minor remissions and plateaus.
- **PPMS** — progression from onset, with occasional plateaus and temporary minor improvements.
- Each is qualified over a defined time frame by:
 - **Activity** = a clinical relapse **or** a new/unequivocally enlarging T2 lesion **or** a gadolinium-enhancing lesion.
 - **Progression** (for progressive forms) = measured by clinical evaluation at least annually.
 - So "progressive relapsing MS" no longer exists — it is **progressive disease with activity**.
- **Relapse definition:** acute/subacute clinical dysfunction peaking over days to weeks, followed by remission; **minimum duration arbitrarily 24 hours**. Average **0.4–0.6 relapses/year** in the relapsing phase.
- **Pseudo-relapse** = worsening of pre-existing deficit with fever, infection, exercise or metabolic upset — must be excluded before giving steroids.
- Two entities short of MS:
 - **Radiologically isolated syndrome (RIS)** — MRI anomalies highly suggestive of MS in an asymptomatic patient (usually scanned for headache or trauma). Risk of a clinical event **34% within 5 years**; higher with enhancing and spinal cord lesions. **RIS cannot be diagnosed as MS** under the McDonald criteria.
 - **Clinically isolated syndrome (CIS)** — a first clinical demyelinating event with typical white-matter lesions that do **not** yet meet DIS and DIT. With abnormal MRI, **70%–80%** convert to CDMS over 10–14 years, versus only **20%** with a normal cerebral MRI.

6. Differential diagnosis and the red flags (Box 80.2)

- With **two or more clinically distinct episodes with at least partial resolution in a patient of typical age**, there is little differential and testing beyond MRI and basic labs rarely yields an alternative.
- The differential broadens with **atypical, monophasic or progressive** presentations:
 - **Inflammatory** — granulomatous angiitis, SLE, Sjögren disease, Behçet disease, polyarteritis nodosa, paraneoplastic encephalomyelopathies, ADEM/post-infectious encephalomyelitis, **NMOSD, MOG antibody-associated disease**.
 - **Infectious** — neuroborreliosis, HTLV-1, HIV, PML, neurosyphilis.

- **Granulomatous** — sarcoidosis, granulomatosis with polyangiitis, lymphomatoid granulomatosis.
- **Diseases of myelin** — metachromatic leukodystrophy (juvenile/adult), adrenomyeloleukodystrophy.
- **Miscellaneous** — spinocerebellar disorders, Arnold–Chiari malformation, vitamin B₁₂ deficiency, isolated optic neuritis, cerebellitis, brainstem encephalitis, CADASIL, compressive cord lesions, AVM, cavernoma.
- **Red flags that should make you reconsider MS** (Miller et al.):
 - **Family history** of neurological disease.
 - A **well-demarcated spinal level with no disease above the foramen magnum**.
 - **Prominent persisting back pain**.
 - Symptoms and signs attributable to a **single anatomical site**.
 - Onset **> 60 years or < 15 years**.
 - **Progressive disease** from the outset.
- **Misdiagnosis remains a real problem** — a relatively high proportion of patients referred to MS centres with a diagnosis of MS are given an alternative diagnosis. **A common error is to equate multiple T2 hyperintensities with MS**; a few white-matter lesions are common in the elderly and in migraineurs and do not indicate MS.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **One-line answer:** MS = dissemination in space + dissemination in time + exclusion of a better explanation; the 2017 McDonald criteria let MRI (and now CSF OCBs) supply both.
- The four DIS locations — **periventricular, cortical/juxtacortical, infratentorial, spinal cord** — **≥ 1 lesion in two of four**. Memorise them as a block.
- **Enhancing + non-enhancing lesions on the same scan = DIT on day one**. This single rule allows MS to be diagnosed from a first attack and a first MRI.
- **OCBs substitute for DIT** in a CIS patient who already fulfils DIS — the headline change of 2017, and the reason LP is back in favour.
- **Open-ring enhancement** is the most specific enhancement pattern for demyelination; a persistent **T1 black hole** means irreversible axonal loss.
- MS cord lesions are **short (< 2 segments) and asymmetric**; a longitudinally extensive lesion (≥ 3 segments) should send you to **AQP4 and MOG antibodies**, not to a diagnosis of MS.
- Red flags to quote: family history, sharp cord level with a clean brain, persistent back pain, one anatomical site, age < 15 or > 60, progression from onset.

Q2. Critically evaluate and discuss the management of multiple sclerosis.

LONG

Demyelinating §Short Q8

10 marks

Also asked as: Demyelinating §Intermediate Q1 — "How will you manage the young female presenting with relapsing remitting MS?" · Paper IV, March 2025, Q8 — "Role of Ocrelizumab in the management of Multiple Sclerosis: mechanism, dose and monitoring"

Source: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 80 *Multiple Sclerosis and Other Inflammatory Demyelinating Diseases of the Central Nervous System*, §Treatment and Management (§Treatment of Acute Attacks, §Treatment Strategies and Goals of Therapy, §Disease-Modifying Therapy, §Treatment of Progressive Disease) and §Clinical Symptoms and Symptom Management, pp. 1242–1250; §Pregnancy in Multiple Sclerosis, p. 1241 (Table 80.4, p. 1250).

1. The four fundamental goals of MS treatment

- **Treat acute relapses** — to shorten their duration and limit residual deficit.
- **Disease modification** — to reduce relapse frequency and prevent accrual of disability.
- **Relief or modification of symptoms.**
- **Support the patient and family** — alleviate social and economic effects and advocate for the disabled.

2. Treatment of the acute relapse

- **High-dose corticosteroids are the most effective treatment for an acute relapse.** They give a **faster rate of recovery**; the **final** degree of recovery is thought to be independent of steroid.
- **Indications:** functionally disabling symptoms with objective neurological impairment, or symptoms causing pain. **Mild sensory attacks may not need treatment.**
- **Regimen:** IV methylprednisolone **1000 mg daily for 3-5 days**, with or without a short oral prednisone taper.
- **The Optic Neuritis Treatment Trial (1992) — the evidence that fixed the regimen**
 - Patients given **oral prednisone alone** were **more likely to suffer recurrent optic neuritis** than those given IV methylprednisolone followed by oral prednisone.
 - Definite MS at 2 years: **7.5%** (IV methylprednisolone) vs **14.7%** (oral prednisone) vs **16.7%** (placebo).
 - Conclusion: use **high-dose IV** methylprednisolone; **do not use low-dose oral** steroid regimens for this purpose.
- **High-dose ORAL methylprednisolone (1000 mg daily × 3 days) is non-inferior to the equivalent IV dose** for disability improvement at 1 month (randomised double-blind study, 199 patients, Le Page 2015); adverse events were similar except **more insomnia** with oral. This makes high-dose oral steroid a legitimate option.
- **Steroid-refractory relapse**
 - **Plasma exchange** — AAN evidence-based guidelines rate it "**probably effective**" for corticosteroid-resistant relapses of relapsing forms of MS. Requires inpatient admission; adverse events include **heparin-associated thrombocytopenia, anaemia and hypotension**.
 - **ACTH** — placebo-controlled studies show it hastens recovery; a commercial subcutaneous preparation exists. Benefit may come from effects on **both corticosteroid and melanocortin pathways**.
- **Mechanism of high-dose corticosteroid in MS** — worth one line of marks:
 - Reduction of **CD4+ cells**; decreased lymphocyte release of **TNF and IFN-γ**; decreased **MHC class II expression**; decreased **intrathecal IgG synthesis**; and **stabilisation of the blood-brain barrier**, reducing cell entry into brain.
- **Adverse effects to warn about:** insomnia, anxiety, mania; GI upset; fluid retention; hyperglycaemia; and with repeated courses, infection, fracture and **avascular necrosis of the femoral head**.

3. Disease-modifying therapy — strategy first

- **As a general rule, all patients with active relapsing forms of MS should receive an immunomodulatory agent indefinitely.**
- Trials of starting DMT at the time of **CIS** show, with remarkable consistency, benefit in **preventing conversion** to clinically definite/McDonald MS, in preventing subsequent relapses and new MRI lesions, and in preventing accumulated disability — i.e. **treat early**.

• Defining the treatment target

- **NEDA** (no evidence of disease activity) = no new/enlarging MRI lesions + no clinical relapse + no examination evidence of progression over time.
- **NEDA-4** adds **no brain atrophy beyond the normal physiological rate**.
- **Critical appraisal:** NEDA is a worthy goal but **may not be achievable long term for most patients**, and it has **not been definitively established** that patients with minimal evidence of disease activity (MEDA) do worse than NEDA patients.

• When to switch DMT

- Most experts agree a patient should be switched after a **clinical relapse occurring once the drug should be fully effective** — relapse on DMT portends a poorer long-term outcome.
- Switching on **MRI activity alone is more debatable**. Compare a baseline scan with one at **6-12 months** after starting; **≥ 2 active lesions** confers a risk of suboptimal clinical response and should prompt consideration of a change.
- **There is no general agreement on the definition of treatment failure**, though tolerance for breakthrough activity is now lower than in the past.

- **Honest caveats to state in a "critically evaluate" answer:** existing drugs are **only partially effective** at preventing relapses and have **limited impact on accrual of disability**; most pivotal trials ran only **2-3 years**; long-term placebo-controlled trials are no longer ethical; trial populations differ from clinic populations; and **responders cannot be identified prospectively**. **Modifying progressive MS remains a major unmet need.**

Agent · route	Mechanism	Key pivotal evidence	Main risks / monitoring
IFN-β-1b 250 µg SC alt. days; IFN-β-1a 30 µg IM weekly or 44 µg SC 3x/week	Antiproliferative, cytokine shift, effects at the BBB, alteration of T-cell subsets	IFN-β-1b: relapses ↓ 34% at 2 yr; T2 volume +3.6% vs +30.2% placebo over 5 yr. IM IFN-β-1a: relapses ↓ 29% , disability progression ↓ 37% . SC 44 µg: relapses ↓ 33%	Influenza-like symptoms (settle over weeks-months; NSAIDs), injection-site reactions, raised transaminases, leukopenia, anaemia — bloods every 3-6 months; depression; neutralising antibodies may reduce efficacy
Glatiramer acetate 20 mg SC daily or 40 mg SC 3x/week	Synthetic polypeptide; interferes with antigen presentation, induces regulatory (T _H 2) cells that traffic to CNS and cause bystander suppression	Relapses ↓ 29% over 2 yr; at 140 weeks disability worsened by ≥ 1.5 EDSS steps in 21.6% vs 41% placebo. GALA (40 mg TIW): ARR ↓ 34% , new T2 ↓ 35%, Gd+ ↓ 45%	Injection-site reactions, lipoatrophy ; transient post-injection systemic reaction (chest pain, flushing, dyspnoea, palpitations, anxiety). No laboratory monitoring needed

Agent · route	Mechanism	Key pivotal evidence	Main risks / monitoring
Natalizuma b IV monthly	Monoclonal antibody to α4-integrin — blocks lymphocyte trafficking from blood into CNS	AFFIRM: relapses ↓ 68% , disability progression ↓ 42% over 2 yr	PML (> 800 cases by mid-2019). Risk stratified by anti-JCV antibody status, prior immunosuppressant use, treatment duration . JCV-negative risk < 1:10 000 (seroconvert 2%–3%/yr — retest every 6 months); JCV-positive ~ 1:200 at 2 yr, 1:150 at 4 yr . Mandatory TOUCH monthly monitoring programme
Alemtuzum ab IV 12 mg/day × 5 days, then × 3 days one year later	Humanised monoclonal antibody to CD52 ; profound sustained lymphocyte depletion, B cells repopulate first then T cells, with relative sparing of regulatory T cells — an immune "reset"; durable effect, dosed once yearly	CARE-MS I (naïve): relapses ↓ 55% vs IFN-β-1a, but no difference in 6-month confirmed disability. CARE-MS II (breakthrough on DMT): relapses ↓ 49% and disability progression ↓ 42%	Infections; autoimmune thyroid disease in 16%–18%; ITP in 0.8%–1% . These are anticipated, detected by scheduled monitoring and managed
Ocrelizuma b IV — 300 mg, repeated at 2 weeks, then 600 mg every 24 weeks	Humanised monoclonal antibody to CD20 (pre-B, memory B and mature B cells) → profound sustained B-cell depletion; plasma cells are spared, so humoral immunity is preserved . Almost identical to rituximab but humanised	OPERA I/II (> 1650 RRMS, 96 weeks, vs SC IFN-β-1a 44 µg): ARR 0.16 vs 0.29 (47% reduction, P < .001) ; new T1-enhancing lesions per MRI 0.02 vs 0.29 (94%–95% reduction). ORATORIO (PPMS, n = 732, 2:1): 30% less 24-week sustained disability progression (P = .04) and less brain atrophy — the first and only DMT approved for PPMS	Infusion reactions 34.3% (rash, itching, throat irritation; none fatal). Overall infections 56.9% vs 54.3% (sinusitis, bronchitis, UTI); herpes infections 5.9% vs 3.4% . PML not reported on ocrelizumab except a few "carry-over" cases after natalizumab/fingolimod — so JCV status does not restrict its use

Agent · route	Mechanism	Key pivotal evidence	Main risks / monitoring
Fingolimod 0.5 mg oral daily	Sphingosine-1-phosphate analogue — sequesters circulating lymphocytes in secondary lymphoid organs ; reduces CD3+, CD4+, CD8+, naïve and memory T cells and CD19+ cells without affecting induction, proliferation or memory function	FREEDOMS: ARR ↓ 60% , less disability progression and MRI activity; no added benefit at 1.25 mg. TRANSFORMS: superior to IM IFN-β	Bradycardia (first-dose ECG monitoring), macular oedema (ophthalmological screening), herpesvirus infection (pre-screen VZV immunity), basal cell carcinoma, abnormal PFTs. Contraindicated with recent MI, unstable angina, stroke/TIA, decompensated heart failure, Mobitz II or third-degree AV block, QTc ≥ 500 ms, or class Ia/III antiarrhythmics
Siponimod oral	S1P ₁ and S1P ₅ selective; less S1P₃ activity, so less first-dose bradycardia than fingolimod	EXPAND (n = 1600, SPMS): 6-month sustained disability progression ↓ 24% , ARR and new lesion formation reduced. Much of the benefit was unrelated to baseline inflammatory activity — implying a neuroprotective effect	S1P-class monitoring as for fingolimod, with less first-dose cardiac concern
Teriflunomide 7 or 14 mg oral daily	Reversibly inhibits dihydro-orotate dehydrogenase , the rate-limiting step of <i>de novo</i> pyrimidine synthesis — selectively targets blasting rather than quiescent lymphocytes	TEMPO: 1088 patients, 108 weeks, placebo-controlled	Hepatotoxicity monitoring; teratogenicity — a critical consideration in women of childbearing age
Dimethyl fumarate oral BID or TID	Immunomodulatory / anti-oxidant (Nrf2 pathway)	DEFINE: disability progression ↓ 38% (BID) and 34% (TID). CONFIRM: ARR ↓ 44% (BID) and 51% (TID) vs placebo (glatiramer 29% in the same trial)	Flushing and GI effects (nausea, abdominal pain, diarrhoea) — often transient; education and close monitoring in the first weeks. Lymphopenia — FBC before treatment and repeated

Agent · route	Mechanism	Key pivotal evidence	Main risks / monitoring
Cladribine oral, 4-5 days in month 1 and again 4 weeks later; cycle repeated in year 2; no redosing for ≥ 2 further years	Purine nucleoside analogue — interferes with DNA synthesis in B and T cells , with less impact on innate immunity	CLARITY (n = 1330): ARR 0.14-0.15 vs 0.33 (P < .001). ORACLE (CIS): risk of a second relapse ↓ 67% . CLARITY Extension: sustained effect to 4 years	Lymphopenia (commonest; severe sustained lymphopenia very rare); malignancy 1.4% in the study; infections increased but usually mild
Mitoxantrone IV	Chemotherapeutic — generalised immunosuppression	European trial: reduced disability progression and relapse rate in worsening RRMS, PPMS and SPMS over 2 years; benefit still evident at 3 years	Dose-related cardiotoxicity — lifetime limit 140 mg/m² ; nausea, alopecia, neutropenia; secondary leukaemia . Use has fallen sharply

Table 3 · Disease-modifying therapies in MS — compiled from Bradley & Daroff 8e, Ch. 80, §Disease-Modifying Therapy and §Treatment of Progressive Disease, pp. 1244-1248.

4. Critical appraisal of the comparative evidence

- **Interferon vs glatiramer acetate: REGARD** (≈ 800 patients) found no difference in time to first relapse or annualised relapse rate; **BEYOND** found no significant difference in relapse risk between IFN-β-1b 500 µg, 250 µg and glatiramer; **BECOME** (triple-dose gadolinium, 3 T MRI endpoints) found no MRI or clinical difference. **Conclusion: no clear evidence of superior efficacy between GA and high-dose IFN — the two are generally considered equivalent.**
- Higher IFN dose is not automatically better: **BEYOND** showed 500 µg IFN-β-1b was no better than 250 µg; fingolimod 1.25 mg was no better than 0.5 mg.
- Head-to-head trials that **did** show superiority: alemtuzumab > IFN-β-1a (CARE-MS I/II); ocrelizumab > IFN-β-1a (OPERA I/II); fingolimod > IM IFN-β (TRANSFORMS).
- **Progressive MS:** most historical trials used chemotherapeutic agents with generalised immunosuppression, systemic toxicity, and limits on cumulative dosing. The two IFN-β-1b SPMS trials **contradicted each other** — the European study showed a 9-12 month delay in disability progression, the North American study showed **no effect**, probably because of differences in baseline disease activity despite near-identical entry criteria. This illustrates the hazard of comparing across trials.
- Practical synthesis: **younger progressive patients with ongoing inflammatory activity are likely to benefit more** than those with a purely progressive phenotype. Treatments that prevent neurodegeneration or repair injury do not yet exist.

5. The examination case — a young woman with relapsing-remitting MS

- **Step 1 — confirm the diagnosis and the phenotype.**
 - Apply the 2017 McDonald criteria; document DIS and DIT; state **RRMS, active or not active** over a defined period.
 - Exclude the mimics that matter most in a young woman: **NMOSD (AQP4-IgG), MOGAD, SLE, Sjögren disease, neurosarcoidosis, B₁₂ deficiency**. Interferons and natalizumab are **suspected to worsen NMOSD** — getting this right first is critical.

- Baseline: brain and whole-spine MRI with gadolinium, EDSS, and a cognitive screen (**SDMT**).
- **Step 2 — treat the current relapse.** IV (or high-dose oral) methylprednisolone 1000 mg daily × 3–5 days; plasma exchange if steroid-refractory and disabling. Exclude pseudo-relapse (UTI is common in MS and may be painless).
- **Step 3 — start disease-modifying therapy, early and indefinitely.**
 - Discuss efficacy against risk and monitoring burden; the choice is a shared decision.
 - **Higher-efficacy options** (ocrelizumab, natalizumab, alemtuzumab, fingolimod, cladribine) for highly active disease; injectables (IFN- β , glatiramer) where safety and pregnancy planning dominate.
 - **Check JCV antibody** before natalizumab; **VZV immunity, ECG and ophthalmology** before fingolimod; FBC and LFT before dimethyl fumarate/teriflunomide/cladribine.
 - Rebaseline MRI and repeat at **6–12 months**; ≥ 2 new active lesions should prompt reconsideration of the DMT.
- **Step 4 — counsel specifically on pregnancy and fertility.**
 - The **PRIMS** study (254 women, 269 pregnancies): relapse rate fell from **0.7/year pre-pregnancy to 0.2/year in the third trimester**, then rose to **1.2/year in the first 3 months postpartum**. **72% of women had no relapse at all** during the study period.
 - Predictors of postpartum relapse: high relapse rate **in the year before** pregnancy, relapses **during** pregnancy, and higher EDSS at the start of pregnancy.
 - **Epidural anaesthesia and breastfeeding do not predict relapse or progression**; more recent studies suggest a **protective effect of exclusive breastfeeding**.
 - **No contraindication to vaginal delivery or caesarean section.**
 - Overall **no compelling evidence of an adverse effect of pregnancy on MS progression**; women who gave birth after MS onset reached EDSS 6 **later** (median 22–23 vs 13–15 years). Weigh this against the **risk of prolonged DMT discontinuation**.
 - MS does not affect fertility, but **assisted reproduction using a GnRH agonist can increase relapse risk**, especially after an unsuccessful cycle.
 - Obstetric data: **~30% higher caesarean rate** and **70% higher rate of intrauterine growth restriction** than healthy women, with no long-term adverse paediatric outcomes.
- **Step 5 — general and exogenous factors.**
 - Relapses are more frequent after **viral infections; trauma, lumbar puncture, myelography, anaesthesia and surgery are not implicated**.
 - **Non-live vaccines (influenza, hepatitis) are safe** and there are no convincing data to justify withholding them; use **caution with live attenuated vaccines** (e.g. yellow fever) — relapse risk may be increased.
 - Stress may worsen existing symptoms without inciting a new inflammatory event.

6. Symptomatic management — where most of the daily benefit lies

Symptom	Frequency / key facts	Treatment
Gait and mobility	Major determinant of quality of life; falls are the key risk	Physiotherapy, occupational therapy, bracing, assistive devices, energy conservation. Dalfampridine (sustained-release fampridine) — a potassium channel blocker that restores conduction in demyelinated axons; ~35% are timed-walk responders vs 8% on placebo . Unique in having an indication for improving walking , and its effect is rapid, reversible and detectable in the individual. Contraindicated if there is a history of seizure .

Symptom	Frequency / key facts	Treatment
Fatigue	Up to 78% ; correlates poorly with disease severity; no MRI correlate	First evaluate sleep, insomnia, anxiety, depression, nocturia, spasticity and pain. Amantadine 100 mg BD (efficacy ~40%; caution in renal failure/seizures). Modafinil 100–400 mg/day (single-blind study positive, double-blind negative), armodafinil, methylphenidate 10–60 mg/day , atomoxetine, activating SSRIs, bupropion (avoid if seizures)
Cognitive impairment	34%–65% on formal testing; 49%–53.7% even in CIS/early RRMS; 29% in early PPMS. Working memory, attention and processing speed are worst affected	Screen with the Symbol Digit Modalities Test ; formal batteries (BRB-N, MACFIMS) are research tools. No convincing evidence that cholinesterase inhibitors help . Treat comorbid depression/anxiety; modafinil may improve focused attention; some evidence for L-amphetamine. Cognitive-behavioural therapy, counselling, job modification
Mood	Lifetime risk of major depression up to 50% — higher than in other chronic diseases. Suicide rate is higher than the general population and than other chronic illnesses. IFN- β itself can cause depression	AAN quality measures require screening for depression and assessing it as two separate steps. Antidepressants, psychological support; reconsider IFN- β
Bladder	50%–80% at some time; severity parallels myelopathy, not disease duration	Distinguish spastic (frequency, urgency, incontinence) from hypotonic (hesitancy, retention, overflow) before treating . Fluid management, timed voiding, bedside commode. Hyperreflexic bladder without outlet obstruction: oxybutynin 2.5–5 mg 1–3 times daily (or tolterodine, trospium, darifenacin, solifenacin); desmopressin at bedtime. With outlet obstruction: Credé manoeuvre, antispasticity drugs, anticholinergic + α-blocker (terazosin) . Refractory: botulinum toxin to detrusor. Retention: intermittent self-catheterisation
Tremor	Often the most disabling cerebellar symptom	Topiramate (anecdotal), primidone 125–250 mg BD/TDS , clonazepam 0.5–2 mg up to four times daily, propranolol; thalamotomy or deep brain stimulation for refractory tremor
Sexual dysfunction	40%–80% overall; 45%–74% of women	Treat contributing depression, fatigue, spasticity, bowel/bladder dysfunction. Urogynaecological referral, pelvic floor exercises, lubricants, devices; sildenafil and related agents for erectile dysfunction (caution with cardiovascular disease); counselling and sexual therapy
Paroxysmal symptoms, Lhermitte sign, Uhthoff phenomenon	Brief, stereotyped attacks — diplopia, focal paraesthesia, trigeminal neuralgia, ataxia, dysarthria, tonic spasms, hemifacial spasm, dystonia. They may arise from a pre-existing lesion, not new activity	Carbamazepine (especially extended-release) is most widely used; benzodiazepines, baclofen, acetazolamide, bromocriptine. A new " flurry " of paroxysmal symptoms may be treated as a relapse with high-dose IV steroid

Symptom	Frequency / key facts	Treatment
Bowel	Constipation very common — cord involvement, immobility, diet, and self-imposed fluid restriction to control urgency	Almost all paraplegic patients need a regular bowel regimen

Table 4 · Symptomatic management of MS — Bradley & Daroff 8e, Ch. 80, §Clinical Symptoms and Symptom Management, pp. 1248–1250.

GUIDELINE UPDATE — BEYOND THE TEXTBOOK

- The 2021 **MAGNIMS-CMSC-NAIMS** consensus MRI protocol, the **2018 AAN** disease-modifying therapy guideline, and the **2023 McDonald criteria update** (addition of the **central vein sign** and **paramagnetic rim lesions** as MS-specific imaging biomarkers, and of the optic nerve as a fifth topographical location) all post-date the prescribed textbooks and are flagged here as outside-source material. Likewise **ofatumumab** (subcutaneous anti-CD20, self-administered monthly) and **ublituximab**, and the use of serum **neurofilament light chain** and **glial fibrillary acidic protein** as treatment-response biomarkers, are beyond Bradley 8e; Bradley notes only that NfL "is still being investigated". Similarly, the concept of **progression independent of relapse activity (PIRA)** and the strategy of **early highly-effective therapy versus escalation** are current debates that the textbook does not adjudicate.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Relapse = IV methylprednisolone 1 g × 3–5 days** (high-dose oral is non-inferior); **steroid-refractory = plasma exchange** (AAN: "probably effective").
- The ONTT number to quote: definite MS at 2 years **7.5% IV vs 14.7% oral prednisone vs 16.7% placebo** — and oral prednisone alone increased recurrent optic neuritis.
- **Ocrelizumab** — anti-CD20, **300 mg IV ×2 two weeks apart, then 600 mg every 24 weeks**; plasma cells spared so humoral immunity preserved; ARR ↓ 47% and enhancing lesions ↓ 94%–95% vs interferon; **the only drug approved for PPMS** (ORATORIO, 30% less 24-week disability progression); JCV status does not restrict it.
- Match the drug to the monitoring: **natalizumab → JCV antibody every 6 months**; **fingolimod → first-dose ECG, VZV serology, macular OCT**; **alemtuzumab → thyroid function and platelets**; **dimethyl fumarate/cladribine → lymphocyte count**.
- No head-to-head trial separates **glatiramer from high-dose interferon** (REGARD, BEYOND, BECOME) — say so explicitly when asked to "critically evaluate".
- Pregnancy: relapses **fall in the third trimester and triple in the first 3 postpartum months**; epidural and breastfeeding are safe; childbirth after onset is associated with **later EDSS 6**.
- **Dalfampridine** is the only MS drug whose indication is to **improve walking**; do not give it to a patient who has had a seizure.

Part 10

Peripheral Nerve, NMJ, Muscle and Anterior Horn Cell

1 · PERIPHERAL NERVE — PATHOLOGY, CLINICAL APPROACH AND THE DYSIMMUNE NEUROPATHIES

Q1. Important causes of neuropathy with emphasis on demyelinating neuropathies. How does GBS in India differ from other parts of the world in terms of clinical manifestations, variants and prognosis?

LONG

Nerves §Long Q1

10 marks

Also asked as: Nerves §Long Q2 — "Discuss in detail about dysimmune neuropathies" · Nerves §Long Q4 — "Discuss autoimmune neuropathies and their Mx" · Nerves §Long Q7 — "Discuss an approach to a case of acute neuropathies"

Source: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 106 *Disorders of Peripheral Nerves*, §Clinical Approach to Disorders of Peripheral Nerves, pp. 1854–1862 (Boxes 106.1–106.9, Tables 106.1–106.2, Figs. 106.1–106.5); §Inflammatory Demyelinating Polyradiculoneuropathies, pp. 1881–1896 (Boxes 106.10–106.13, Tables 106.11–106.12, Figs. 106.17–106.22); §Peripheral Nerve Vasculitis, pp. 1912–1915; §Paraneoplastic Neuropathies, pp. 1909–1911. Supplementary: Preston & Shapiro, *Electromyography and Neuromuscular Disorders*, 4th ed. — Ch. 29 *Polyneuropathy*, pp. 494–502 (Box 29.5, p. 499).

1. The four pathological reactions of peripheral nerve — everything follows from these

- Despite the very large number of causes, the reactions of peripheral nerve to insult are **limited to four** (Ch. 106, p. 1854):
- **(1) Wallerian degeneration** — the response to **axonal interruption** (compression, traction, laceration, thermal, chemical, ischaemic).
 - CMAP amplitude distal to the lesion begins to fall by **day 2** and reaches nadir by **day 5–6**; SNAP loss is delayed a further 2–3 days, normal for 5–6 days, nadir at **day 10–11**.
 - Fibrillation potentials appear on needle EMG at **10–14 days** and are full at **3 weeks**.
 - Regeneration from the proximal stump starts at **24 hours** but advances at only **2–3 mm/day**; collateral sprouting becomes visible on EMG after **1 month**.
- **(2) Axonal degeneration (axonopathy)** — the **commonest** reaction; metabolic derangement or ischaemia causes distal breakdown of the axon with its myelin — the **dying-back** or **length-dependent** pattern (Fig. 106.1).
 - Clinically: symmetrical **stocking-and-glove** sensory loss, distal weakness and wasting, loss of distal reflexes.
 - Electrically: **low SNAPs and CMAPs** with only slight effect on distal latency and conduction velocity.
 - Causes: systemic metabolic disorders, toxins, vasculitis, some inherited neuropathies.
- **(3) Neuronopathy** — loss of the **cell body** and hence of its entire peripheral *and* central axon.
 - Anterior horn cell → focal weakness **without** sensory loss (poliomyelitis, motor neuron disease).
 - Dorsal root ganglion (sensory neuronopathy / polyganglionopathy, Fig. 106.2) → **sensory ataxia, sensory loss, diffuse areflexia**; causes are organic mercury, doxorubicin, high-dose pyridoxine, vitamin E deficiency, **anti-Hu paraneoplastic** syndrome, Sjögren syndrome. **Recovery is poor** — no axonal regeneration is possible.
- **(4) Segmental demyelination (myelinopathy)** — injury to myelin or Schwann cell with **sparing of the axon** (Fig. 106.3).
 - Remyelination occurs within **weeks**; new internodes are **thinner and shorter**; repeated cycles give **onion bulbs**.

- The physiological consequence of **acquired** (but not hereditary) demyelination is **conduction block** → weakness with **little atrophy**.
- Clinical clues: **early generalised areflexia**, weakness (proximal and distal) out of proportion to atrophy, **neuropathic tremor**, **palpably enlarged nerves**, relative sparing of pain and temperature.
- Bradley's electrophysiological definition: motor and sensory NCV reduced to **< 70% of the lower limit of normal** with relative preservation of CMAP/SNAP amplitude; partial conduction block, temporal dispersion and markedly prolonged distal and F-wave latencies indicate **acquired** demyelination.

2. Classification of peripheral nerve disease (Box 106.1) — say this before listing causes

- **Mononeuropathy** — a single nerve; implies a local process (trauma, compression, entrapment, vascular, neoplastic infiltration).
- **Plexopathy** — brachial, lumbar, sacral (Ch. 105).
- **Radiculopathy** — cervical, thoracic, lumbosacral.
- **Multiple mononeuropathy (mononeuritis multiplex)** — simultaneous or sequential damage to non-contiguous nerves; when confluent it mimics a length-dependent polyneuropathy.
- **Polyneuropathy** — symmetrical or asymmetrical; and **polyradiculoneuropathy** when roots are involved (proximal *and* distal weakness).

3. Important causes of neuropathy — arranged by the pattern that brings the patient

Pattern	Axonal causes	Demyelinating causes
Symmetrical polyneuropathy	Diabetes mellitus and impaired glucose tolerance; uraemia; alcohol and thiamine deficiency; B12, B6 excess, folate, niacin, vitamin E and copper deficiency; hypothyroidism, acromegaly; liver disease; COPD; critical illness; amyloidosis; drugs and toxins (cisplatin, taxanes, vincristine, bortezomib, thalidomide, isoniazid, metronidazole, nitrofurantoin, dapsone, phenytoin, colchicine, chloroquine, gold, linezolid, nitrous oxide, arsenic, thallium, lead, n-hexane); HIV; CMT2; chronic idiopathic axonal polyneuropathy	Acquired: CIDP and its variants, IgM-MGUS/anti-MAG, osteosclerotic myeloma (POEMS), Waldenström, HIV-associated CIDP. Inherited: CMT1, CMT3 (Dejerine-Sottas), CMTX, HNPP, Refsum disease, metachromatic leukodystrophy, Krabbe disease, adrenomyeloneuropathy, Cockayne, Niemann-Pick, cerebrotendinous xanthomatosis
Acute (days-4 weeks)	AMAN / AMSAN; acute intermittent porphyria; vasculitis; critical illness polyneuropathy; acute arsenic/thallium poisoning; organophosphates, n-hexane, acrylamide, buckthorn	AIDP (GBS); diphtheritic neuropathy; acute-onset CIDP
Multiple mononeuropathy (Box 106.2)	Systemic and non-systemic vasculitis; diabetes; sarcoidosis; leprosy; HIV-1 infection	MMN with conduction block; MADSAM (Lewis-Sumner); multiple compressive neuropathies (hypothyroidism, diabetes); HNPP
Predominantly motor (Box 106.3)	AMAN*, lead intoxication, diabetic lumbar radiculoplexopathy	GBS, CIDP, MMN*, osteosclerotic myeloma, CMT (HMSN)

Pattern	Axonal causes	Demyelinating causes
Predominantly sensory / sensory ataxic (Boxes 106.7, 106.8)	Diabetes; carcinoma (anti-Hu); Sjögren; dysproteinaemia; AIDS; B12 deficiency; coeliac disease; cisplatin, thalidomide, pyridoxine; HSAN; Fabry; Tangier; cryptogenic small-fibre neuropathy	Miller-Fisher variant of GBS; anti-MAG IgM paraproteinaemic neuropathy; CANOMAD ; chronic immune sensory polyradiculopathy
Autonomic (Box 106.6)	Acute: acute pandysautonomia, GBS, porphyria, vincristine, Vacor. Chronic: diabetes, familial and primary amyloid, paraneoplastic sensory neuronopathy, HIV, HSAN	—
Facial nerve involvement (Box 106.4)	Gelsolin (Finnish) familial amyloid; Tangier disease	GBS , Lyme disease, sarcoidosis, CIDP (rare), HIV-1

Table 1 · Important causes of neuropathy by pattern and by pathology — Bradley & Daroff 8e, Ch. 106, Boxes 106.1–106.8, pp. 1857–1862 and §Toxic and Drug-Induced Neuropathies, pp. 1921–1926. *Pure motor syndromes with normal SNAPs.

4. Clinical approach — history and examination (the marks are here)

- The text is explicit that the **"shotgun" approach of ordering panels of tests must be avoided**. The logical sequence is: detailed history → full neurological examination → a **limited** set of laboratory tests → detailed electrodiagnostic studies → ancillary testing (autonomic testing, skin biopsy, nerve biopsy) only in special situations.
- **History — the five questions**
 - **Which fibre types?** Negative motor (weakness, atrophy, tripping on uneven ground, difficulty opening jars) vs positive motor (cramps, fasciculations, myokymia, tremor); positive sensory (prickling, burning, band-like tightness, allodynia, hyperalgesia, neuropathic pain worse at night) vs negative sensory (numbness, imbalance); autonomic (orthostatic intolerance, sweating change, gastroparesis, bladder, bowel, sexual).
 - **Acquired or inherited?** Spontaneously reported **paraesthesiae in > 60% of acquired** vs **< 20% of inherited** neuropathies. Inherited neuropathies account for about **30%** of undiagnosed neuropathies referred to tertiary centres — ask about pes cavus and hammer toes in relatives, and examine the relatives.
 - **What is the time course?** Acute — GBS, acute porphyria, vasculitis, neuralgic amyotrophy, some toxic neuropathies. Relapsing — CIDP, acute porphyria, Refsum, HNPP, hereditary neuralgic amyotrophy, repeated toxin exposure.
 - **Is there a systemic disease?** Weight loss, malaise, anorexia; diabetes, hypothyroidism, renal failure, liver disease, malabsorption, malignancy, connective tissue disease, HIV.
 - **Any exposure?** Drugs including over-the-counter **vitamin B6**, alcohol, diet, solvents, pesticides, heavy metals.
- **Examination — localise first, then characterise**
 - Weakness in a **dying-back** pattern is greater in extensors than flexors, so **heel walking fails before toe walking**.
 - The **marching sensory level**: when leg sensory loss reaches the knees the finger tips are involved; at mid-thigh a **tent-shaped** area of hypoaesthesia appears on the anterior chest and abdomen (third-longest nerves); hoarseness may follow.

- **Asymmetrical weakness without sensory loss** ⇒ motor neuronopathy — motor neuron disease or MMN.
- **Small-fibre pattern:** loss of pain and temperature, burning pain, autonomic features, with **preserved reflexes, balance and strength**; classically distal loss of pinprick with a **band of hyperalgesia above it**.
- **Large-fibre pattern:** areflexia, sensory ataxia, loss of joint position and vibration, **pseudoathetosis** and Romberg sign.
- **Palpate the nerves.** Generalised or multifocal hypertrophy occurs in a limited list — **leprosy, neurofibromatosis, CMT1 and CMT3, acromegaly, Refsum disease, rarely CIDP**.
- **Look at skin, nails and hair** (Table 106.1): purpura and livedo (vasculitis, cryoglobulinaemia); angiokeratoma (Fabry); hypopigmented patches (leprosy); hyperpigmentation and hypertrichosis (POEMS); bullae (variegate porphyria); ichthyosis and overriding toes (Refsum); **Mees lines** (arsenic, thallium); alopecia (thallium); curled hair (giant axonal neuropathy); orange tonsils (Tangier); pes cavus (CMT).

5. Investigation — a decision pathway, not a panel (Fig. 106.5)

- **Electrodiagnosis first.** EDX studies (i) confirm the neuropathy, (ii) localise focal lesions precisely, and (iii) define the underlying pathology as axonal or demyelinating.
 - Routine sensory studies assess **only large myelinated fibres** and are normal in pure small-fibre neuropathy — then use **QST** (cold/heat pain thresholds), **QSART** (sensitivity ~80%) and skin biopsy.
- **Routine bloods in every patient with polyneuropathy**
 - CBC, ESR, CRP, renal function, fasting glucose and **HbA1c**, thyroid function, **vitamin B12**, and **serum protein electrophoresis with immunofixation**.
 - **10% of patients over 60 with chronic undiagnosed neuropathy have a monoclonal gammopathy** — screen everyone.
- **CSF** — for suspected demyelinating neuropathy and for polyradiculopathy from meningeal carcinomatosis or lymphomatosis.
- **Autoantibodies (Table 106.2) — only a few are clinically useful**
 - **IgM anti-GM1** → multifocal motor neuropathy (70%).
 - **IgG anti-GM1 / anti-GD1a** → GBS (30%), especially axonal forms.
 - **IgG anti-GQ1b** → **Miller-Fisher syndrome (> 90-98%)**.
 - **Monoclonal IgM anti-GD1b** → CANOMAD.
 - **Monoclonal IgM anti-MAG** → DADS / IgM neuropathy (50-70%).
 - **Anti-Hu (ANNA-1)** → paraneoplastic sensory neuronopathy (> 95%). A positive antibody **mandates a search for malignancy**.
 - Bradley states plainly that for most other antibodies **clinical relevance is not established and testing is not cost-effective**.
- **Neuromuscular ultrasound** — readily available and painless.
 - Focal enlargement (cross-sectional area) is the commonest sign of entrapment (CTS, ulnar neuropathy at elbow).
 - **Multifocal enlargement at non-entrapment sites and of the brachial plexus is highly diagnostic of CIDP** and distinguishes acquired demyelinating from axonal neuropathy and from motor neuron disease.
 - Muscle ultrasound shows fasciculations more readily than needle EMG and separates DMD (severe, homogeneous increase in echo intensity) from SMA (inhomogeneous increase with severe atrophy).

- **Skin biopsy** — punch or blister biopsy with PGP 9.5 immunostaining for **intraepidermal nerve fibre density**.
 - Best when small-fibre neuropathy is suspected and nerve conduction studies are normal; diagnosis is best made when **at least two** of clinical findings, QST, QSART and skin biopsy are abnormal.
 - It rarely gives an aetiological diagnosis, does not assess myelinated fibres, and cannot show interstitial pathology.
- **Nerve biopsy** (Box 106.9) — restricted, and only in experienced centres.
 - **Diagnostic and essential:** vasculitis*, amyloidosis*, sarcoidosis*, **leprosy**, giant axonal neuropathy, tumour infiltration, polyglucosan body disease (*combine distal nerve *and* muscle biopsy).
 - **Supportive only:** CMT1 and CMT3, CIDP, IgM anti-MAG paraproteinaemic neuropathy.
 - Usual nerve = **sural**; the **superficial fibular nerve** allows simultaneous peroneus brevis muscle biopsy through one incision and raises the yield in vasculitis.
 - Complication rate is up to **15%**, and about one-third report persistent unpleasant sensory symptoms at 1 year.

APPROACH TO EVALUATION OF PERIPHERAL NEUROPATHIES

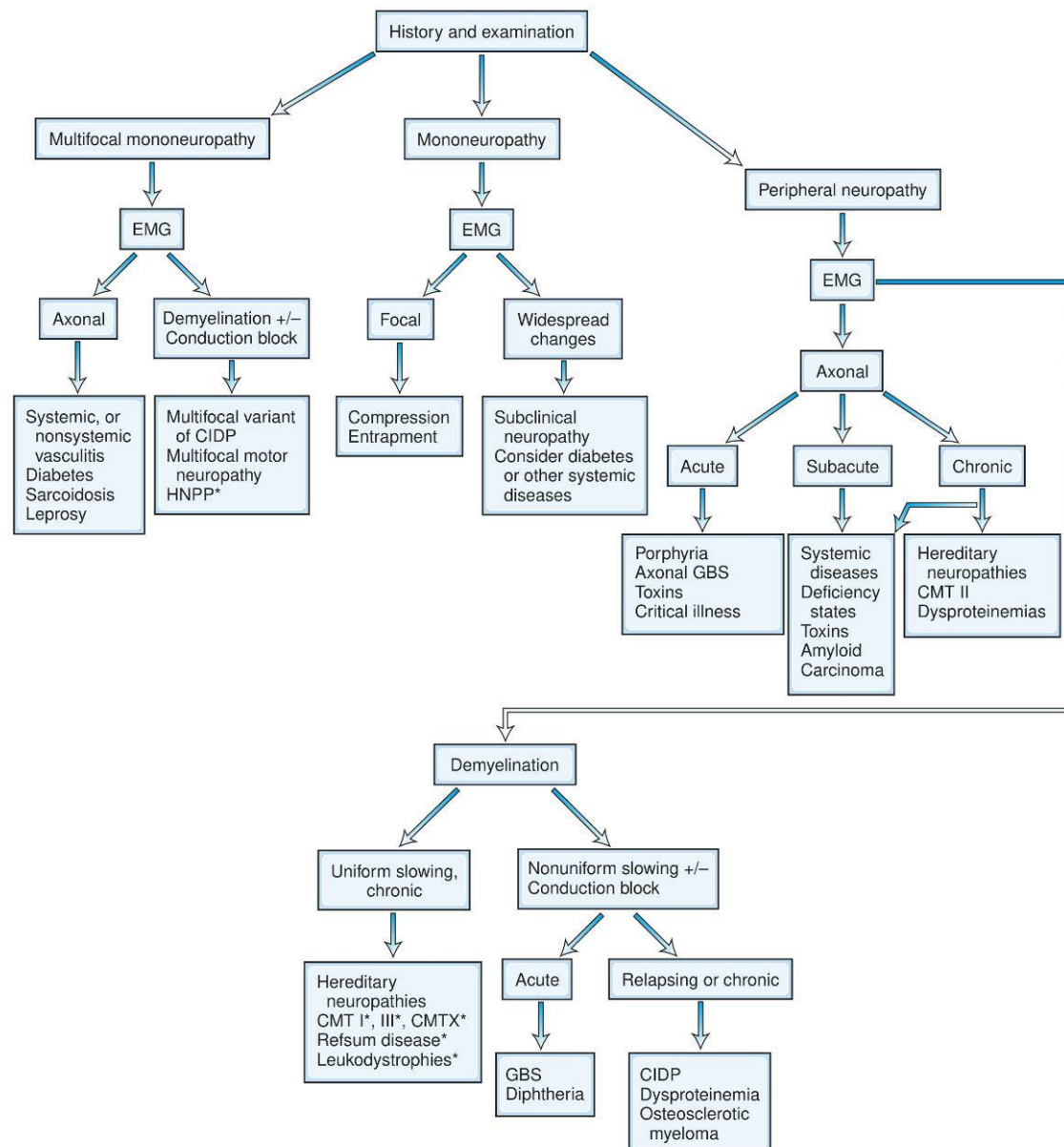


Fig. 106.5 Diagnostic Approach to Evaluation of a Patient with Peripheral Neuropathy. Electromyography (EMG) denotes electrodiagnostic studies including nerve conduction studies and needle EMG. DNA diagnostic testing or specific biochemical tests are available for conditions marked with asterisks. CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy; CMT, Charcot-Marie-Tooth disease; CMTX, Charcot-Marie-Tooth disease X-linked; GBS, Guillain-Barré syndrome; HNPP, hereditary liability to pressure palsies.

Reproduced from Bradley & Daroff 8e, **Fig. 106.5**, p. 1861 — the diagnostic algorithm to reproduce in the exam. Three arms from history and examination (multifocal mononeuropathy · mononeuropathy · polyneuropathy) → EMG → axonal vs demyelinating → for axonal, time course (acute / subacute / chronic); for demyelination, **uniform slowing = inherited vs non-uniform slowing ± conduction block = acquired**, then acute (GBS, diphtheria) vs relapsing/chronic (CIDP, dysproteinemia, osteosclerotic myeloma).

6. The dysimmune (autoimmune) neuropathies — the core of this answer

- Inflammatory demyelinating polyradiculoneuropathies are **acquired, immunologically mediated** polyneuropathies, classified by **clinical course** into **(1) GBS** (maximum deficit within 4 weeks, then plateau and recovery) and **(2) CIDP** (progressive for 2 months or more, or relapsing-remitting).
- To these are added the **other immune-mediated neuropathies**: multifocal motor neuropathy, the paraproteinaemic neuropathies, vasculitic neuropathy, and the paraneoplastic neuropathies.

6a · Guillain-Barré syndrome

- **Definition (Box 106.10):** *required* — progressive weakness of both legs and arms + areflexia/hyporeflexia. *Supportive clinical* — progression over days to 4 weeks, relative symmetry, mild sensory symptoms, **bifacial palsies**, autonomic dysfunction, **absence of fever at onset**, recovery beginning 2–4 weeks after progression ceases. *Supportive laboratory* — raised CSF protein with < 10 cells/μL, and nerve conduction slowing or block.
- Incidence **1.8 per 100 000/year**, rising with age (0.8 under 18 years → 3.2 at ≥ 60 years); **M:F 1.5:1**. With the eradication of polio it is the leading cause of acute paralytic disease in Western countries. Mortality has fallen from 33% before positive-pressure ventilation to **1%–5%**.
- **Clinical features**
 - Ascending symmetrical limb weakness over hours to days; occasionally descending or starting in cranial muscles.
 - **Cranial nerve involvement in 45%–75%**; facial paresis, usually bilateral, in at least half.
 - Sensory loss is **not prominent** (often limited to distal vibration), but **moderate-to-severe pain in ~70%** of patients in the acute phase, persisting for a year in a third.
 - **Autonomic dysfunction in 65%** of hospitalised patients, mostly in the first 2–4 weeks: orthostatic hypotension, urinary retention, ileus, iridoplegia, labile hypertension, sinus tachycardia, arrhythmia, anhidrosis or diaphoresis. Excessive vagal activity gives "**vagal spells**" — bradycardia, heart block, asystole — often triggered by tracheal suctioning.
 - Respiratory failure requiring ventilation in **9%–30%** (up to 30%).
- **Subtypes and variants (Box 106.11)**
 - **Common subtypes:** AIDP, AMAN, AMSAN.
 - **Rare variants:** Miller-Fisher syndrome, ataxic variant, **pharyngeal-cervical-brachial** variant, multiple cranial neuropathy variant, **facial diplegia with paraesthesiae**, paraparetic variant, **acute pandysautonomia**.
- **Pathogenesis**
 - Two-thirds report a **preceding event 1–4 weeks earlier** (Table 106.11): respiratory illness **58%**, gastrointestinal **22%**, both 10%, surgery 5%, vaccination 3%.
 - Named agents: **Campylobacter jejuni**, CMV, EBV, VZV, hepatitis A and B, HIV, *Mycoplasma pneumoniae*, *H. influenzae* and — recently — **Zika virus**.
 - **Molecular mimicry** between GM1 ganglioside and *C. jejuni* lipo-oligosaccharide is the established pathogenic link. Note the perspective: 2.4 million *C. jejuni* infections a year in the USA yield only ~2500 cases of GBS — **host factors matter**.
 - **AIDP (Fig. 106.17):** antibody binds the **outermost (abaxonal) Schwann cell membrane** → complement activation (C3d, C5b-9) → vesicular myelin change → macrophage recruitment → demyelination; intense inflammation gives secondary axonal degeneration.
 - **AMAN (Fig. 106.18):** anti-GM1 binds the **nodal axolemma of motor fibres** → complement and macrophage invasion of the periaxonal space → wallerian-like degeneration. Rabbits immunised with GM1 develop AMAN, fulfilling the postulates for autoimmunity.
 - Influenza vaccination: current risk is **one extra case per 2.5 million vaccinated**; previous GBS should **not** preclude influenza vaccination in high-risk individuals.

6b · The other dysimmune neuropathies — one table

Disorder	Clinical hallmark	Key investigation	Treatment
AIDP / GBS	Ascending areflexic weakness, max < 4 weeks; bifacial palsy; dysautonomia	Albuminocytological dissociation; sural sparing + abnormal F waves (96% specific); conduction block at non-entrapment sites	IVIG 0.4 g/kg/day × 5 days or PLEX 4-5 exchanges (40-50 mL/kg) alternate days ; equally effective, no benefit from combining. Steroids are of no benefit
AMAN	Pure motor acute flaccid paralysis, summer epidemics in children and young adults in northern China; now the commonest GBS subtype in Asia	Normal SNAPs, low CMAPs, no demyelinating features; anti-GM1/GD1a; <i>C. jejuni</i> in 76% in northern China	As for GBS. Prognosis comparable to AIDP because much of the deficit is reversible conduction failure at the node
AMSAN	Fulminant, maximum deficit < 7 days, profound quadriparesis with wasting, prolonged ventilation	Markedly reduced or absent CMAPs and absent SNAPs without slowing; abundant fibrillations later	As for GBS; poor prognosis
Miller-Fisher syndrome	Ophthalmoplegia + ataxia + areflexia ; ~5%–6% of GBS in the West but 18% in Taiwan	Anti-GQ1b in 98% ; SNAPs normal in half, reduced with sural sparing in a third; motor studies and EMG usually normal	IVIG or PLEX; favourable prognosis , recovery at a mean of 10 weeks
CIDP	Symmetrical proximal and distal weakness ≥ 2 months, generalised areflexia, large-fibre sensory loss, postural hand tremor, palpable nerves	NCS demyelination in ≥ 2 nerves; CSF protein > 45 mg/dL in 95% ; nerve US shows multifocal enlargement; MRI root enhancement (Fig. 106.20)	All three work in 50%–70% : prednisone 60–80 mg/day, PLEX, or IVIG (ICE study: 2 g/kg then 1 g/kg every 3 weeks). Azathioprine, methotrexate, mycophenolate as steroid-sparing; rituximab for anti-CNTN1/NF155
Multifocal motor neuropathy	Progressive asymmetrical distal weakness in individual nerve territories, arms > legs , wrist drop/grip weakness, no sensory loss , no UMN signs , bulk preserved despite weakness	Motor conduction block confined to motor axons at non-compression sites (Fig. 106.22); IgM anti-GM1 in 50%–60% ; CSF protein normal in 70%	IVIG only (70% respond, FDA approved) 0.4 g/kg every 1–8 weeks. Steroids and PLEX do not work and may worsen it
Paraproteinaemic (IgM-MGUS / anti-MAG, DADS)	Distal, symmetric, sensory > motor, sensory ataxia; older patients	Serum immunofixation; anti-MAG in 50%–70% ; uniform slowing of distal latencies more than conduction velocities , few conduction blocks	Poor response in general; some respond to IVIG or rituximab

Disorder	Clinical hallmark	Key investigation	Treatment
Vasculitic neuropathy	Painful, stepwise multiple mononeuropathy (fibular, then ulnar); 60%–70% confluent; ~30% present as a symmetrical distal neuropathy	ESR, CRP, ANCA, cryoglobulins, hepatitis B and C, ANA/ENA; combined nerve and muscle biopsy is diagnostic — occlusion of epineurial arterioles 50–300 µm with differential fascicular involvement	Corticosteroids plus cyclophosphamide; treat the underlying systemic disease or virus
Paraneoplastic sensory neuronopathy	Subacute asymmetrical sensory loss, sensory ataxia, pseudoathetosis, areflexia; may precede the tumour by 4–12 months	Anti-Hu (ANNA-1) > 95% ; SCLC in most; antibodies to intracellular antigens are highly predictive of cancer and of irreversible neuronal loss	Treat the tumour. Neurological recovery is generally poor

Table 2 · The dysimmune neuropathies at a glance — Bradley & Daroff 8e, Ch. 106, pp. 1881–1915.

7. Approach to the patient with an ACUTE neuropathy

- **Step 1 — Is it really a neuropathy?** Exclude the mimics of acute flaccid weakness (Box 106.12): myopathy (polymyositis, necrotising autoimmune myopathy, rhabdomyolysis, critical illness myopathy), muscle membrane disorders (periodic paralysis, thyrotoxic and secondary hypokalaemic paralysis), NMJ disorders (myasthenic crisis, botulism, organophosphate, tick paralysis, snake envenomation, hypermagnesaemia, hypophosphataemia), anterior horn cell (polio, West Nile, enterovirus), spinal cord (transverse myelitis, compression, anterior spinal artery infarction) and brainstem (central pontine myelinolysis, basilar thrombosis).
 - **Early urinary retention and a sharp sensory level on the trunk mean spinal cord disease — get an urgent MRI.**
 - **CSF pleocytosis > 50 cells/µL casts doubt on uncomplicated GBS** and suggests HIV, Lyme, CMV or a neoplastic meningoradiculopathy.
- **Step 2 — Confirm and characterise.** CSF (protein may be normal in up to 50% in week 1, and in 10% throughout) and **serial** nerve conduction studies. About half of patients have normal NCS in the first 4 days apart from **absent H reflexes**; only ~10% are still normal at one week; the studies become specific in weeks **3–4**.
- **Step 3 — Look for the treatable non-GBS causes.** Acute intermittent porphyria (abdominal pain, psychiatric features, predominantly motor with arm and radial predominance), diphtheria (palatal paralysis and impaired accommodation first), vasculitis, heavy metals (arsenic, thallium), and critical illness polyneuropathy.
- **Step 4 — Assess severity and admit appropriately.** Predictors of ventilation: onset to admission < 7 days, severe limb weakness, facial weakness, bulbar weakness. Use the **20/30/40 rule** — vital capacity < 20 mL/kg, maximal inspiratory pressure < 30 cm H₂O, maximal expiratory pressure < 40 cm H₂O. Intubate when **FVC falls below 12–15 mL/kg** (or 18 mL/kg with severe oropharyngeal weakness) or Pao₂ < 70 mm Hg on room air. Tracheostomy if ventilation is needed beyond 2 weeks.
- **Step 5 — Treat.** See Fig. 106.19 and section 8.

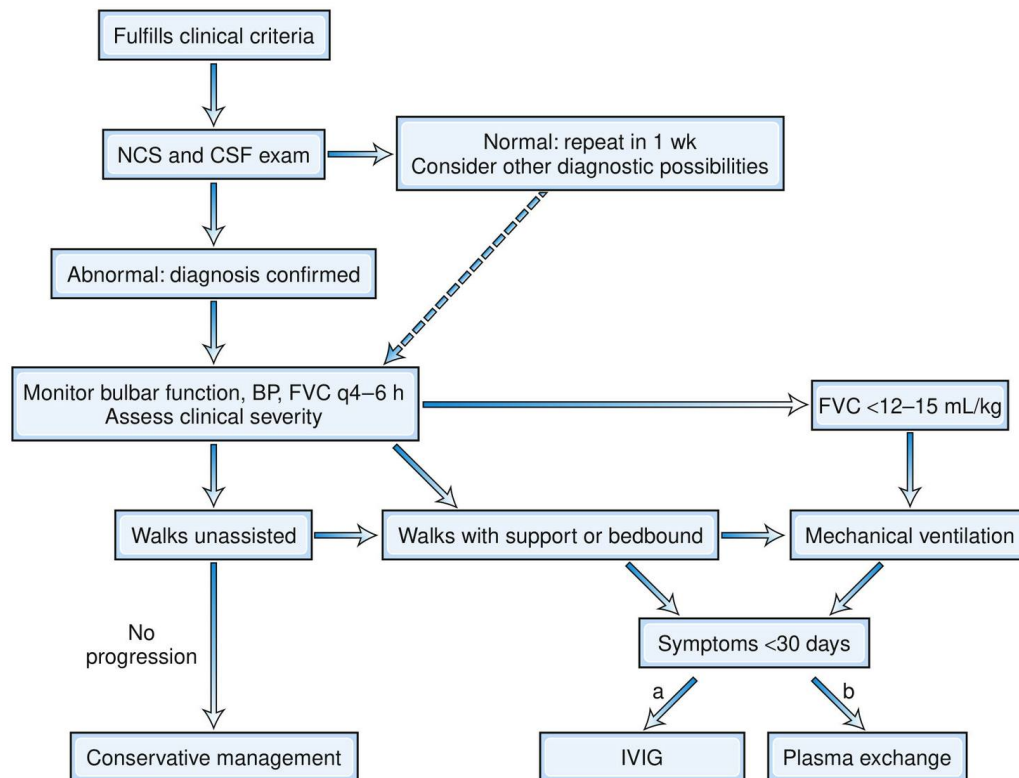


Fig. 106.19 Decision-Making Pathway in Management of Guillain-Barré Syndrome. Both treatment options, intravenous immunoglobulin (IVIG) (a) and plasma exchange (b), are equally efficacious. IVIG is preferred because of its ease of administration. BP, Blood pressure; CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome; FVC, forced vital capacity; NCS, nerve conduction studies. (Adapted from Bosch, E.P., 1998. Guillain-Barré syndrome: an update of acute immune-mediated polyradiculoneuropathies. *Neurologist* 4, 211-226.)

Reproduced from Bradley & Daroff 8e, **Fig. 106.19**, p. 1889 — the GBS management flowchart. Label: clinical criteria → NCS + CSF (normal → repeat in 1 week and reconsider the diagnosis) → monitor bulbar function, BP and FVC every 4-6 h → stratify as walks unassisted / walks with support or bedbound / mechanical ventilation (FVC < 12-15 mL/kg) → if symptoms < 30 days, IVIG (a) or plasma exchange (b).

8. Management of the dysimmune neuropathies

- **General supportive care is the mainstay in GBS** — "the prevention of complications ... provides the best chance for a favourable outcome".
 - Monitor FVC and negative inspiratory force every 4-6 h while awake; overnight pulse oximetry; continuous ECG and BP monitoring if dysautonomia.
 - **Use antihypertensive and vasoactive drugs with extreme caution** in autonomic instability; tracheal suctioning can trigger hypotension or bradyarrhythmia.
 - Prophylactic subcutaneous/LMW heparin and calf compression; chest physiotherapy; skin, eye (artificial tears, taping lids), mouth, bowel and bladder care; padding of ulnar and fibular nerves; early physiotherapy; high-calorie protein feeding; NSAIDs or opioids for the back and radicular pain; psychological support.
- **Specific immunotherapy in GBS**
 - **Plasma exchange** — 6 RCTs, > 600 patients. Indicated for moderate-to-severe weakness (able to walk only with support or worse). **Two exchanges benefit even mild cases; four are optimal for moderate and severe; six add nothing.** Best within 2 weeks of onset; valuable up to 30 days. Contraindications: septicaemia, active bleeding, severe cardiovascular instability.
 - **IVIG** — 0.4 g/kg/day × 5 days (total 2 g/kg), begun within the first 2 weeks. **Equally effective as plasma exchange; combining the two adds nothing.** IVIG is the preferred treatment in US hospitals because of ease of administration.

- IVIG is **contraindicated** in hyperviscosity, congestive cardiac failure, chronic renal failure (especially diabetic) and congenital IgA deficiency — use plasma exchange.
- **Corticosteroids are not recommended** — two RCTs (oral prednisolone and IV methylprednisolone) found no benefit; a Cochrane review confirms no significant benefit or harm.
- **Treatment-related fluctuations** occur in **10%-20%**; repeat IVIG or plasma exchange may help. More than two fluctuations, deterioration after 8 weeks, prominent sensory signs, multifocal nerve enlargement on ultrasound, or new demyelinating features months later should raise **acute-onset CIDP** (~5% of apparent GBS).
- **Treatment of CIDP (Fig. 106.21)**
 - Prednisone 60–80 mg/day (1–1.5 mg/kg in children) — improvement starts within 2 months, may take 3–5 months; convert to alternate-day then taper slowly. **Pulsed oral dexamethasone 40 mg/day × 4 days every 4 weeks** gives the same remission rate but patients improve **twice as fast**.
 - Plasma exchange — 10 exchanges over 4 weeks improve **80%**, but **70% of responders relapse within 14 days** of stopping.
 - IVIG — first neurological disease for which IVIG was FDA-approved (2008, ICE study). Subcutaneous immunoglobulin 0.2–0.4 g/kg weekly is an effective maintenance alternative.
 - Steroids, when effective, are **more likely to induce remission** and less often followed by deterioration after stopping than IVIG.
 - **Failure to respond should prompt reappraisal of the diagnosis** — the commonest causes of treatment failure are incorrect diagnosis, inadequate dose or duration, and concurrent illness.
- **MMN:** IVIG is the treatment; **prednisone and plasma exchange may worsen it**.
- **Vasculitic neuropathy:** corticosteroids with cyclophosphamide; in paraneoplastic vasculitis two-thirds respond to treatment of the tumour or to cyclophosphamide ± steroids.

9. Course, prognosis — and how GBS differs between world regions

- **15%** of GBS patients remain ambulant and recover in a few weeks; **5%-20%** have a fulminant course with flaccid quadriplegia and ventilator dependence, often within 2 days.
- After progression stops there is a **plateau of 2–4 weeks. 70% complete recovery by 12 months and 82% by 24 months; 20% still have residual motor weakness at 1 year; 2%-5% die; up to 5% recur.**
- **Predictors of poor recovery** (< 20% probability of walking independently at 6 months)
 - Age > 60 years; preceding **diarrhoeal illness**; recent **CMV** infection; need for ventilation; rapid progression to maximum deficit in < 7 days; hyponatraemia; **distal CMAP ≤ 20% of the lower limit of normal** or inexcitable nerves.
- **Geographical differences that the textbook does document**
 - **AMAN** was first described in **northern China** in summer epidemics among children and young adults and "is now considered **the most common GBS subtype in Asia**" — in contrast to AIDP, which is the commonest form in Europe and North America.
 - **Campylobacter jejuni** is found in **76% of AMAN** and 42% of AIDP patients in northern China, versus 17%–39% of all GBS in the USA, Netherlands, Germany, Australia and 26% in the UK.
 - **Miller-Fisher syndrome** accounts for **6% of GBS in Western countries but 18% in Taiwan** — an explicit statement of geographical difference.
 - Because AMAN is driven by **reversible conduction failure at the node of Ranvier** rather than axonal transection, **patients with AMAN have a prognosis comparable to AIDP** — an important corrective to the old teaching that "axonal GBS does badly".

GUIDELINE UPDATE — BEYOND THE TEXTBOOK

- **Beyond the prescribed textbooks — the specifically Indian data an examiner is asking for.** Bradley & Daroff 8e documents the Asian predominance of AMAN and the Taiwanese excess of Miller–Fisher syndrome but contains **no India-specific GBS epidemiology**; a full-text search of the three prescribed books returns no Indian GBS series. The following is therefore flagged as outside-source material, to be written in the exam as "Indian series report...".
- **Subtype mix:** Indian series consistently report a **higher proportion of axonal GBS (AMAN/AMSAN), of the order of 30%–50%**, against roughly 5%–10% in Europe and North America, with AIDP still the single commonest subtype in most Indian cohorts but by a much narrower margin. North Indian series report a higher axonal fraction than southern ones.
- **Antecedent events:** a higher proportion of antecedent **diarrhoeal illness** and *C. jejuni* seropositivity, reflecting endemic enteric infection; clustering in the summer and monsoon months rather than the winter peak seen in temperate countries.
- **Clinical profile:** younger mean age, male preponderance, more frequent presentation with pure motor quadriparesis, and (in the axonal forms) **less prominent sensory and cranial nerve involvement** with preserved or even brisk reflexes early on.
- **Differential diagnostic pressure:** in India the diagnosis must actively exclude **hypokalaemic periodic paralysis, acute poliomyelitis/enterovirus and vaccine-derived polio, diphtheritic neuropathy, organophosphate poisoning, snake-bite neurotoxicity, hypokalaemia from dengue and renal tubular acidosis, and myasthenic crisis** — a far wider list than in the Western setting.
- **Prognosis and access:** outcomes are worse in Indian series than in Western cohorts, but the dominant determinants are **cost and delayed access to IVIG or plasma exchange, and limited ICU/ventilator availability**, rather than a biologically different disease. **Small-volume plasma exchange** has been developed in India as a low-cost alternative where conventional apheresis is unaffordable. The 2016 **Zika** and, in India, the **dengue and chikungunya** associations should be mentioned as emerging triggers.
- **How to write it:** state the textbook fact first (AMAN is the commonest Asian subtype; *Campylobacter* drives it; AMAN has an AIDP-like prognosis because of reversible conduction failure), then add the Indian series as supporting epidemiology, then close with the cost-of-treatment point. That sequence answers the question as set.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- **Four pathologies, four patterns.** Wallerian degeneration, axonopathy, neuronopathy, segmental demyelination — name them first and the rest of the answer writes itself.
- **Amplitude = axons; velocity and latency = myelin.** Bradley's cut-off for demyelination is NCV < **70% of the LLN** with preserved amplitudes; conduction block and temporal dispersion at **non-entrapment** sites mean **acquired** demyelination.
- **Sural sparing plus abnormal F waves is 96% specific for AIDP** and is present in about half of patients in the first 2 weeks; the **sensory ratio** (sural + radial ÷ median + ulnar SNAPs) > 1 is the substitute in the elderly or in pre-existing CTS.
- **Palpably enlarged nerves** narrow the differential to six: leprosy, neurofibromatosis, CMT1/CMT3, acromegaly, Refsum disease and (rarely) CIDP.
- **MMN vs CIDP vs ALS** (Table 106.12) is a favourite viva: MMN — nerve-territory weakness, no sensory loss, prominent block, normal CSF, anti-GM1 50%–60%, **IVIG only**. CIDP — symmetrical, sensory loss present, high CSF protein, responds to steroids. ALS — myotomal weakness, UMN signs, no block.
- Steroids help CIDP but **not** GBS, and may **worsen** MMN. Getting that one line right is worth several marks.

Q2. Electrophysiological evaluation of AIDP.**INTERMEDIATE****Nerves §Intermediate Q1****6–8 marks**

Also asked as: Electrophysiology §Short Q11 — "Electrophysiological criteria for diagnosing GBS"

Source: Preston & Shapiro, *Electromyography and Neuromuscular Disorders*, 4th ed. — Ch. 29 *Polyneuropathy*, §Guillain-Barré Syndrome, pp. 498–500 (Box 29.5, p. 499; Figs. 29.7, 29.8). Supplementary: Bradley & Daroff, *Neurology in Clinical Practice*, 8th ed. — Ch. 106, §Diagnostic Studies, pp. 1883–1884.

1. Why the study is requested, and when

- NCS and EMG "play an important role in the diagnosis of GBS because **early recognition is necessary to begin appropriate treatment** and avoid potential medical complications".
- The electrodiagnostic consultant is asked to do two things: **exclude the mimics** (botulism, myasthenia gravis, critical illness neuropathy, porphyria) and **confirm multifocal demyelination**, the hallmark of acquired demyelinating polyneuropathy.
- **The picture evolves.** During the first few days all nerve conduction studies may be normal. About **half of patients have normal studies in the first 4 days** (apart from absent H reflexes) and only ~10% at one week. Demyelinating changes are present in **50% by 2 weeks and 85% by 3 weeks**; the studies become most specific in weeks 3 and 4. **A normal early study never excludes GBS — repeat it.**

2. The sequence in which abnormalities appear

Time from onset	Expected finding	Interpretation
Days 1–4	Absent H reflexes ; delayed, absent or impersistent F waves ; otherwise often normal	Earliest change; reflects proximal (root-level) demyelination — pathologically AIDP often begins as a polyradiculopathy

Time from onset	Expected finding	Interpretation
Week 1-2	Prolonged distal motor latencies ; sural sparing pattern on sensory studies; multiple or complex A waves ; reduced recruitment on needle EMG with normal MUAP morphology	Distal (nerve terminal) demyelination and proximal block. Sural sparing occurs in ~50% in the first 2 weeks
Week 2-4	Conduction block and temporal dispersion at non-entrapment sites; conduction velocity slowing; significant CMAP dispersion	The specific signature of acquired multifocal demyelination. Conduction block is seen in only 15%-30% of early GBS
> 3 weeks	Fibrillation potentials and positive sharp waves	Secondary axonal degeneration; appear 2-4 weeks after onset and carry a worse prognosis

Table 3 · Temporal evolution of electrodiagnostic findings in AIDP — Preston & Shapiro 4e, pp. 498-500; Bradley & Daroff 8e, pp. 1883-1884.

3. Preston's electrophysiological criteria for acute demyelinating polyneuropathy (Box 29.5) — learn the numbers

- **Demonstrate at least THREE of the following four in motor nerves:**
- **1. Prolonged distal latencies** — two or more nerves, not at entrapment sites
 - DL > **115% of ULN** when CMAP amplitude is normal.
 - DL > **125% of ULN** when CMAP amplitude is below the lower limit of normal.
- **2. Conduction velocity slowing** — two or more nerves, not across entrapment sites
 - CV < **90% of LLN** when CMAP amplitude is > 50% of LLN.
 - CV < **80% of LLN** when CMAP amplitude is < 50% of LLN.
 - *Note:* conduction velocities are commonly **preserved early** in AIDP.
- **3. Prolonged late responses** — one or more nerves
 - F response or H reflex > **125% of ULN**, or **absent F responses**.
 - *Note:* if the distal CMAP amplitude is very low, absent F waves may not be abnormal.
- **4. Conduction block / temporal dispersion** — one or more nerves
 - **Unequivocal conduction block:** proximal/distal CMAP **area** ratio < 0.50.
 - **Possible conduction block:** proximal/distal CMAP **amplitude** ratio < 0.70.
 - **Temporal dispersion:** proximal/distal CMAP **duration** ratio > 1.15.
- Preston notes that **for acute polyneuropathies the criteria for segmental demyelination are deliberately liberalised** compared with those used for CIDP.
- Bradley adds the alternative conduction-block rule used in GBS: a **> 50% decrease in CMAP amplitude** from distal to proximal stimulation in the absence of temporal dispersion. About **two-thirds** of patients fulfil criteria for highly suggestive or definite AIDP in the first 2 weeks, with specificity 95%-100%.

4. Sensory studies — the sural sparing pattern

- **Sural sparing** = normal sural sensory response with reduced or absent median and ulnar sensory potentials. "Many believe that sural sparing in the presence of a typical clinical picture is **virtually diagnostic of AIDP**."
- **Why it happens:** AIDP preferentially affects the **smaller myelinated fibres** first. Counter-intuitively the recorded sural fibres are **larger** (recorded in the calf, where the nerve is

not tapered) than the median and ulnar sensory fibres recorded over the fingers, and larger fibres resist the early inflammatory attack.

- This pattern is **very unusual in a typical axonal dying-back polyneuropathy**, in which the sural is affected first.
- **Sural sparing + abnormal F waves is 96% specific** for AIDP (Bradley, p. 1883); the **sensory ratio** — (sural + radial SNAPs) ÷ (median + ulnar SNAPs) — is a good substitute in the elderly with absent sural responses or pre-existing CTS, a **ratio > 1** being fairly specific and separating GBS from diabetic and other axonal neuropathies.

5. Needle EMG in AIDP

- The characteristic **demyelinating pattern: no denervation, normal MUAP morphology, reduced recruitment in weak muscles**.
- Exceptionally, **larger MUAPs** appear early — these are **not** reinnervated units. The small MUAPs (innervated by small myelinated fibres) are blocked first, "uncovering" the normally late-recruited large MUAPs that are usually buried in the interference pattern.
- Usually **no abnormal spontaneous activity at rest** early; the only exception is occasional **myokymic discharges**, especially in the face, even without clinical myokymia.
- Fibrillation potentials at 2–4 weeks indicate secondary axonal loss.

6. Pitfalls and prognostic value

- **10% of patients never fulfil criteria** for acquired demyelination, sometimes simply because motor responses are absent.
- Some patients have **inexcitable nerves** early, from either secondary wallerian degeneration or presumed **distal demyelination** — low distal CMAPs therefore do not by themselves prove axonal loss. **Rapid recovery of low distal CMAPs and SNAPs on serial studies confirms distal demyelination**.
- Inability to distinguish demyelinating conduction block from **reversible conduction failure** and from axon-discontinuity block caused **erroneous classification in up to one-third** of GBS patients, the initial classification changing after serial recordings (Rajabally, 2015). **Serial studies are therefore mandatory before labelling a patient AMAN**.
- **Prognosis:** "EDX parameters are the most reliable indicators of prognosis" — a mean distal CMAP amplitude < **20% of LLN** predicts poor outcome.
- If the syndrome is **pure motor and axonal** → AMAN; if **motor and sensory axonal** → AMSAN, and Preston insists these patients must be **screened for porphyria**.

HIGH-YIELD — CLINICAL PEARLS / EXAM POINTS

- Order the study but **do not expect it to be diagnostic in the first four days** — absent H reflexes and abnormal F waves are all you may get.
- **Three of four criteria** in Box 29.5: DL > 115%/125% ULN, CV < 90%/80% LLN, F > 125% ULN or absent, and block (area ratio < 0.50) or dispersion (duration ratio > 1.15).
- **Sural sparing** is the single most quotable sign; explain it by fibre size, not by length-dependence.
- Needle EMG early shows **reduced recruitment with normal-looking motor units and no fibrillations** — that combination is the demyelinating pattern.
- Repeat the study at 3–5 weeks: it distinguishes **AIDP** from **AMAN with reversible conduction failure**, and picks up the patients who are really developing **acute-onset CIDP**.

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