Cognitive load in neurodegeneration: Predictive processing, dopaminergic modulation, and AI modeling for mitigating decline

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Abstract

Cognitive load (CL) reflects the brain's finite information-processing capacity; performance declines when task demands exceed available resources. In Parkinson's disease, CL is amplified by frontostriatal dysfunction, producing deficits in attention, working memory, and cognitive control. Dopamine modulates CL by shaping signal-to-noise ratios, gating information, and balancing cognitive stability and flexibility. In a predictive processing framework, the brain minimizes CL by building internal models and selectively responding to prediction errors, with dopaminergic signaling encoding their precision. Similar constraints arise in AI systems, where attention mechanisms, context limits, and optimization objectives mirror biological resource allocation. These parallels support AI-based modeling of cognitive decline, integrating biomarkers and cognitive reserve to improve predictive accuracy. Extending this view, socially informed approaches treat cognition as an emergent property of human-AI interaction, offering directions to understand and mitigate CL in aging and neurodegeneration and to develop hybrid systems that exceed traditional modeling limits.

Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
6-OHDA	6-hydroxydopamine
Aβ42	amyloid-β_{1-42}
ACC	anterior cingulate cortex
AD	Alzheimer's disease
ADHD	attention-deficit/hyperactivity disorder
AI	artificial intelligence
ANNs	artificial neural networks
ANS	autonomic nervous system
APOE	apolipoprotein E
AR/VR	augmented/virtual reality
ASD	autism spectrum disorder
BDNF	brain-derived neurotrophic factor
BG	basal ganglia
BP	backpropagation
BPR	backpropagation rule
ΔC	complexity gap
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CL	cognitive load
CLT	cognitive load theory
CNNs	convolutional neural networks
CNS	central nervous system
COG-LOAD	cognitive load test
COMT	catechol-O-methyltransferase
CR	cognitive reserve
CRP	C-reactive protein
CSF	cerebrospinal fluid
D	distortion of information
DAT	dopamine transporter

DAT-SPECT	dopamine transporter single-photon emission computed tomography
DLB	dementia with Lewy bodies
dlPFC	dorsolateral prefrontal cortex
DMC	Dual Mechanisms of Control framework
DMN	default mode network
DNNs	deep neural networks
DOPA	3,4-dihydroxyphenylalanine
ECL	extraneous cognitive load
EDA	electrodermal activity
EDS	excessive daytime sleepiness
EEG	electroencephalography
EGF	epidermal growth factor
EM-COGLOAD	recordings of eye movement under different cognitive loads
ERE	expertise reversal effect
ERP	event-related potentials
ExPlas	exercised plasma
FFP	fresh frozen plasma
FGF	fibroblast growth factor
FLOPs	floating-point operations
fMRI	functional magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
ΔG	generalization gap
GARS	Genetic Addiction Risk Score
GBA	glucocerebrosidase
GCL	germane cognitive load
GFAP	glial fibrillary acidic protein
GPUs	graphics processing units
HPA	hypothalamic–pituitary–adrenal (axis)
HR	heart rate
HRV	heart rate variability
I1–I3	first to third intracellular loops of dopamine receptors
IB	information bottleneck
ICL	intrinsic cognitive load
IES	inverse efficiency score
IL-6	interleukin-6
L-DOPA	levodopa (S) enantiomer of DOPA
LLMs	large language models
lPFC	lateral prefrontal cortex
LTM	long-term memory
MAPT	microtubule-associated protein tau
MCI	mild cognitive impairment
MDD	major depressive disorder
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MEG	magnetoencephalography
ML	machine learning
MMSE	Mini-Mental State Examination

MoCA	Montreal Cognitive Assessment
MS	multiple sclerosis
MSA	multiple system atrophy
MSE	mean squared error
MSNs	medium spiny neurons
NAc	nucleus accumbens
NASA-TLX	NASA Task Load Index
NfL	neurofilament light chain
NLRP1	Nucleotide-binding oligomerization Leucine-rich Repeat Protein 1
NLRP3	Nucleotide-binding oligomerization Leucine-rich Repeat Protein 3
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PD-MCI	Parkinson's disease – mild cognitive impairment
PET	positron emission tomography
PFC	prefrontal cortex
PP	predictive processing
pRBD	probable REM sleep behavior disorder
R	rate of representation
RAM	random access memory
REM	rapid eye movements
RDS	reward deficiency syndrome
RT	reaction time
SAA	seed amplification assay
scRNAseq	single cell RNA sequencing
SCD	subjective cognitive decline
SCZ	schizophrenia
SE	squared error
SHAP	SHapley Additive exPlanations analysis
SMA	supplementary motor area
SNc	substantia nigrapars compacta
SPNs	striatal projection neurons
STN	subthalamic nucleus
STSP	short-term synaptic plasticity
SVMs	support vector machines
TCL	total cognitive load
TH	tyrosine hydroxylase
TMS	transcranial magnetic stimulation
TNF-α	tumor necrosis factor-α
vlPFC	ventrolateral prefrontal cortex
VMAT	vesicular monoamine transporter (for dopamine noradrenaline and serotonin)
VRAM	video RAM
VTA	ventral tegmental area
WM	working memory
XANN	explainable artificial neural network

1. Introduction

1.1 Cognitive load: Theory and core concepts

Cognitive load theory (CLT), introduced by Sweller (Sweller, 1988), focuses on how working memory (WM) handles information during learning. Because WM has limited capacity, learning is most effective when CL is managed effectively. CLT defines three main types of CL. Intrinsic CL (ICL) refers to the inherent difficulty of the material (complex topics naturally demand more cognitive resources) and cannot be eliminated, only managed (e.g., by chunking or sequencing). Extraneous CL (ECL) arises from poorly designed instruction or irrelevant information and should be minimized. Germane CL (GCL) represents the cognitive effort devoted to creating schemas and understanding; thus, it should be fostered. Fig. 1 illustrates these loads and their relationships.

ICL is determined by task complexity, specifically the number of interacting elements processed simultaneously. For example, learning simple

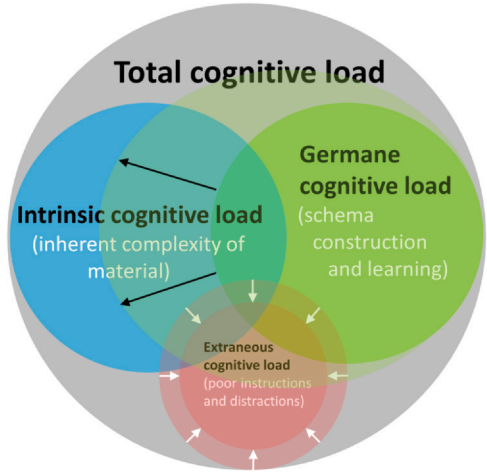

Fig. 1 Schematic representation of three types of cognitive load. The intrinsic CL (ICL) circle denotes inherent task complexity; extraneous CL (ECL) denotes unnecessary load from poor instruction or distraction; and germane CL (GCL) denotes resources allocated to learning and schema construction. CLT posits that effective instructional design minimizes ECL and optimizes GCL through clear presentation, elimination of irrelevant information, and promotion of active integration with prior knowledge. The aim is to reduce ECL and its overlap with other loads (shown by white arrows), while expanding GCL to maximize its overlap with ICL (shown by black arrows), illustrating their dynamic interplay and the need to free cognitive resources for meaningful learning. The total area reflects total CL (TCL). See text for details.

definitions imposes low ICL, whereas multi-step problems or complex physiological mechanisms impose high ICL. As an inherent property, ICL cannot be eliminated but can be managed (e.g., by breaking material into smaller parts or sequencing). GCL reflects mental effort devoted to schema construction and long-term memory (LTM) consolidation. Activities such as explaining concepts in one's own words, making associations, or integrating new information with prior knowledge increase GCL. The size of the ICL circle addresses task difficulty answering the question "How hard is the material?", whereas GCL reflects beneficial learner effort, i.e. answers the question "How much effort is going into actually learning it?". A central CLT objective is to manage ICL so that it fits within WM limits while maximizing GCL, ensuring that learners use their cognitive resources for meaningful learning rather than being overwhelmed. ECL arises from instructional design: poorly structured materials, such as cluttered diagrams, split attention/sources of information, or unnecessary repetition, impose unnecessary WM load without supporting learning.

CLT is grounded in a model of human cognitive architecture that emphasizes the dynamic relationship between WM and LTM. This architecture has been shaped by evolutionary pressures, resulting in a distinction between biologically primary knowledge, such as language and social interaction, acquired effortlessly (i.e. without formal instruction), and biologically secondary knowledge (e.g., literacy, mathematical abilities), which requires deliberate effort and explicit teaching and is the core focus of CLT (Sweller, 2011). Acquisition of secondary knowledge parallels evolutionary processes, governed by principles of information storage, generation, and selection. Effective cognition relies on well-organized schemas in LTM that support pattern recognition and efficient problem solving. Research on expertise, such as studies of chess players, shows that experts outperform novices not due to superior general intelligence but because they possess richly developed schemas enabling rapid pattern recognition and decision-making (Williams et al., 2025). Most knowledge in LTM is acquired through interaction with others and the environment; learners assimilate information through instruction, imitation, or reading and reorganize it to fit existing knowledge structures. When faced with unfamiliar situations, novel problems are addressed through trial and error, with solutions tested until an effective one is found. This process is constrained by the limited capacity and duration of WM, which can hold only a small number of elements for a brief period, making WM highly susceptible to overload. These constraints necessitate structured instruction. The environment also guides cognition, as external cues facilitate

relevant schemas stored in LTM, enabling individuals to interpret and respond to new information efficiently. With increasing expertise, reliance on stored schemas effectively extends WM capacity for familiar tasks.

Instructional design in CLT targets all three CLs: reducing ECL, managing ICL relative to learner expertise, and fostering GCL to promote meaningful learning. Effective strategies include worked examples to reduce unnecessary processing, integration of information sources to avoid split attention, and coordinated use of visual and auditory channels (modality effect). Redundant information should be avoided, as it consumes limited resources. Instructional effectiveness is expertise-dependent: as knowledge increases, previously beneficial guidance may become redundant or detrimental (*expertise reversal effect*, ERE) (Kalyuga et al., 2023). Accordingly, guidance should be progressively withdrawn. With sufficient expertise, even mental rehearsal alone can be a powerful learning strategy. Conversely, some technologies increase CL by presenting transient information that is difficult to process and retain (typical examples include fast-moving slides or animations; audio- or video-only explanations without options to pause, rewind or capture content; live lectures and webinars in which information is delivered continuously; scrolling feeds with ephemeral content; and AR/VR overlays that present changing information in real time without persistence, requiring users to remember earlier information while processing new instructions).

Despite its contributions, CLT has been criticized for overemphasizing CL minimization within a WM framework, potentially constraining active learning and exploration in modern learning environments (Gkintoni et al., 2025), and for limited consideration of individual, motivational, and affective factors such as autonomy and self-determination (Evans et al., 2024). In a study of 136 university students, pre-training using concept maps and glossaries reduced ECL across all learners and increased GCL in those with higher prior knowledge, indicating enhanced schema refinement (rather than the CLT-predicted effects of overload and redundancy) (Gorbunova et al., 2025). Contrary to ERE-predictions, pre-training benefited even more knowledgeable learners. Although ICL did not decrease for low prior-knowledge learners, reduced ECL improved performance, underscoring the importance of aligning instruction with prior knowledge. Despite concerns regarding replicability, CLT remains a robust framework that provides practical principles and tools for improving learning efficiency, fostering deep understanding, and supporting expertise development, particularly in domains of biologically secondary knowledge.

1.2 Measuring cognitive load

CL denotes the mental effort required to perform a task and reflects limits in information-processing capacity during task execution. These limits arise from finite cognitive resources, including attention, WM, and executive functions; when task demands exceed available resources, processing efficiency declines. Thus, there is an upper bound on the information that biological or artificial intelligence (AI) systems can process at a given time. High-demand or concurrent tasks create cognitive bottlenecks, slowing processing, increasing errors, and inducing fatigue, particularly by taxing attention and WM (Bažadona et al., 2020). Although relatively stable, these limits vary across individuals and are modulated by age, fatigue, stress, task complexity (Plass & Kalyuga, 2018; Wang et al., 2025), autonomic arousal and emotional load (Šimić et al., 2021; Chikhi et al., 2022), experience (Boos et al., 2022), and intrinsic motivation (Kührt et al., 2023).

CL is typically assessed using four complementary approaches: (1) subjective reports, (2) behavioral performance (the most common; accounting for approximately 19 % of studies), (3) physiological signals, and (4) neurophysiological measures. Multimodal approaches increasingly combine these methods with machine learning (ML) to improve validity and enable real-time classification of CL (Darejeh et al., 2026).

Subjective measures rely on self-reported task demand. Widely used instruments include the *Paas Cognitive Load Scale* (nine-point mental effort rating) and the *NASA Task Load Index* (NASA-TLX), which assesses mental, physical, and temporal demand, performance, effort, and frustration. NASA-TLX is the second most frequently used method (~12 %) (Darejeh et al., 2026). These tools are simple and cost-effective but are susceptible to bias, memory effects, and imperfect correspondence with actual resource use; baseline or control tasks are therefore recommended for comparison.

Behavioral measures infer CL from task performance, including accuracy, error rates, processing speed, reaction times, and response pacing. Dual-task paradigms probe resource limits by requiring simultaneous task execution; performance decrements indicate reduced available capacity. Learning curves and adaptation patterns provide additional insight into demand dynamics. Although objective, these measures can be confounded by motivation, fatigue, or strategy. Accordingly, studies often pre-register expected load differences and combine behavioral with other indices.

The cognitive load (COG-LOAD) paradigm, often applied in Parkinson's disease (PD), probes executive and WM load sensitivity but is

not disease-specific. Its strongest effects occur in disorders affecting frontostriatal systems. In PD, performance declines disproportionately with increasing CL, reflecting frontostriatal dysfunction in basal ganglia, BG, – prefrontal cortex, PFC, loops, and manifesting as reduced WM capacity, impaired dual-tasking, and load-dependent slowing. These effects are detectable early, including in PD with mild cognitive impairment (PD-MCI) and PD dementia (PDD). Similar but non-specific patterns occur in schizophrenia (SCZ, marked WM deficits, often larger than PD), attention-deficit/hyperactivity disorder (ADHD, difficulty sustaining performance under increasing CL), Alzheimer's disease (AD, impairment at higher loads reflecting memory storage deficits rather than executive dysfunction), and Multiple sclerosis (MS, fatigue and slowed processing under load). Thus, CL paradigms are most characteristic of frontostriatal dysfunction (e.g., PD, ADHD) but lack diagnostic specificity. The Eye Movement under differing COGnitive LOADs (EM-COGLOAD) dataset (from 75 healthy adults) demonstrated that deep learning applied to eye movements can classify high vs. low CL with 87.5 % accuracy and distinguish age groups with 76 % accuracy, supporting non-invasive assessment of cognitive function and age-related changes (Miles et al., 2024).

Among task paradigms, the most sensitive to early PD-related executive dysfunction are the N-back task, dual-task gait, and Stroop under load. The *N-back task* assesses WM updating by requiring detection of stimuli presented N steps earlier. Load increases with N, engaging the dorsolateral PFC (dlPFC). In PD, performance is near-normal at low loads (0-back or 1-back) but declines disproportionately at higher loads (2 to 3-back), with increased reaction times (RT) even when accuracy is preserved. This sensitivity reflects disruption of dopaminergic frontostriatal circuits and often precedes global cognitive decline and development of PDD.

Dual-task gait paradigms capture competition between motor and executive processes. In PD, concurrent cognitive tasks (e.g., serial subtraction or word generation) induce gait slowing or freezing, reflecting impaired attentional allocation and reduced locomotor automaticity (Raffegeau et al., 2019; Imaizumi et al., 2026). Neurophysiological data show load-dependent modulation of subthalamic nucleus (STN) activity (Georgiades et al., 2023) and increased PFC activation measured by functional near-infrared spectroscopy (fNIRS), consistent with compensatory recruitment (Kvist et al., 2026). Increased prefrontal activity correlates with gait variability and dual-task costs, indicating reduced efficiency. This paradigm is clinically relevant for early detection, fall risk, and disease progression. Regarding electroencephalography

(EEG) spectral changes in PD, dual-task walking is associated with an early reduction in delta and theta power, followed by a later increase in beta power. Compared with older adults, individuals with PD also exhibit increased alpha and beta power during both single- and dual-task conditions (Possti et al., 2021). Task difficulty further modulates these effects: individuals with PD show greater dual-task-related declines in step length and velocity during more demanding cognitive tasks, accompanied by decreases in delta power in frontal and motor regions and beta power in parietal regions (Imaizumi et al., 2026).

The *Stroop task* measures inhibitory control and interference resolution under CL. The typical pattern in PD patients is increased Stroop interference, i.e. slower, more error-prone responses on incongruent trials (e.g., the word "red" printed in blue ink, where the correct response is "blue"), regardless of their impulsivity (Djamshidian et al., 2012). The neural correlate of this pattern reflects dysfunction in dlPFC – anterior cingulate cortex (ACC) – BG circuits. The BG, particularly the striatum and STN, play an essential role in the Stroop task as they contribute to action selection and gating by enabling the correct response (color naming) while suppressing the competing automatic response (word reading). They are also central to inhibitory control, as the hyperdirect pathway, involving the STN, allows rapid suppression of automatic responses. In addition, the BG help adjust response thresholds, modulating how much evidence is required before making a response, which is particularly important under conditions of conflict. This system is highly relevant in PD, where dopamine depletion disrupts BG circuits, leading to impairments in efficient response selection, inhibition, and threshold adjustment, and resulting in inefficient suppression of automatic (habitual) responses. As a result, PD patients typically show greater Stroop interference, reflected in slower and more error-prone performance on incongruent trials. In a full network view, the ACC detects conflict, the dlPFC sets control, the ventrolateral PFC (vlPFC) and inferior frontal gyrus support response inhibition, the parietal cortex allocates attention, the supplementary motor area (SMA) and pre-SMA prepare responses, and the BG gate and select the final action.

Additional neuropsychological tests include the *Trail Making Test, especially part B*, which assesses cognitive flexibility and shows disproportionate slowing in PD (relative to Part A and is therefore widely used as a screening tool for PD-MCI), and the *Wisconsin card sorting test*, which reveals increased perseverative errors due to impaired cognitive flexibility and set shifting. Collectively, these findings indicate that CL sensitivity in PD arises from frontostriatal dysfunction, in contrast to AD, where deficits primarily reflect medial temporal lobe episodic memory impairment.

Physiological measures provide indirect indices of effort and arousal and support real-time monitoring. As pupil diameter typically increases with greater WM demand or mental calculation, *pupillometry* is used in about 11 % of CL studies. It tracks load-related pupil dilation but requires strict control of luminance and pharmacological influences (Darejeh et al., 2026). *Cardiac measures*, including heart rate and heart-rate variability (HR/HRV), reflect autonomic effort but are also sensitive to stress, fitness, caffeine intake, respiration, and physiological state. Skin conductance, electrodermal activity (EDA), measures sweat gland activity and is sensitive to arousal and engagement, but lacks specificity to CL. Respiration rate and perceived breathing effort can reflect workload but are less commonly used in isolation and are typically included in multi-sensor setups. Additional eye-tracking metrics, including fixation duration, saccade rate, and scan-path complexity, provide further insight into processing demands and strategies under varying levels of CL.

Neurophysiological measures directly capture brain dynamics. EEG and event-related potentials (ERPs) provide high temporal resolution for tracking load-dependent processes. While frontal theta power often increases with higher WM load, intracranial recording data reveal region-specific patterns (decreases in theta activity in the PFC and increases in the hippocampus), suggesting context-dependent roles in prediction-error signaling and precision weighting (Brzezicka et al., 2019; Snipes et al., 2022). As WM load increases, brain oscillations are modulated not only by elevated frontal theta but also by changes in theta-gamma and theta-beta cross-frequency coupling. Together, these dynamics help regulate how frontal control hubs coordinate with posterior sensory areas to update predictions and optimize behavior (Fernández et al., 2021). The apparent contradiction, often referred to as the "theta paradox", whereby increased theta activity is observed in both during cognitive control and WM tasks and during states of low-alertness or disengagement, reflects the spatial heterogeneity of underlying processes: different brain regions contribute distinct prediction-error signals and precision-weighting mechanisms, depending on the functional context (Chikhi et al., 2022). For example, a study examining EEG power and coherence in patients with PD-MCI during a WM task (Jiang, 2005) found that PD-MCI patients exhibited higher EEG power and coherence compared to healthy controls. This pattern may indicate compensatory effort, with the brain working harder to maintain performance despite cognitive deficits, consistent with CLT's notion that mental effort increases under high cognitive demands. Although this evidence remains indirect, the observed

negative correlation between EEG power and Mini-Mental State Examination (MMSE) scores further supports this interpretation: as cognitive impairment increases (i.e., lower MMSE scores), neural effort (indexed by higher EEG power) also rises during WM tasks. The study also suggests that PD-MCI is associated with disrupted cortical connectivity, implying that impaired neural efficiency necessitates greater activation to achieve performance levels comparable to healthy individuals (Jiang, 2005).

As exemplified above, when it was coupled with single- and dual-task paradigms, fNIRS measures changes in cortical blood-oxygenation and is commonly used to assess PFC engagement. It is portable and relatively tolerant of movement but is limited to superficial cortical regions and offers lower spatial resolution. Functional magnetic resonance imaging (fMRI), identifies distributed CL-related networks (dlPFC, parietal, cingulate) with high spatial, but low temporal resolution. Magnetoencephalography (MEG) and multimodal combinations (e.g., EEG with pupillometry or fNIRS), can further improve sensitivity to load-related neural dynamics. Increasingly, studies integrate subjective, behavioral, and physiological data to improve reliability and enable ML-based classification of CL levels. Common features include EEG theta power, pupil dilation, and composite performance metrics such as the inverse efficiency score (IES), which is calculated by dividing mean RT by the proportion of correct responses. This composite measure captures both speed and accuracy, with higher values indicating slower/less accurate performance (Wang et al., 2025). Calibration tasks are used to establish participant-specific baselines, although models may still require task- or domain-specific training to generalize effectively.

Method selection depends on research context: educational studies often combine subjective and physiological measures; safety-critical domains (aviation, driving) favor real-time EEG and pupillometry, supplemented by HRV and EDA; human-computer interaction studies frequently rely on lightweight wearable sensors and performance metrics; and controlled laboratory experiments employ fMRI or MEG to obtain deeper mechanistic insight. Regardless of modality, careful attention to *validity and reliability* is essential. Validity requires controlling confounding variables (e.g., fatigue, stress, lighting) and using within-subject baselines. Because CL is dynamic and multidimensional, converging evidence across methods provides the most robust assessment. Future directions include non-intrusive sensing, explainable ML, ecologically valid multimodal datasets, and adaptive systems that respond to user cognitive state, with applications spanning education, augmented/virtual reality (AR/VR), human-computer interaction, and safety-critical operations.

1.3 Cognitive load in Parkinson's disease: Clinical and neurobiological correlates

Using paper chromatography, Montagu first demonstrated the presence of dopamine – or, more precisely, its precursor – in human central nervous system (CNS) tissue in 1957 (Montagu, 1957). Later that year, Carlsson and colleagues showed that the effects of intraperitoneal administration of reserpine, an inhibitor of the vesicular monoamine transporter (VMAT) for dopamine, noradrenaline, and serotonin, in mice and rabbits could be reversed by injection of a racemic mixture of the dopamine precursor 3,4-dihydroxyphenylalanine (DOPA). Carlsson was subsequently awarded the Nobel Prize (2000) for this work, shared with Greengard, who demonstrated that dopamine can produce long-term modulation of neuronal function via receptor-mediated intracellular signaling. In 1960, Hornykiewicz, using fluorimetric analysis of post-mortem brain samples from individuals with PD, demonstrated profoundly reduced levels of dopamine in the striatum, particularly in the putamen and caudate nucleus (80–90 %) (Ehringer & Hornykiewicz, 1960), linking nigrostriatal degeneration to major motor symptoms of PD (bradykinesia, resting tremor, rigidity, and postural instability), thereby establishing PD as a *disorder of dopaminergic transmission*.

These discoveries soon led to the development of dopaminergic replacement therapy for PD with levodopa (L-DOPA), the (S)-enantiomer of DOPA. In 1961, Birkmayer and Hornykiewicz reported rapid motor improvement following intravenous levodopa administration, marking a therapeutic breakthrough and the foundation of modern PD treatment (Birkmayer & Hornykiewicz, 1961). The results were striking: rigid, akinetic patients regained motor function within minutes. This milestone marked the beginning of the era of dopaminergic replacement therapy and ultimately led to the development of oral levodopa treatment. Dopamine is now recognized as central not only to PD but also for explaining a wide range of normal human behaviors, from romantic love to planned (proactive, instrumental) aggression (Šimić et al., 2021), as well as numerous psychiatric and neurological disorders, including SCZ, addiction, AD, autism spectrum disorder (ASD), major depressive disorder (MDD), ADHD, Down syndrome, and fragile X syndrome (Cragg & Walton, 2025). Research on the neuroanatomy of the dopaminergic system, including the topographical organization of dopaminergic neuronal groups, their projections, and circuitry, is therefore crucial for elucidating both its physiological function and disease mechanisms.

Pharmacological modulation of dopamine underpins treatment of multiple psychiatric disorders, including SCZ and ADHD (Howes & Kapur, 2009). SCZ is typically treated with antipsychotics such as haloperidol, risperidone, olanzapine, and clozapine, which primarily act as D2 receptor antagonists, reducing mesolimbic hyperdopaminergia associated with positive symptoms such as hallucinations and delusions (Stahl, 2021). This is consistent with the classic dopamine hypothesis of psychosis, supported by the psychotomimetic effects of amphetamines that cause a paranoid psychosis similar to the psychosis in schizophrenia, and the efficacy of drugs that block dopamine D2 receptors (which have been the mainstay of treatment for essentially all forms of psychosis for over 50 years) (Stahl, 2021). However, mesocortical hypodopaminergia contributes to negative and cognitive symptoms in SCZ, which are much more difficult to treat (Howes & Kapur, 2009). In contrast, ADHD treatments, such as methylphenidate and amphetamines, increase synaptic dopamine release by inhibiting the dopamine transporter (DAT), thus enhancing attention, executive control, and impulse regulation (Faraone & Buitelaar, 2010).

Dopamine receptor subtype and pathway specificity are critical: D1-like receptors (D1, D5) support prefrontal cognitive processes, while D2-like receptors (D2, D3, and D4) regulate motivation and motor function and represent primary antipsychotic targets. D1 and D2 dopamine receptors are illustrated in Fig. 2.

Drugs differ in their modulation: many antipsychotics combine D2 antagonism with 5-hydroxytryptamine (5-HT) 2A serotonergic receptor blockade or partial agonism to balance efficacy and tolerability, while ADHD stimulants boost cortical dopamine (and noradrenaline) to improve attention and cognitive control. Treatment choice is shaped by receptor pharmacology, network effects (e.g., dopamine-rich circuits), safety, and individual response, with clinicians tailoring therapy to specific symptom domains and tolerability.

In PD, D1 and D2 receptor agonists aim to compensate for deficient dopaminergic transmission in the direct motor pathway through the BG, but D1 agonists proved clinically impractical due to poor pharmacokinetics, tolerability issues, and inconsistent efficacy (Connolly & Lang, 2014). Consequently, D2/D3 agonists (pramipexole, ropinirole, and rotigotine) became the mainstay of PD therapy (as well as for restless legs syndrome and periodic limb movement disorder), as they are easier to develop, provide reliable motor benefit by suppressing the overactive indirect motor pathway through the BG, and can be used alone in early

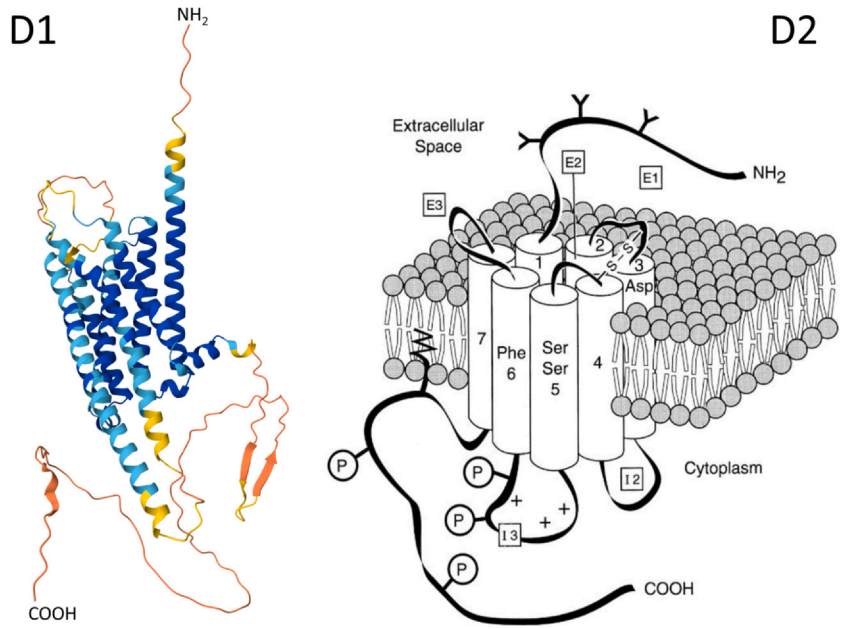

Fig. 2 Illustration of the structures of D1 and D2 receptors. All dopamine receptors have seven transmembrane domains. Left: the D1 dopamine receptor, visualized based on a primary sequence of 446 amino acids using AlphaFold 3 https://alphafoldserver.com/; (Abramson et al., 2024). Right: the D2 dopamine receptor is schematically represented, showing seven transmembrane domains (labeled 1–7), three extracellular loops (E1–E3) and three intracellular loops (I1–I3). Dopamine and its agonists bind within the so-called binding pocket, located in the hydrophobic region of the transmembrane domains. Potential phosphorylation sites, which are important for regulating receptor function, are located in the third intracellular loop (I3) and at the C-terminal end of the receptor. Potential glycosylation sites are mainly located at the N-terminal end. *Adapted from Missale et al. (1998).*

disease or with levodopa in advanced stages (Isaacson et al., 2023). However, in a minority of patients, D2/D3 agonists may cause impulse control disorders (e.g., gambling, compulsive shopping, hypersexuality), a risk that requires monitoring but is not a strict contraindication (Seeman, 2015). These effects are linked to stimulation of the mesolimbic dopaminergic reward system, which enhances reward-seeking behavior mainly through D3 receptors.

Beyond these behavioral effects, dopamine dysfunction also underlies the motor and cognitive features of PD. These symptoms may be understood as the brain's attempt to compensate for reduced dopaminergic efficiency, particularly within frontostriatal circuits, and therefore reflect an

increased CL. The major motor deficits of PD are traditionally summarized as four cardinal features arising from degeneration of dopaminergic neurons in the *substantia nigra, pars compacta* (SNc) and dysfunction of BG circuits. The core feature is *bradykinesia*, or slowness of movement, which manifests as delayed initiation and reduced speed and amplitude of voluntary and repetitive movements. Clinically, it may present as hypomimia (reduced facial expression), micrographia (abnormally small handwriting), and difficulty with fine motor tasks such as buttoning clothes or typing. *Resting tremor*, typically 4–6 Hz, often begins unilaterally and is classically described as a "pill-rolling" movement; it diminishes with voluntary movement and during sleep. *Rigidity* refers to increased muscle tone independent of movement velocity and may appear as *lead-pipe or cogwheel rigidity*. The fourth cardinal feature, *postural instability*, reflects impaired balance and defective postural reflexes and becomes more prominent with disease progression, often leading to falls. Findings such as retropulsion, propulsion, and impaired righting reflexes are characteristic. Together, these features define the parkinsonian syndrome.

Apart from this tetrad, additional motor manifestations are common, including *gait disturbances* such as shuffling gait, reduced arm swing, freezing of gait, and festination that progressively impair mobility. These features are particularly relevant in the context of CL, as gait becomes increasingly dependent on higher-order cognitive control in PD. Dual-task paradigms, where motor and cognitive demands are combined, have demonstrated that cognitive control is more easily disrupted under increased load, revealing deficits not always apparent under single-task conditions (Montero-Odasso et al., 2012). In this context, quantitative gait analysis, increasingly supported by wearable technologies, provides a non-invasive window into the brain's ability to manage simultaneous motor and cognitive demands (Amboni et al., 2012; Pyo et al., 2017). Wearable devices further enable continuous and ecologically valid monitoring of gait performance and fall risk in real-world settings (Mason et al., 2022). Speech disturbances, such as *hypokinetic dysarthria* characterized by soft, monotonous speech, and postural abnormalities (e.g., camptocormia, Pisa syndrome) may also develop. Beyond motor impairment, PD is a multisystem disorder with prominent *non-motor symptoms*, which are highly prevalent and often precede the classic motor syndrome, reflecting widespread neurodegeneration beyond the dopaminergic system. Neuropsychiatric manifestations include depression, anxiety, apathy, impulse control disorders (often associated with

dopaminergic therapy), and psychosis, while cognitive impairment frequently involves executive dysfunction, slowed processing, and visuospatial deficits, potentially progressing to PDD.

Sleep disturbances represent another major non-motor feature of PD, including insomnia, excessive daytime sleepiness (EDS), restless legs syndrome, and probable REM sleep behavior disorder (pRBD), which may precede motor symptoms by years or even decades (St Louis & Boeve, 2018). RBD, characterized by loss of normal REM (rapid eye movements) sleep atonia and dream enactment behaviors (Hu, 2020), is considered a reliable early marker of synucleinopathies, particularly dementia with Lewy bodies (DLB) and PD (Boeve, 2013). In contrast, although sleep-wake disturbances also occur in AD, notably reduced slow-wave sleep associated with cognitive decline (Šimić et al., 2014), RBD is typically absent (Boeve et al., 2013). RBD is more prevalent in men and is often associated with vivid, action-filled, and sometimes violent dreams. Motor activity during episodes is usually simple, although injuries to patients and bed partners are relatively common due to falls or abrupt movements during sleep (Hu, 2020). Neurobiologically, REM sleep regulation depends on brainstem circuits involving pontine centers including the noradrenergic subcoeruleus (A4)/glutamatergic sublateral dorsal nucleus, the noradrenergic locus coeruleus (A6), the cholinergic pedunculopontine (Ch5) and laterodorsal tegmental nuclei (Ch6), as well as the medullary magnocellular reticular formation, with additional modulation by the hypothalamus, thalamus, SNc, basal forebrain, limbic system, and frontal cortex (Sakai et al., 1979). RBD is thought to arise from dysfunction within this network, particularly involving mechanisms that regulate REM atonia. Degeneration in these pathways – commonly associated with α-synuclein accumulation – likely underlies its strong link to synucleinopathies such as PD, DLB, and multiple system atrophy (MSA) (Boeve et al., 2013). Although most cases are neurodegenerative in origin, RBD may also occur secondary to autoimmune, inflammatory, or structural brain disorders, as well as certain medications (Hu, 2020). In addition to sleep disturbances, cortical features such as visuospatial deficits, visual hallucinations, and fluctuations in attention and awareness are frequently observed, particularly in DLB (Pizzi et al., 2015; Matar et al., 2020). These fluctuations are especially relevant in the context of CL, as they reflect instability in attentional control and cognitive processing, which may further compromise motor performance under dual-task conditions. In conclusion, sleep disturbances (specifically pRBD, EDS,

and insomnia) are associated with cognitive decline in early PD (Zhong et al., 2024). Furthermore, EDS and pRBD are linked to a decrease in CSF Aβ42, and pRBD is associated with a higher risk of conversion to PDD (Zhong et al., 2024).

Autonomic nervous system (ANS) dysfunction, sensory abnormalities (including hyposmia – reduced ability to smell, or anosmia – total inability to detect odors), and gastrointestinal symptoms (constipation) further emphasize the multisystem nature of PD. Notably, olfactory impairment, constipation, RBD, depression or anxiety, and subtle ANS dysfunction are among the earliest recognized features of the disease. These non-motor features can precede the clinical diagnosis by as much as 10–20 years, and often follow a temporal progression described by the Braak staging, beginning in the olfactory bulb and brainstem and eventually involving cortical regions (Braak et al., 2003). In the early clinical phase, motor symptoms begin to emerge, while non-motor symptoms continue to accumulate. Common features at this stage include sleep disturbances, fatigue, mood disorders, PD-MCI, urinary symptoms, and orthostatic hypotension. As the disease progresses to the moderate stage and the underlying pathological changes spread to limbic and cortical regions, cognitive impairment becomes more pronounced, hallucinations or psychosis may develop, autonomic dysfunction worsens, and pain syndromes become increasingly common. In the advanced stage, more extensive cortical degeneration occurs, leading to features such as PDD, severe autonomic dysfunction, dysphagia, marked sleep disruption, and prominent hallucinations accompanied by behavioral disturbances. Furthermore, anxiety, highly prevalent in PD, can amplify the effects of CL on motor control, whereas elevated anxiety levels may further increase the inefficiency of motor control in individuals with PD, particularly under conditions of high cognitive demand (Ehgoetz Martens et al., 2018). Therefore, the concept of CL provides a unifying framework for understanding the interaction between diverse symptoms. As dopaminergic and network efficiency declines, the brain requires greater effort to maintain performance, particularly under dual-task or complex conditions. This is supported by neuroimaging studies demonstrating disrupted functional connectivity, including alterations in the default mode network (DMN), as well as reduced frontal activation and cerebral blood flow in patients with PDD (Tessitore et al., 2019).

In parallel with these functional changes, there is growing interest in identifying biomarkers that reflect cognitive decline and increased CL

in PD. While cerebrospinal fluid (CSF) biomarkers provide valuable insights, such as lipid alterations and α-synuclein dynamics, their clinical utility is limited by the invasiveness of collection procedures. Blood-based biomarkers offer a more accessible alternative. For instance, lower plasma epidermal growth factor (EGF) and elevated neurofilament light chain (NfL) levels have been associated with worse cognitive outcomes (Chen-Plotkin et al., 2010; Lim et al., 2019; Ma et al., 2021; Gu et al., 2024). Genetic factors, including variations in genes for apolipoprotein E (*APOE*), catechol-*O*-methyltransferase (*COMT*), microtubule-associated protein tau (*MAPT*) (Vandrovcova et al., 2009), and glucocerebrosidase (*GBA*), further influence cognitive trajectories in PD, underscoring the importance of individual variability. Some of them may confer shared risk for several neurodegenerative diseases, for example, *MAPT* haplotype H1 is a risk factor for both PD and AD (Vandrovcova et al., 2009; Babić Leko et al., 2018, 2024).

CL itself is associated with measurable physiological responses that may be captured through blood biomarkers. Acute cognitive stress can increase cortisol levels and catecholamines such as noradrenaline and adrenaline, reflecting activation of the hypothalamic–pituitary–adrenal (HPA) axis and ANS. Changes in metabolic markers, including glucose and lactate, may indicate the brain's energy demands during cognitively demanding tasks. Additionally, chronic cognitive stress has been linked to inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), as well as alterations in neurotrophic factors like brain-derived neurotrophic factor (BDNF) (Nikolac Perković et al., 2025). Markers of neuronal injury, particularly NfL, usually reflect longer-term neurodegenerative processes rather than acute CL (Kahn et al., 2025).

However, despite these advances, no single biomarker reliably captures the complexity of cognitive decline or CL in PD (Carceles-Cordon et al., 2023). Variability in laboratory methods, disease phenotypes, and longitudinal trajectories remains a major limitation (Tanaka, 2025). Therefore, a multimodal approach combining clinical assessment, neuroimaging, gait analysis, genetic profiling, and fluid biomarkers is likely necessary to achieve clinically meaningful predictions. Importantly, it should be noted that anxiety, highly prevalent in PD, can amplify the effects of CL on motor control, particularly under conditions of increased task complexity (Ehgoetz Martens et al., 2018). In summary, CL exerts a substantial and multifaceted influence in PD, interacting with motor and non-motor symptoms, network-level alterations, and emerging biomarker profiles.

Further research and advancing multimodal biomarker strategies will be needed to understand these complex relationships and improving disease characterization to enable the development of targeted, individualized therapeutic strategies.

2. Neurobiological mechanisms of cognitive load

2.1 Dopaminergic modulation of cognitive load

Dopaminergic neurons are primarily located in midbrain nuclei, particularly the *substantia nigra pars compacta* (SNc) and the *ventral tegmental area* (VTA) (Fig. 3). These nuclei give rise to the brain's major dopaminergic pathways: the nigrostriatal pathway (originating in the SNc) and the mesolimbic and mesocortical pathways (originating from the VTA) (Cragg & Walton, 2025) (Fig. 3).

Although these systems are classically associated with motor control and reward processing, they also contribute significantly to higher-order cognition. The distinction among different dopaminergic neuronal subtypes was traditionally based on the location of cell bodies and axon terminals. However, with recent advances in single cell RNA sequencing (scRNAseq) technology, these neurons can now be classified based on their unique gene expression profiles. In one such study in mouse brains (Carmichael et al., 2021), seven dopaminergic neuron subtypes were identified: three in SNc ($Aldh1a1^{+}/Sox6^{+}$, $Aldh1a1^{-}/Sox6^{+}$, and $Aldh1a1^{-}/Vglut2^{+}$) and four in the

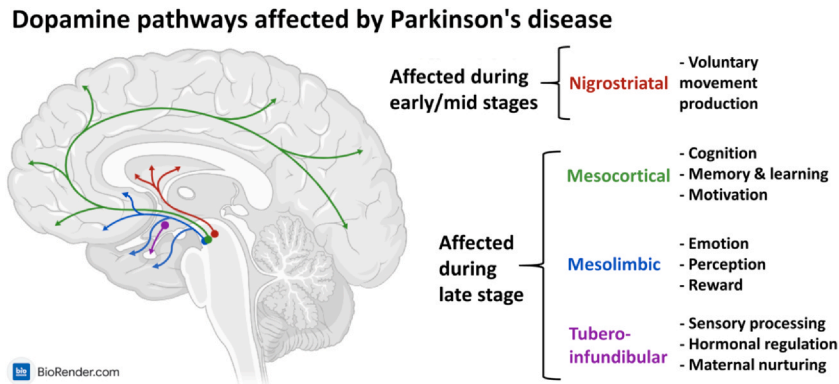

Fig. 3 Schematic illustration of the major dopamine projections in the human brain and the timing of their involvement in Parkinson's disease. See text for details. *Figure created using BioRender.com.*

VTA ($Aldh1a1^{+}/Otx2^{+}/Vglut2^{+}$, $Aldh1a1^{-}/Vglut2^{+}$, $Vgat^{+}$, and Vip^{+}) (Carmichael et al., 2021). These findings may help to better understand the diverse clinical symptoms of PD.

The mesocortical pathway, which projects from the VTA to the PFC (Fig. 3), is especially critical for CL regulation. The PFC supports WM, decision-making, and attentional control – functions highly sensitive to dopamine levels. Notably, dopamine in the PFC follows an "inverted-U" relationship with cognitive performance: both insufficient and excessive dopaminergic activity impair function, whereas an optimal level enhances the maintenance and manipulation of information (Cools & D'Esposito, 2011). Low dopamine weakens neural representations, increasing susceptibility to distraction and effectively raising CL. In contrast, excessive dopamine can lead to overly rigid representations, reducing cognitive flexibility and impairing the updating of information.

The mesolimbic pathway, projecting from the VTA to the ventral striatum and limbic structures such as the nucleus accumbens (NAc), modulates motivation and effort allocation (Fig. 3). CL depends not only on task complexity but also on an individual's willingness to engage. Dopaminergic signaling in this pathway encodes reward prediction and effort valuation, influencing whether cognitive resources are mobilized or conserved. Tasks perceived as rewarding or meaningful increase dopaminergic activity, thereby enhancing focus and reducing the subjective burden of CL. *The nigrostriatal pathway*, which connects the SNc to the dorsal striatum, is traditionally linked to motor control but also contributes to habit formation and procedural learning (Fig. 3). Through its interactions with cortical and thalamic circuits, this pathway supports the automation of behavior. As tasks become automated, they require fewer cognitive resources, effectively lowering CL. Dopamine facilitates this shift from effortful to automatic processing by reinforcing repeated patterns of neural activity.

Finally, dopaminergic pathways include the less well-known incerto-hypothalamic pathway, involved in visceral and sensorimotor activities, and the hypothalamo-spinal pathway, which modulates locomotor spinal networks (Klein et al., 2019).

Dopamine receptors are members of the G protein-coupled receptor (GPCR) family, which initiates their biological function by coupling to guanosine triphosphate (GTP)-binding regulatory proteins (G proteins). In humans, five dopamine receptor subtypes, DRD1 through DRD5, are conserved across mammals. D1-like receptors (DRD1 and DRD5), stimulate adenylyl cyclase, whereas the D2-like receptors (DRD2, DRD3, and

DRD4) are coupled to inhibitory G proteins, and their activation leads to inhibition of adenylyl cyclase (Wolstencroft et al., 2007). Like other GPCRs, dopamine receptors are not expressed only in the cell membrane, but undergo trafficking: they can be internalized into early endosomes from which they may be recycled to the plasma membrane or targeted for degradation in late endosomes (Wolstencroft et al., 2007).

In addition to neurons, both D1-like receptors (Guidolin et al., 2023) and D2-like receptors (Mladinov et al., 2010) are also expressed in astroglial cells, where D2 receptor activation decreases intracellular calcium levels whereas D1 receptor activation increases them. Thus, astrocytes are not merely supporting cells but active modulators of dopaminergic signaling, using both D1 and D2 receptors to sculpt calcium dynamics and tune neural circuits.

Adaptive behavior relies critically on dopaminergic signaling, which regulates reward prediction, motivation, and the selection and initiation of motor and cognitive actions, enabling organisms to balance effort, risk, and expected outcomes. These functions are largely mediated in the striatum, a central component of the BG, where striatal projection neurons (SPNs, also known as medium spiny neurons, MSNs), integrate cortical and dopaminergic inputs to facilitate or suppress actions. SPNs are traditionally classified into two principal subtypes based on dopamine receptor expression: D1 receptor-expressing neurons (D1-SPNs), which form the direct pathway and promote movement through dopamine-induced excitation, while D2 receptor-expressing neurons (D2-SPNs), which contribute to the indirect pathway and inhibit movement via dopamine-mediated inhibition. Conceptually, D1-SPNs and D2-SPNs represent complementary components of a regulatory system: D1-SPNs promote action (a "go" signal or "gas pedal"), whereas D2-SPNs inhibit action (a "stop" signal or "brake pedal"). This classical dichotomous model has been challenged by the identification of a third SPN population co-expressing both D1 and D2 receptors (D1/D2-SPNs) (Bonnavion et al., 2024). These neurons project to inhibitory nuclei within the BG, where D1 receptor activation can paradoxically enhance inhibitory output, indicating that dopamine signaling can both facilitate and inhibit actions depending on circuit architecture rather than operating through strictly opposing pathways.

Dopamine also supports habit formation, reducing CL by enabling previously learned, context-appropriate actions to be executed automatically. Dopamine modulation is necessary not only for habit formation but also for prioritizing habits as the dominant mode of behavioral control. According to reward prediction error theory, dopamine release serves as a

critical signal linking sensory stimuli with contiguous action primitives, which then lead to reward. In this framework, bursts of dopamine help bind patterns of cortical activity that are relayed to the striatum in association with reward (Bertran-Gonzales & Balleine, 2025). As a result, motor primitives of habits, assembled through stimulus-response associations, are selected by reinforcement.

Dopamine neuromodulation has an essential role in the learning, formation, and execution of action sequences. It is involved in action vigor, initiation, movement speed and kinematics, discrimination learning, and context-dependent behavior (for review, see Bertran-Gonzales & Balleine, 2025). Overall, dopamine facilitates the transition from effortful, attention-demanding processing to automatic, habitual behaviors, thereby reducing cognitive burden. By dynamically regulating signal-to-noise ratios, WM, attention, and learning, dopamine optimizes the allocation of limited cognitive resources, especially in WM, supporting both adaptive cognition and behavior, thus playing a central role in modulating CL.

A critical question concerns how the brain maintains information in WM. Persistent neuronal activity during delay periods was considered the canonical substrate. However, increasing evidence supports complementary or alternative mechanisms in which memory traces are stored in short-term synaptic plasticity (STSP) and other activity-silent substrates rather than sustained spiking (Mongillo et al., 2008; Wolff et al., 2017; Barbosa et al., 2021; Fields, 2022). In this view, transient changes in synaptic efficacy, such as facilitation and depression, can maintain information in a latent state until needed, enabling reactivation without continuous neural firing (Stokes, 2015; Rose et al., 2016; Miller et al., 2018).

Empirical findings suggest that WM relies on multiple, task-dependent mechanisms. In some cases, delay-period activity is sparse or dynamic, with representations stored in latent, rapidly reactivatable states. Short-term synaptic dynamics within recurrent networks can preserve information even after spiking subsides, enabling robust readout when triggered (e.g., by cues or perturbations). In humans, such latent representations are often inferred using perturbation-based approaches, such as single-pulse transcranial magnetic stimulation (TMS) or task-irrelevant probes, combined with high-temporal-resolution methods, which reveal memory content not evident in ongoing activity alone (Rose et al., 2016).

At the circuit level, prefrontal and parietal regions, together with thalamic interactions, support a heterogeneous mix of mechanisms, including activity-silent traces, transient bursts, and selective reactivations. However, directly

demonstrating synaptic maintenance in vivo, particularly in humans, remains challenging. To test how synaptic dynamics support WM, current approaches therefore integrate computational modeling (e.g., recurrent networks with STSP), invasive recordings in animal models, and perturbation-based human studies (Kozachkov et al., 2022; Malleret et al., 2024). The emerging consensus is that WM reflects a dynamic interplay of mechanisms (activity-silent synaptic storage, latent reactivation, and, in some contexts, persistent spiking) rather than a single process. Key open questions include when STSP dominates over sustained activity, how synaptic traces can be measured or manipulated in humans, and how memory load, interference, and task demands shape the balance between these mechanisms. Addressing these questions will improve our ability to predict and optimize CL in real-world contexts.

2.2 Dopamine as a regulator of brain circuitry and mental health

PD increases CL primarily through the degeneration of dopaminergic neurons in the SNc, which disrupts signaling in cortico-striatal loops, especially those involving the PFC. As a result, processes that were once automatic become effortful, and the brain is forced to recruit conscious control for routine actions. This shift markedly increases CL, because more mental resources are required to perform even simple tasks. This increased cognitive burden is reflected in several characteristic clinical symptoms, most notably executive dysfunction, which includes difficulties with planning, organizing, multitasking, and slowed thinking and decision-making (*bradyphrenia*). Bradyphrenia is evident in the longer time patients need to think, respond, or solve problems, and it reflects reduced processing efficiency caused by diminished dopaminergic modulation. WM and task-switching processes become less efficient, so each task demands greater mental effort and the brain must allocate more resources even to relatively simple cognitive operations. As described above, reduced dopamine levels in prefrontal circuits further disrupt optimal processing, consistent with the inverted-U relationship between dopamine and cognitive performance (Cools & D'Esposito, 2011).

In parallel, patients experience impaired automaticity: activities such as walking, writing, or speaking, *which are normally handled unconsciously by the BG*, now require deliberate attention (Redgrave et al., 2010). This represents a fundamental shift from automatic to controlled processing and significantly increases CL, because more attention is needed to perform the same actions. This principle of automatization extends beyond PD and

reflects a general property of neural processing applicable to other cognitive domains, such as language. In individuals with high language proficiency, certain linguistic processes become automated, reducing the involvement of lower sensorimotor and BG regions, while language and speech rely more heavily on associative (transmodal) hubs. This increases efficiency by reducing the conscious effort required for language comprehension and processing (Balboni et al., 2025). Likewise, individuals with dyslexia show weaker activation and connectivity between language and sensorimotor regions than typical readers, who display better convergence of linguistic and non-linguistic abilities, such as automation, speed, and lexical access (Balboni et al., 2025). Speech and language are also affected in PD. PD patients may show reduced fluency, monotone speech, and difficulty finding words, reflecting the fact that speech production becomes less automatic and requires greater executive control. This added demand contributes to the overall increase in mental effort. Unsurprisingly, many patients report significant mental fatigue, even when performing simple tasks. This subjective exhaustion is a direct correlate of increased CL: the brain is working harder but achieving less efficient output. In advanced stages, PDD can develop, characterized by memory impairment, visuospatial deficits, and severe executive dysfunction. At this point, neural processing becomes so inefficient that even minimal tasks can exceed the patient's cognitive reserve (CR) capacity.

A particularly revealing manifestation of increased CL in PD is dual-task interference, in which patients struggle to perform two tasks simultaneously; for example, walking while talking may cause them to stop walking altogether. This phenomenon directly exposes the limits of CL capacity in PD: as cognitive demands rise, the already strained system becomes overloaded, leading to deterioration in motor performance. Attention deficits further compound the problem, with reduced sustained attention and increased distractibility. Impaired dopamine signaling lowers the signal-to-noise ratio in neural processing, allowing irrelevant information to intrude and thereby effectively increasing the load on the system.

Across these symptoms, a unifying mechanism emerges: dopamine loss impairs BG gating and cortical efficiency, leading to reduced automaticity and poor filtering of information. As a result, everyday tasks require disproportionately high cognitive resources. A simple clinical example illustrates this clearly: a healthy individual can walk and talk effortlessly, as both processes rely largely on automatic mechanisms and impose minimal CL. In contrast, a person with PD must consciously focus on walking; when a

second task such as conversation is introduced, their limited cognitive capacity is exceeded, often causing them to stop walking. This vividly demonstrates the restricted "bandwidth" of CL in the disorder.

A recent study examined how dispositional cognitive effort investment – reflecting a tendency toward effortful thinking, linked to need for cognition and self-control – relate to actual effort deployment during cognitive tasks (Kührt et al., 2023). In a sample of 148 participants, multiple indicators of effort were assessed, including subjective load, behavioral performance, neural activity (frontal midline theta, N2, P3), and pupil dilation, during flanker and n-back tasks that varied in demand and payoff. The results showed that effort indicators were primarily sensitive to task demand and, to a lesser extent, to incentives. Higher dispositional effort investment was associated with better accuracy in the n-back task and interacted with payoff to influence RT in both tasks and P3 amplitude in the n-back task. Task demand also modulated early frontal midline theta power in the flanker task. Overall, individuals with higher cognitive effort investment tend to deploy effort more efficiently and are capable of maintaining performance even when external rewards are low, highlighting that effort allocation arises from an interaction between stable individual traits and situational factors such as task demands and incentives (Kührt et al., 2023).

Artificial increases in dopamine transmission represent a common mechanism through which addictive substances exert their effects, contributing to the development of addiction. Substantial progress has been made in identifying intracellular signaling pathways mediating both the immediate and long-term effects of dopamine, as well as molecular targets with therapeutic relevance. From this perspective, dopamine can be conceptualized as a key regulator of brain circuitry, with widespread influence across genetic systems underlying mental health (Blum et al., 2025). However, dopamine does not operate in isolation; its effects emerge from a highly interactive network – the brain reward cascade, which involves multiple neurotransmitters working in concert (Lewandrowski et al., 2025). Individuals with a genetic or epigenetic predisposition to *hypodopaminergia*, a state characterized by reduced dopaminergic function, may be especially vulnerable to these conditions. Variations in genes such as *DRD2* have been linked to reduced receptor density and increased risk of addictive behaviors, with neuroimaging studies demonstrating lower D2 receptor availability in carriers of specific alleles (e.g., Taq A1). These findings support the broader concept of reward deficiency syndrome (RDS), in which impaired dopaminergic signaling contributes to maladaptive behaviors and reduced reward sensitivity. In response, a therapeutic approach based on "pro-dopaminergic agonism" has

been proposed, aiming to gently and consistently stimulate dopamine receptors. This strategy is hypothesized to enhance dopaminergic tone over time, potentially increasing D2 receptor density and restoring balance within reward circuitry, thereby reducing cravings and improving behavioral regulation in individuals with addiction or depressive symptoms. Importantly, stress-related mechanisms further complicate this picture: while stress can acutely increase dopamine release, it also elevates glutamatergic activity, which can dysregulate dopaminergic signaling over time. In individuals with underlying genetic vulnerabilities, this interaction may exacerbate hypodopaminergic states and increase susceptibility to addiction (Lewandrowski et al., 2025).

These insights have prompted growing interest in personalized, precision-based interventions. Genetic tools such as the Genetic Addiction Risk Score (GARS) have been proposed to identify individuals at elevated risk, enabling targeted therapeutic strategies aimed at restoring dopaminergic balance. Compounds such as KB220Z, a dopaminergic agonist, have been suggested as potential interventions for addressing RDS-related behaviors, although further research is needed to validate their efficacy and clarify underlying mechanisms (Lewandrowski et al., 2025). Overall, a deeper understanding of the interactions among dopamine signaling, genetic predisposition, and environmental factors such as stress may support more effective and individualized treatments for addiction and depression, moving beyond one-size-fits-all approaches toward targeted modulation of brain reward systems. Maintaining a delicate balance of dopaminergic state is essential for optimal cognitive performance and underscores its central role in both normal cognition and neuropsychiatric disorders (Blum et al., 2025).

2.3 Regenerative capacity of dopaminergic systems: Lessons from salamanders

Salamanders, particularly urodele species such as the axolotl (*Ambystoma mexicanum*), exhibit a remarkable capacity to regenerate midbrain dopaminergic neurons after injury (Joven et al., 2019), a capability that stands in stark contrast to the limited regenerative potential of the mammalian brain, as exemplified in PD. Following lesions in key dopaminergic regions such as the VTA and SNc, salamanders can restore both neuronal populations and their function within weeks, leading to recovery of dopamine levels and motor behavior (Parish et al., 2007). Ablation of dopamine neurons activates quiescent ependymoglia, driving neurogenesis, whereas dopamine signaling, via L-dopa or receptor activity, suppresses proliferation, revealing that stem cell quiescence is reversibly modulated by dopamine (Berg et al., 2011).

The regenerative response is initiated by the activation of normally quiescent ependymal cells lining the midbrain ventricles. Upon injury, whether induced chemically (e.g., 6-OH-dopamine, 6-OHDA) or through surgical ablation, these cells rapidly proliferate and act as the principal progenitor population. They express neural stem cell markers such as Sox2 and begin producing neuroblasts within approximately 3–5 days post-lesion; these progenitors subsequently migrate ventrally toward the site of injury, where they differentiate into tyrosine hydroxylase (TH)-positive dopaminergic neurons. This process involves radial glia-like intermediates and is tightly regulated by morphogen gradients, particularly fibroblast growth factor (FGF) and Wnt signaling pathways (Berg et al., 2011).

While dopamine's role in vertebrate locomotion has traditionally been attributed to ascending projections to the BG, a direct descending dopaminergic pathway to brainstem locomotor networks is conserved across vertebrates (Ryczko et al., 2016). Dopamine is released in salamander and rat brainstem networks and is potentiated by amphetamine in vivo; human brainstem tissue contains dopaminergic terminals, emphasizing a direct modulatory role of dopamine in locomotion (Ryczko et al., 2016).

Altogether, the study of salamander midbrain regeneration holds significant promise for informing therapeutic strategies in humans, particularly for PD. The identification of ependymal cells as a key endogenous progenitor population suggests a potential target for inducing regeneration in the mammalian brain. However, important limitations remain: human ependymal cells exhibit far less plasticity, and the molecular environment of the injured mammalian brain is less permissive to regeneration. Moreover, critical gaps persist, including the need for high-resolution single-cell atlases of regenerating cell populations and a deeper characterization of the long-term stability and plasticity of reconstituted neural circuits. Addressing these challenges will be essential for translating insights from salamanders into viable future regenerative therapies.

3. Predictive processing as a unifying framework

3.1 The role of predictive processing in reducing cognitive load

Predictive processing (PP) conceptualizes cognition as a hierarchical inferential system that continuously generates and updates internal models of the

environment in order to anticipate incoming sensory input (Clark, 2013; Friston, 2010). Within this framework, higher cortical levels generate predictions that are compared with sensory signals at lower levels; any mismatch, or *prediction error*, is propagated upward to update and refine the generative model (Friston, 2010). This hierarchical architecture promotes computational efficiency: when predictions are accurate, sensory input is largely explained away, minimizing processing demands and keeping CL low. By contrast, unexpected or uncertain inputs generate larger prediction errors that require additional neural resources to resolve, thereby increasing CL (Clark, 2013). Thus, the brain optimizes resource allocation by prioritizing surprising or behaviorally relevant information while attenuating predictable inputs. *Active inference* extends this framework by proposing that organisms not only update internal models but also act on the environment to minimize prediction error, thereby making sensory input more predictable (Friston et al., 2011; Pezzulo et al., 2024). Accordingly, CL can be understood as a function of the balance between model accuracy and environmental uncertainty: accurate, well-calibrated models reduce processing demands, whereas persistent mismatches require greater computational effort and adaptive updating. Within this framework, dopamine plays a central regulatory role by modulating the *precision* – that is, the estimated reliability or confidence – assigned to prediction errors (Friston, 2010; Schwartenbeck et al., 2015). Rather than encoding error magnitude per se, dopaminergic signaling determines the extent to which prediction errors influence belief updating and behavioral selection. At the circuit level, this modulation is closely linked to BG dynamics. Although there is no single canonical predictive-coding circuit in the BG, as often described for cortico-cortical systems, BG circuits support prediction-related computations, particularly those involving action outcomes, expectations, and learning from prediction errors. Specifically, the direct and indirect pathways implement gating and learning mechanisms that can be interpreted within a predictive-coding framework, including priors, predictions, errors, and updates, especially when the BG are considered within broader cortico-thalamo-cortical loops involved in reinforcement learning and error signaling.

Classical work showed that dopamine neurons encode prediction error signals related to reward learning (Schultz, 1998), and more recent accounts extend this role to the precision-weighting of belief updating under uncertainty (Friston et al., 2012; Schwartenbeck et al., 2015). In cortico-striatal and prefrontal circuits, this mechanism effectively tunes attention and learning: elevated dopamine enhances the impact of salient, task-relevant

prediction errors and stabilizes goal-directed representations, whereas reduced or dysregulated dopamine may lead either to underweighting of relevant signals, resulting in cognitive rigidity, or to overweighting of irrelevant inputs, leading to distractibility and increased noise sensitivity (Cools, 2016; Friston et al., 2012). In this sense, dopamine functions as a dynamic gain-control mechanism within PP, calibrating the trade-off between stability and flexibility and thereby directly shaping CL through its influence on the filtering, prioritization, and integration of prediction errors (Fig. 4).

Hierarchical PP was first described in the visual system (Rao & Ballard, 1999), where feedback projections from higher-order associative visual areas convey predictions about the activity of lower-level neurons, while feedforward connections carry information about the mismatch between predictions and the actual lower-level activity. In this way, receptive fields are formed that support efficient hierarchical processing of visual stimuli (Friston, 2018). Similar mechanisms have since been described in other systems, including the auditory system (Caucheteux et al., 2023).

In PP, neural oscillations reflect hierarchical information flow. Gamma (30–100 Hz) supports feedforward signaling by carrying prediction errors from lower to higher areas with high precision. Alpha (8–12 Hz) and beta (12–30 Hz) mediate feedback: beta primarily conveys top-down predictions, especially during active cognition, whereas alpha regulates inhibition, attention, and sensory gating. Rather than forming a strict hierarchy, these rhythms interact flexibly, with theta (4–8 Hz) providing broad temporal coordination, and alpha and beta serving complementary functions. Overall, gamma transmits errors upward, beta carries predictions downward, and alpha modulates information flow within this predictive architecture.

In the healthy brain, CL is minimized through efficient PP, as internal models allow the brain to anticipate and automate routine actions (Friston, 2010; Clark, 2013). Processes such as walking, speaking, or writing are executed largely automatically, relying on well-established sensorimotor predictions mediated by the BG (Raghanti et al., 2008; Redgrave et al., 2010). This automation reduces the need for conscious control and minimizes cognitive effort. In PD, however, this predictive efficiency is disrupted. As a result, processes that were once automatic become effortful, and the brain is forced to recruit conscious, attention-dependent control for routine actions (Wu & Hallett, 2005). This shift from automatic to controlled processing, substantially increases CL, as more mental resources are required to perform even simple tasks.

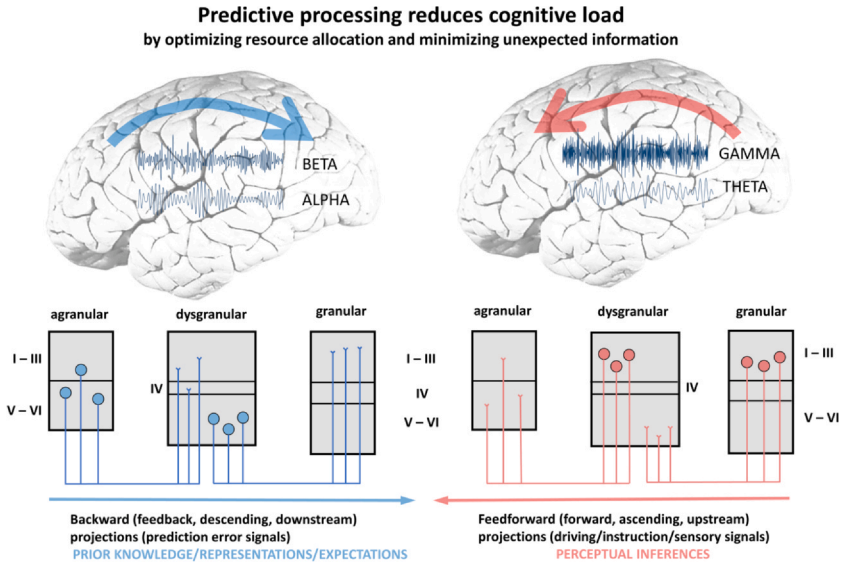

Fig. 4 Simplified illustration of predictive processing hierarchical flow and oscillatory dynamics. Left: Feedback (top-down) projections, from higher- to lower-level cortical areas, are commonly associated with beta (12–30 Hz) and alpha (8–12 Hz) oscillations. Functionally, these rhythms support contextual modulation, attentional control, and the suppression of predictable inputs, allowing the system to prioritize unexpected or surprising signals, often conceptualized as prediction errors. **Right:** Feedforward (bottom-up) projections, from lower- to higher-level areas, are commonly associated with gamma oscillations (30–100 Hz), which support the precise transmission of sensory information. During learning, gamma bursts are often nested within the phase of slower theta waves (4–8 Hz). Within PP frameworks, theta rhythms coordinate context-dependent information flow, supporting both feedforward and feedback signaling across hierarchical levels and brain regions. During bottom-up processing, theta couples with gamma bursts in cortical and hippocampal circuits (theta-gamma coupling), a process in which slow theta phases organize the timing of fast gamma signals carrying sensory details or prediction errors. During top-down feedback processing, theta interacts with alpha and beta rhythms that convey predictions from higher-order areas, providing a temporal scaffold for large-scale coordination of distributed activity. Rather than directly encoding predictions or prediction errors, theta oscillations organize the timing of feedforward gamma activity and integrate feedback via alpha and beta bands, thereby supporting coherent information flow across distributed neural networks. This coordination is critical for memory-guided predictions, spatial navigation, and expectation-driven attention. **Below:** A schematic representation of the cytoarchitectural hierarchy of PP: feedforward sensory signals originate in the supragranular layers (II–III) of highly differentiated sensory areas and project to the deep layers of less differentiated dysgranular and agranular areas, whereas prediction error signals arise from the deep layers (V–VI) of less differentiated agranular cortical areas and project to the superficial layers of more differentiated dysgranular and granular primary and unimodal sensory cortical areas. Note that granular cells in layer IV of V1 project to V2 and area MT/V5, *which are also granular* (Sincich & Horton, 2003), and are therefore not shown in this schematic. *Adapted from Rao and Ballard (1999), Shipp (2005, 2016), Friston (2010), Shipp et al. (2013), Lundqvist et al. (2016), Bastos et al. (2020), and Katsumi et al. (2023).*

This loss of automaticity is evident in both motor and cognitive domains. Patients commonly show impaired automatic execution of movements, including reduced arm swing, micrographia, and difficulty maintaining posture (Morris et al., 1994). Activities such as walking, which are typically performed effortlessly, now require continuous attentional monitoring. Speech production is likewise affected, becoming less fluent and more effortful, reflecting increased reliance on executive control (Illes et al., 1988). A particularly illustrative example is dual-task interference. Healthy individuals can perform tasks such as walking and talking simultaneously with little effort because both rely on automated processes. In contrast, individuals with PD often struggle to perform two tasks at once; the introduction of a secondary task may disrupt or even halt motor activity altogether (Yogev-Seligman et al., 2008). This reduced capacity for parallel processing highlights how the loss of predictive automation increases CL.

3.2 Precision weighting and the role of dopamine

PD impairments stem from the degeneration of dopaminergic neurons in the SNc, disrupting cortico-striatal circuit signaling (Obeso et al., 2008). Dopamine critically regulates precision weighting, that is, the balance between relevant signals and background neural noise (Friston et al., 2012). Reduced dopaminergic modulation lowers signal-to-noise ratio, impairing the brain's ability to efficiently filter and prioritize information. Consequently, irrelevant stimuli intrude into processing streams, increasing CL. At the same time, weakened signal precision destabilizes internal representations, further compromising task performance (Schwartenbeck et al., 2015). In PD, reduced dopamine levels in prefrontal circuits shift processing from the optimal range, contributing to inefficient cognition and reduced flexibility (Cools & D'Esposito, 2011). Furthermore, dopaminergic dysfunction disrupts BG gating mechanisms essential for selecting appropriate actions and suppressing alternatives (O'Reilly & Frank, 2006; Redgrave et al., 2010). These changes collectively result in a less precise, more variable, and computationally demanding system, increasing CL across motor and cognitive domains.

3.3 Active inference, adaptive resource allocation, and "reserve paradox"

As neural efficiency declines, the brain compensates by reallocating cognitive resources, consistent with active inference principles (Friston, 2010; Clark, 2013; Pezzulo et al., 2024). However, this comes at the cost of increased

mental effort and conscious control for previously effortless tasks. This shift manifests as executive dysfunction, including difficulties with planning, multitasking, organizing behavior, and slowed decision-making (*bradyphrenia*) (Kudlicka et al., 2011). These impairments arise because WM and task-switching become less efficient, requiring greater cognitive effort. Bradyphrenia itself reflects reduced processing efficiency, arising from diminished dopaminergic modulation and increased computational demands (Cools & D'Esposito, 2011), necessitating recruitment of additional neural resources for simple operations and accentuating capacity limitations. Dual-task situations are particularly revealing; for example, patients may walk relatively well when focused on movement, but adding a secondary task such as conversation can disrupt gait or halt it entirely (Yogev-Seligman et al., 2008), reflecting overload in cognitive-motor integration systems. Mental fatigue is another key consequence, reflecting the sustained effort to maintain performance, with the brain expending more resources for less effective output.

Motor symptoms in PD are not purely motoric but also reflect increased CL. Healthy movement is largely automatic, mediated by BG circuits requiring minimal attention. In PD, dopamine loss disrupts these circuits, forcing movements to be consciously controlled via cortical systems, making motor execution cognitively expensive. This loss of automaticity requires continuous monitoring and control, so even simple actions increase attentional demands and slow performance. Bradykinesia involves slower, reduced-amplitude movements because actions are consciously guided rather than automatically executed. Gait disturbances, particularly freezing of gait, further illustrate this relationship; patients may suddenly feel their feet "glued" to the floor, especially during dual-tasking or in complex environments (such as doorways or turns), resulting in temporary breakdown of motor output. These episodes reflect a failure in cognitive-motor integration, where competing demands exceed available processing capacity. Deficits in cognitive control, especially monitoring self-generated actions and errors under high CL, further exacerbate these difficulties and disrupt gait performance (Walton et al., 2015).

The loss of automaticity is also evident in reduced arm swing and impaired habitual movements, as control shifts from the BG to the capacity-limited PFC, transforming motor activity into a cognitively demanding task requiring sustained attention. Similarly, micrographia reflects impaired internal scaling of movement, as patients must consciously regulate writing output, increasing effort and leading to performance deterioration under distraction. Postural instability, normally relying on automatic sensorimotor

integration, becomes attention-dependent, competing with other cognitive demands and worsening when attention is divided. Motor variability also increases, with performance improving when attention is focused and deteriorating when distracted. This variability is a hallmark of CL dependency, as motor output becomes tightly linked to available cognitive resources.

These effects can be further understood within the framework of CR: when CL remains below available capacity (i.e., is lower than CR), performance is efficient and accurate; when CL approaches reserve, performance slows and becomes more effortful; when CL exceeds CR, errors increase and performance breaks down (Stern, 2009). Healthy individuals with higher CR tolerate greater CL, apply efficient strategies, and show reduced brain activation or flexibly recruit additional resources when required. Individuals with lower CR reach their limits sooner and decline earlier, meaning that CR effectively shifts the threshold for tolerating cognitive demands. In PD, this balance is disrupted. Neurodegeneration reduces processing capacity, lowering available CR. Tasks become increasingly demanding, leading to slower processing, greater effort, increased fatigue, and impairments in executive functioning. Compensation through recruitment of additional regions or alternative networks may occur, so individuals with higher CR can maintain function longer and show clinical symptoms later despite underlying pathology. This gives rise to the "reserve paradox": *higher CR may delay symptom onset, but once symptoms emerge, decline can be more rapid because the disease is already advanced* (Steffener & Stern, 2012). CL represents the weight being lifted, while CR represents muscle strength: when the "muscle" weakens, even the same weight becomes difficult to manage.

4. Cognitive (computational) load in AI systems

4.1 Analogies of cognitive load and decline in humans and AI systems

Analogies, while powerful for understanding complex phenomena, can oversimplify, obscure crucial nuances, and ultimately be misleading, particularly in the context of CL. Drawing parallels between healthy and PD brains and AI models can result in flawed understandings of both systems. We aim to dissect the limitations of these analogies, highlighting key differences and the potential for misinterpretation. CL, central to human performance, refers to the mental effort required to process information and execute tasks. It is a multifaceted construct shaped by

task complexity, individual skill, and available cognitive resources (often conceptualized as CR). In healthy brains, efficient resource allocation emerges from dynamic interplay among distributed neural networks supporting attention, WM, and executive function. Disruptions within these networks impair cognitive performance, increasing subjective effort and reducing processing efficiency.

Although often framed as a computational limitation, human cognition operates within *biological constraints* rarely incorporated into classical CL frameworks. Integrating genetic, epigenetic, environmental, pathogen-related, and immune factors (Szabo et al., 2025), emerging evidence indicates that low-grade ("silent") neuroinflammation, driven by activation of NLRP3 (microglial) (Španić et al., 2019) and NLRP1 (neuronal) inflammasomes, plays a crucial role in PD (Hirsch & Hunot, 2009), AD (Ising et al., 2019; Španić et al., 2022), and SCZ (Španić Popovački et al., 2024), tightly linked to mitochondrial dysfunction (Marchi et al., 2023). This appears to be a central mechanism linking gut microbiota dynamics to increased CL, driven by persistent peripheral immune signals and CNS inflammatory cascades. Animal models and microbiota-focused reviews show that gut microbiome alterations can modulate amyloid pathology, microglial activation, and synaptic function, demanding greater neural effort to sustain performance (Medina-Vera et al., 2023; Hao et al., 2025). Microbiota-modulating interventions, including probiotics or dietary components affecting polyphenol metabolism, have been linked to reduced CNS inflammation and preserved/improved cognitive function in some contexts. Overall, these data support a model in which smoldering neuroinflammation, sustained by gut-immune signaling and peripheral inflammatory insults, increases CL and cognitive problems in aging and at-risk populations (Strzępa & Szczepanik, 2025).

Such smoldering neuroinflammation may be associated with inflammatory bouts across the lifespan, increased gastrointestinal barrier permeability, microbiota-brain interactions, and protein accumulations and aggregations, involving amyloid-β, tau, α-synuclein, progranulin, TDP-43, apolipoprotein E, transthyretin, FUS, huntingtin, ubiquitin, p62, heat shock and other proteins, as well as various dipeptide repeats due to hexanucleotide repeat expansion in the *C9ORF72* gene (Babić Leko et al., 2019) that can substantially influence neural efficiency and cognitive capacity. These mechanisms impose *dynamic physiological limits* on information processing that fundamentally differ from artificial systems' constraints. These biological constraints become especially salient in

neurodegenerative conditions. PD is frequently associated with a substantial cognitive burden, encompassing a spectrum from PD-MCI to PDD, capturing deficits in executive function, visuospatial processing, and processing speed. The neuropathological basis of this burden is complex, involving not only dopaminergic depletion within the BG, but also widespread synucleinopathy (Lewy body pathology), cholinergic dysfunction, and, in some cases, co-existing AD-related pathology (Jellinger, 2022), modulated by genetic susceptibility and systemic physiological factors.

The rise of AI, particularly deep learning, has encouraged comparisons between human cognition and artificial neural networks (ANNs), based on shared abstract features such as modular information processing, weighted connections encoding learned associations, and performance optimization through iterative training. Within this framework, CL in humans is often likened to computational load in AI systems. In ANNs, especially deep convolutional neural networks (CNNs), quantities analogous to CL include: the number of parameters, floating-point operations (FLOPs), memory usage (random access memory, RAM / video RAM [VRAM] for graphics processing units, GPUs), and inference time. For example, deeper architectures (e.g., ResNet-152) impose substantially greater computational demands than shallower models (e.g., ResNet-18), manifesting as higher memory requirements, a dramatic rise in computational operations, and significantly longer training times, often requiring distributed computation across multiple GPUs. Beyond computational cost, model capacity provides another parallel. Networks with insufficient capacity underfit and fail to represent task-relevant structure, while excessively large models risk overfitting, memorizing noise, conceptually resembling the CLT trade-off: insufficient cognitive resources impair task performance, while excessive or poorly regulated processing can lead to inefficiency and susceptibility to irrelevant information (Frankle & Carbin, 2019).

These parallels have motivated attempts to conceptualize CL in both healthy and diseased brains through the lens of AI. A healthy brain under high CL may be likened to a system operating near capacity, with slower processing and increased error rates (Schultz et al., 1997). Similarly, a PD-affected brain might be compared to a network with degraded connectivity or inefficient information transfer, resulting in reduced effective capacity and increased vulnerability to overload (Aarsland et al., 2003). However, such analogies, while intuitive, have important limitations: AI models remain drastic simplifications of the human brain. They lack the biological complexity

of neurons, neurotransmitter systems, glial modulation, and the structural and functional heterogeneity of brain networks (Dayan & Abbott, 2001). Similar concerns extend to current in vivo animal models of cognition and PD, which also fail to fully capture human neurobiological complexity. The human brain depends critically on neuromodulatory systems, particularly dopaminergic and cholinergic pathways, to regulate excitability, plasticity, and attentional control (Babić Leko et al., 2021). Most AI models lack explicit representations of neuromodulation, limiting their ability to capture dynamic, state-dependent changes associated with CL. Cognitive decline in PD reflects a complex interaction of pathological processes, including Lewy body deposition, neuronal loss, network-level disruption, and systemic influences (e.g., inflammation, protein aggregation). These interacting mechanisms introduce nonlinear and heterogeneous effects poorly approximated by simplified network analogies. Human cognition is fundamentally embodied, shaped by sensory input, motor activity, interoception, and emotional states (Wilson, 2002). AI systems, typically disembodied and operating in constrained environments, cannot model this critical dimension. Finally, learning mechanisms differ profoundly. While AI systems adapt through parameter optimization (e.g., back-propagation, BP; see below), the brain relies on synaptic plasticity embedded within a broader biological context including neuromodulation, neurogenesis, synaptic pruning, and apoptosis, among other mechanisms. These processes are disrupted in neurodegenerative diseases, leading to patterns of adaptation and decline that fundamentally diverge from AI systems.

Therefore, although analogies between CL in humans and computational load in AI can be heuristically useful, they risk oversimplifying the biological reality of cognition. A more productive approach lies in developing computational models that explicitly incorporate key features of brain physiology and pathology, including neuromodulation, inflammation, and protein aggregation. Such biologically grounded models offer a more accurate framework for understanding the interplay between CL, brain function, and neurodegeneration, while also informing the development of more effective diagnostic tools, therapeutic strategies, and AI-based assistive technologies.

There is a fundamental difference in how the human brain and AI solve problems. Based on current knowledge, the human brain primarily uses PP, whereas CNNs are engineered to manage informational flow through: pooling layers, strided convolutions, bottleneck blocks (e.g., three convolutions: $1 \times 1 \rightarrow 3 \times 3 \rightarrow 1 \times 1$ in ResNet, which, simplified, correpond

to squeezing information → processing it efficiently → expand it), or autoencoders (NNs that learn to compress data into a latent representation and reconstruct it). These compression mechanisms functionally replace biological selective attention, reducing "load" by forcing models to retain and analyze only relevant information. This reasoning has been formalized in the information bottleneck (IB) theory of deep learning (Tishby & Zaslavsky, 2015), which frames training as "retaining task-relevant information and discarding the rest".

It is well established that the delta rule of supervised learning applies to single-layer ANNs and linear regression, involving supervised adjustment of input weights to minimize the discrepancy between predicted outputs and actual targets. While perceptrons can only represent linearly separable problems, the application of gradient descent to search the space of weight vectors transformed the field (Rumelhart et al., 1986), leading to the first general optimization algorithm for multilayer (deep) ANNs: back-propagation of errors (the backpropagation rule, BPR) (work that contributed to the foundations of modern neural-network research, for which Hinton shared the 2024 Nobel Prize in Physics with Hopfield). BP is now a central component in training various types of ANNs, including feed-forward, recurrent, and CNNs, enabling networks to learn from errors by adjusting connection weights based on the difference between predicted and desired outputs. The BP algorithm comprises two main phases: the forward pass (forward propagation) and the backward pass (Fig. 5).

Analysis of DNNs through the IB principle frames deep learning as a process of successive compression of inputs while preserving crucial predictive features. Each layer discards irrelevant detail and retains only the most pertinent information, effectively solving an optimization problem of maximal compression with minimal loss of accuracy (Tishby & Zaslavsky, 2015). Layered architectures emerge as stages of abstraction and refinement. The IB framework also provides theoretical performance limits, indicating how close a model is (proximity) to optimality and highlighting potential improvements. However, while parallels can be drawn between CL and computational constraints in DNNs (capacity limits, compression, efficiency trade-offs), these analogies fail to capture essential features of brain's CL, including embodiment, heterogeneous pathologies, and other biologically grounded mechanisms. Therefore, deeper insights are likely to arise from developing computational models informed by biology, rather than relying on simplified brain-AI analogies.

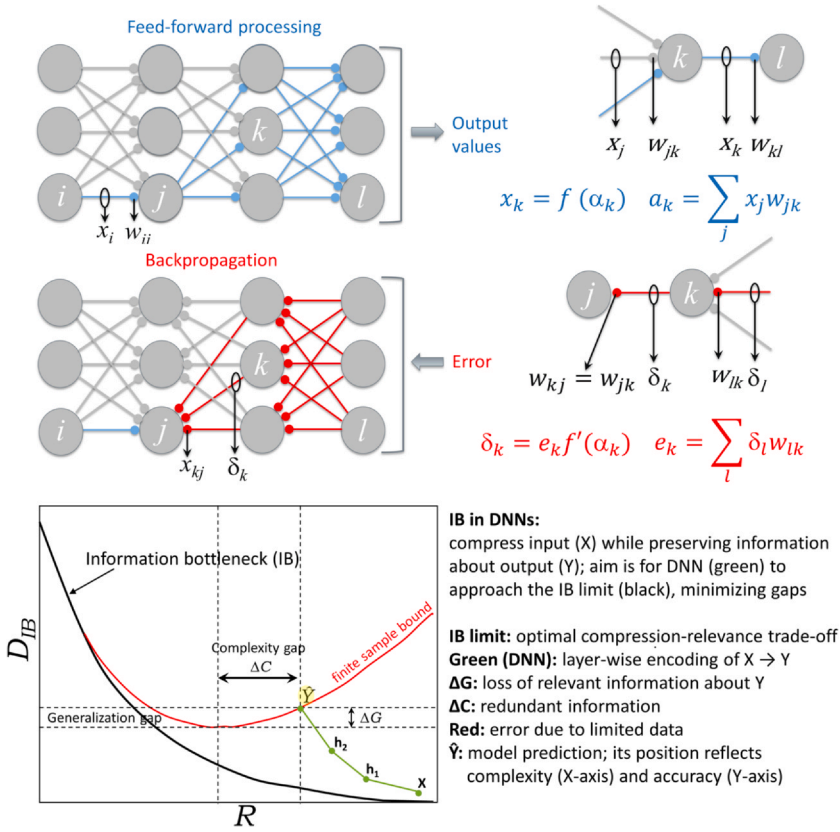

Fig. 5 The upper part of the figure illustrates the backpropagation rule (BP), whereas the lower part qualitatively illustrates the information bottleneck (IB) in deep neural networks (DNNs). BP is an algorithm for computing gradients in ANNs, enabling efficient weight updates via gradient descent and is used by most modern ANNs trained with gradient-based optimization, including feedforward NNs/multilayer perceptrons, DNNs used for deep learning, CNNs widely used in image processing, recurrent NNs designed for sequential data that use a variant called BP through time, transformers used in large language models (LLMs), as well as autoencoders and generative models. The total input activity to a node ("neuron") *j*, including the bias, is denoted αj, and its output activity is $xj = f(\alpha j)$. The "synaptic" weight w_{ij} represents the connection strength linking node *i* to node *j*. The error function measures the degree to which the final output values of the last layer (y_l) deviate from their target values (t_l). A common choice for the error function is the squared error (SE), and for the total error, the mean squared error (MSE) is typically used. BP computes, for each individual weight in the network, the gradient of the error with respect to that weight at the current setting of all weights. The simplest way to use BP is to adjust each weight

(Continued)

Fig. 5—Cont'd proportionally to the negative of its average error gradient. For any layer that is not the output layer, the updated weight w_{ij} is given by:

$$\Delta w_{ij} = -\eta \frac{\partial E}{\partial w_{ij}} = -\eta x_i \delta_j \text{ where } \delta_j = e_j f'(\alpha_j) = \left[\sum_k \delta_k w_{jk}\right] f'(\alpha_j)$$

The key principle behind this formula for the BP algorithm is that δ, the error signal, can be computed recursively using the chain rule. In the output layer, the error signal is given by $\delta_l = y_l - t_l$. In all other layers, δ_l is computed from all δ_k values of the layer above it, such that the signals flow backward through the network. This backward propagation starts from the error signals in the final (output) layer, which are derived from the derivatives of the error function. The scheme has been modified and adapted from (Lillicrap et al., 2020). **Explanation of elements in the bottom part of the figure:** Imagine summarizing a long book (the input data, *X*) for someone, ensuring they understand the main point (the output, *Y*). The X-axis represents information distortion (*D*), i.e., how much relevant information is lost (higher *D* is worse). The Y-axis represents rate (*R*), i.e., the complexity or description length of the representation (higher *R* means more complex). $\hat{Y}$ is the final output layer of the DNN after processing the input through all hidden layers and represents the network's prediction of the true output. The *X* position of $\hat{Y}$ indicates how much information the predicted output retains about original input, reflecting the complexity of the retained representation. The *Y* position of $\hat{Y}$ indicates how much information the predicted output captures about the true output, reflecting the accuracy of the prediction. The *black line* (optimal IB limit) represents the theoretical perfect summary i.e. the best trade-off between compressing information (low *R*) and preserving important information (low *D*). The *red line* shows the potential error in the summary due to incomplete information (imagine reading only a few pages of the book before writing the summary), with each point showing the information retained about the input (*X*) versus the output (*Y*) at that specific layer, quantifying how much the *true* information about Y can be affected in reality versus the training data (i.e., the best it can be achieved due to generalization from training data; such that all DNN layers should ideally be below this line). The *green line* represents how the DNN actually summarizes the book, with each hidden layer like a step in creating the summary, and each point representing the information retained about the input (*X*) versus the output (*Y*) at that specific layer. Starting from a low distortion (low *D*) but high rate (high *R*) at the input layer (***X***), the hidden layers (***h1***, ***h2***, etc.) progressively move toward the output $\hat{Y}$, approaching the optimal IB limit. The *generalization gap (ΔG)* measures how much important information about Y is missed by the DNN compared to the perfect summary, i.e. the difference between what DNN achieves and what the IB limit suggests is possible (relevant context about Y is missing). The *complexity gap (ΔC)* measures how much unnecessary detail is included in DNN's summary compared to the optimal summary (lower complexity requires less energy to process). The goal is to compress the input (*X*) while preserving relevant information about the output (*Y*), to bring the green line of the DNN as close as possible to the black IB limit line, minimizing both Δ*G* and ΔC, producing an accurate and concise summary. Altogether, this simplified illustration captures the essence of deep learning through the lens of the IB: finding the optimal balance between compressing data (reducing *R*) and preserving relevant information (minimizing *D*). The lower part of the illustration is adapted from Tishby & Zaslavsky, (2015).

4.2 Dopamine-attention analogies: Biological vs artificial systems

A productive convergence between biological and artificial systems lies in how they prioritize relevant information under constraints. In the brain, dopaminergic modulation regulates signal-to-noise ratio, particularly within PFC networks. Dopamine enhances task-relevant neural activity while suppressing irrelevant inputs, enabling efficient selection and stabilization of goal-relevant representations. In artificial systems, particularly transformer-based architectures, attention mechanisms perform an analogous function by weighting inputs, so salient elements dominate processing, and irrelevant components are attenuated. Despite different implementations, both systems address the same problem: determining what information matters at a given moment. Dopamine can be understood as a form of *dynamic gain control*, modulating neural responsiveness in a state-dependent manner, while attention operates as *weighted selection*, redistributing computational resources across inputs. Optimizing signal-to-noise ratio is central to performance: when this balance is disrupted, whether through dopaminergic dysregulation or poorly calibrated attention, task performance deteriorates.

A further correspondence lies in gating mechanisms. In the brain, the BG, under dopaminergic control, regulate WM updating by determining when new information is admitted into PFC representations and when existing representations are maintained. This prevents interference and protects limited cognitive resources from overload (O'Reilly & Frank, 2006). In AI systems, analogous (though less explicit) mechanisms are implemented through attention distributions, positional encoding, and memory/retrieval modules, which determine which information is integrated, retained, or ignored during processing.

These mechanisms are closely tied to the balance between stability and flexibility. In biological systems, interactions between the PFC and subcortical structures, modulated by dopamine, govern whether cognitive representations remain stable or are updated in response to new information. In artificial systems, similar trade-offs emerge through attention allocation and decoding strategies, which can produce outputs that are either stable/rigid or flexible/prone to noise. Dopamine and attention both act as regulators of computational mode, shaping how systems navigate the trade-off between persistence and adaptability. An important distinction, however, lies in motivation. Dopamine is deeply

involved in reward prediction and effort allocation, influencing whether cognitive resources are engaged and whether task pursuit is maintained, while artificial systems lack intrinsic motivation, instead having priorities defined externally. This loose functional analogy does not capture the endogenous, state-dependent nature of biological motivation. Finally, the analogy has clear limits: dopamine is a biochemical neuromodulator operating across multiple spatial and temporal scales, enabling continuous, context-sensitive adjustment of neural processing, while attention mechanisms are fixed mathematical operations during inference and lack autonomous regulation of effort/resource allocation. AI systems do not "choose" to invest more or less effort; they execute predefined computations. Thus, while dopamine-attention analogies are conceptually useful, they remain abstractions that cannot fully capture the biological richness of neuromodulatory control.

4.3 Cognitive load vs context saturation: Failure modes in humans and AI

Although artificial systems do not possess CL in a biological sense, they show functionally analogous behavior under conditions of limited capacity and increasing complexity. Hence CL provides a useful interpretive lens for comparing failure modes across biological and AI systems. A central parallel exists between human WM and the AI context window: both are capacity-limited and modulated by system-internal factors. WM is constrained and dopaminergic modulation affects the stability and flexibility of representations where both insufficient and excessive dopamine impair performance (Cools & D'Esposito, 2011; Weber et al., 2022). Similarly, AI systems operate within a fixed context window in which information competes for influence; as input length or complexity grows, *context saturation* can dilute relevant signals and degrade performance. In both realms, this limitation manifests as interference and decay.

Excessive CL in humans leads to reduced processing efficiency, slower responses, and higher error rates. In AI models, lengthy or conflicting inputs can produce inconsistencies, loss of coherence, or hallucination-like outputs. A unifying account emerges from PP. Core features of SCZ are thought to reflect imprecise predictive coding arising from dysfunction in corticostriatothalamocortical loops (Liddle & Sami, 2025). Much of human inference is unconscious, including perception, language parsing, and rapid judgments (e.g., recognizing a face, extracting a word from noisy audio, interpreting masked stimuli). Perception is predominantly

unconscious inference: the brain combines prior beliefs with sensory input to produce percepts, with the conscious, "final products" competing to enter awareness. Prediction errors, as learning signals, are modulated by dopamine (Corlett et al., 2022) and drive belief updating in the search for meaning. In PP, volatility refers to how frequently the environment changes. Misestimating volatility, particularly overestimating it, is linked to psychotic symptoms such as paranoia and delusional ideation (Reed et al., 2020). Elevated priors about volatility have been found in individuals with high paranoia and are associated with persecutory delusions in SCZ; paranoia can indirectly amplify volatility priors and worry (Sheffield et al., 2022).

Active inference models propose that hallucinations arise from an imbalance between prior beliefs and sensory evidence, especially when sensory precision is reduced (Benrimoh et al., 2019). In-context hallucinations occur when subjects cannot use sensory input to update priors about hearing a voice, while beliefs about content (e.g., sentence order) remain intact. When beliefs about state transitions are also inaccurate, out-of-context hallucinations emerge, producing disordered speech content. Here, "out-of-context" denotes false perceptual inference driven by degraded sensory precision rather than contextual inference. Prodromal SCZ patients, who retain intact sensory updating but harbor inaccurate state-transition beliefs, may not hallucinate, suggesting distinct computational mechanisms across the hallucination spectrum.

This view aligns with the broader concept of context saturation: both human WM and AI systems fail under excessive load. High CL increases errors in humans, and the out-of-context hallucinations illustrate how distorted internal models combined with reduced sensory precision generate disorganized content – mechanisms relevant to AI as well. In both systems, performance degrades when input exceeds processing capacity, underscoring the importance of accurate priors and reliable sensory or contextual input for coherent function. Together, these observations support a functional equivalence between CL in humans and context or attention overload in AI systems.

The trade-off between stability and flexibility in control further illustrates shared failure modes. The Dual Mechanisms of Control (DMC) framework (Braver, 2012; Braver et al., 2026) posits two key control dimensions: proactive and reactive. Proactive control reflects the sustained and anticipatory maintenance of goal-relevant information within lateral PFC (lPFC) to enable optimal cognitive performance, whereas reactive

control reflects transient, stimulus-driven goal reactivation that recruits lPFC and a wider brain network, based on interference demands or episodic associations. This framework's central tenets are that proactive and reactive control modes reflect intrinsic, domain-general dimensions of individual variation, with distinctive neural signatures, involving the lPFC as a central hub within associated brain networks (fronto-parietal, cingulo-opercular). Dopaminergic dysregulation disrupts the balance between maintaining stable representations and updating them appropriately, leading to either rigidity or distractibility. Clinically, this is evident in conditions such as PD and schizophrenia (SCZ), where deficits in WM, attention, and cognitive flexibility can produce overload even during simple tasks (Grace, 2016; Sonnenschein et al., 2020). In AI systems, analogous failures arise when attention mechanisms fail to appropriately weight relevant inputs, resulting in either overly rigid outputs or unstable/noisy responses under high input complexity (Dai et al., 2019).

Gating failures provide another convergence point: impaired BG gating allows irrelevant information to enter WM, increasing CL and reducing efficiency. In AI systems, insufficient filtering of inputs or suboptimal attention distributions similarly leads to ineffective prioritization, exacerbating context saturation and degrading output quality.

Despite these parallels, important differences remain. Human CL reflects not only computational limitations but also underlying biological constraints, including neuromodulation, metabolic factors, and pathological processes. In contrast, AI system failures arise from architectural and computational constraints, such as fixed context windows, parameter limitations, and optimization trade-offs. Thus, while the analogy between CL and context saturation is informative, it simplifies the multidimensional nature of human cognitive failure.

Taken together, both biological and AI systems face the challenge of allocating limited processing resources under increasing complexity. In humans, this is mediated by neuromodulation, WM, and gating mechanisms; in AI, it is governed by attention, context windows, and optimization objectives. Within this framework, CL can be understood as the strain placed on a system's capacity to prioritize, maintain, and process relevant information, while context saturation represents its computational analogue. This perspective not only clarifies differences between human and AI but also links neurological dysfunction to identifiable computational failure modes, providing a useful bridge between cognitive neuroscience and AI research.

5. From mechanisms to prediction: Cognitive decline in Parkinson's disease

5.1 Cognitive reserve and vulnerability to cognitive decline

CR refers to the brain's resilience against pathology, achieved through lifelong cognitive engagement, education, intellectually demanding occupations, social interaction, and physical activity. While physical activity helps maintain neuronal structure and brain volume ("hardware"), cognitive activity enhances the efficiency and plasticity of neural circuits ("software"), supporting CR through complementary mechanisms (Cheng, 2016). CR does not prevent disease pathology, but delays emergence of clinical symptoms and influences coping with neurodegenerative changes. CR is typically indexed by proxies such as education level, occupational complexity, sustained cognitive activity, bilingualism and social networks (all of these factors are thought to promote more efficient neural processing, flexible network recruitment, and compensatory strategies that sustain function despite pathology). In practice, higher CR is linked to later onset of symptoms in AD and may modulate cognitive trajectories in PD, though relationships are complex and disease-specific. In AD, greater CR is associated with a delayed clinical manifestation of cognitive impairment for a given burden of amyloid and tau pathology (Šimić et al., 2016, 2017) when physiological mechanisms for clearing/combating pathological protein forms are effective. For individuals susceptible due to specific genetic variants, as well as environmental and lifestyle risk factors, these mechanisms become less effective, allowing pathological protein forms to increasingly promote each other – a process that is also central to the unique pathology of AD. Once impairment begins, individuals with higher CR may experience faster decline, because a higher damage threshold must be surpassed before symptoms emergence, or compensatory networks become exhausted (the "reserve paradox"). Neuroimaging studies suggest high-CR individuals may show more efficient or redistributed network activity to preserve performance, reflecting neural compensation rather than slowed pathology.

In PD, the role of CR is supported by associations between education, cognitive activity, and reduced risk or delayed onset of PD-related cognitive impairment and dementia (Hindle et al., 2014). CR may particularly influence executive and visuospatial domains, where PD often shows early deficits. However, PD-related pathological changes (alpha-synuclein

spread, dopaminergic loss) interact with aging and motor features, leading to heterogeneous CR effects across patients. Overall, CR appears to buffer cognitive symptoms in PD, but with more variable magnitude than in typical AD cohorts.

Clinically, fostering CR through education, ongoing cognitive stimulation, social engagement, and physical activity could modestly delay symptom onset and support quality of life in both AD and PD. Limitations include reliance on imperfect CR proxies, potential reverse causation, and the modest size of observed effects; robust longitudinal and intervention studies are needed to clarify causality and optimize strategies. In sum, CR provides a nonpharmacological buffer against neurodegeneration, with evidence for disease-specific benefits in AD and PD and strong rationale for lifelong cognitive health strategies.

5.2 Biomarkers of cognitive load in Parkinson's disease

Clinical features of PD often overlap with other parkinsonian syndromes, contributing to misdiagnosis and highlighting the need for reliable, clinically applicable biomarkers. Cognitive decline, whether in normal aging or PD, profoundly impacts quality of life and independence. Early prediction is therefore crucial for timely intervention, patient stratification, and optimized clinical trial design (Monchi et al., 2016). While normal aging and PD share some risk factors and biological signatures, PD-related cognitive decline is typically more aggressive and driven by distinct neurodegenerative mechanisms. Accurate prediction models must integrate diverse data sources and account for disease-specific trajectories (Beheshti et al., 2024).

Biomarkers, objectively measurable indicators of biological or pathological processes, comprise clinical assessments, biochemical measures, neuroimaging findings, and genetic data. Established biomarkers already support predicting cognitive deterioration. Reduced CSF amyloid-β_{1-42} (Aβ42) and elevated tau protein levels predict cognitive decline in both normal aging and PD, reflecting overlapping AD pathology (Dennis & Strafella, 2024; Beheshti et al., 2024). Comprehensive neuropsychological assessments outperform the MMSE in detecting early impairment (Chen et al., 2020). Predictive models integrating age, motor severity (e.g., Movement Disorder Society - Unified Parkinson's Disease Rating Scale, MDS-UPDRS), and cognitive performance demonstrate high accuracy (Andújar-Castillo et al., 2025).

Genetic and molecular biomarkers further refine risk stratification. *APOE* ε4 increases the risk of cognitive decline, while *GBA* variants are linked to earlier cortical degeneration and faster progression (Ren et al., 2023). Dopaminergic dysfunction, assessed via DAT imaging, enhances predictive power when combined with clinical and CSF measures (Schrag et al., 2017; Tropea et al., 2018). Multimodal approaches that combine clinical, genetic, biochemical, and imaging data consistently outperform single-modality models, reflecting the biological heterogeneity of cognitive decline (Delgado-Alvarado et al., 2016). Advances in fluid biomarkers, particularly blood-based, enable scalable, minimally invasive detection. Plasma phosphorylated tau (pTau217) correlates with AD co-pathology and cognitive performance in PD (Musso et al., 2025). Neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) levels are elevated in PD and correlate with cognitive impairment (Lorenz et al., 2025; Shrestha & Leier, 2025). Proteomic markers such as CHI3L1 and TMSB4X, and metabolic indicators including phenylacetylglutamine and L-arginine, capture disease-related biochemical changes (Zhao et al., 2022). Notably, biomarker panels outperform individual markers in predicting cognitive decline (Dennis & Strafella, 2024).

α-Synuclein pathology plays a central role in PD. Misfolding and aggregation into oligomers and fibrils contribute to neuronal dysfunction and Lewy body formation. While total α-synuclein levels show limited specificity, advanced seed amplification assays (SAA) detect pathogenic aggregates even in prodromal stages (Šimić, 2024). Distinguishing physiological from pathogenic protein forms is critical for developing effective biomarkers. Inflammatory processes and extracellular vesicle-derived markers are also increasingly recognized as contributors to PD pathophysiology. Neuroinflammation, particularly early in disease, is reflected in elevated inflammatory mediators and astrocytic markers such as GFAP, which associate with motor and cognitive symptoms. Variability across studies emphasizes the need for standardized methodologies. Neuroimaging further enhances early detection. Structural MRI identifies atrophy in hippocampus and orbitofrontal cortex predictive of cognitive decline (Beheshti et al., 2024). Dopamine transporter single photon emission computed tomography (DAT-SPECT) reveals dopaminergic deficits, with early caudate involvement linked to cognitive impairment. Positron emission tomography (PET) detects early metabolic and amyloid changes preceding atrophy, while fMRI shows network disruptions in default mode, salience, and attention systems (Delgado-Alvarado et al., 2023).

Advanced techniques like texture analysis and network topology metrics enable detection of subtle microstructural and connectivity alterations before overt degeneration (Zuo et al., 2026). Multimodal imaging integrating structural, functional, and molecular data provides the most comprehensive view of disease progression.

Mechanistically, cognitive decline in PD differs from normal aging. PD shows distinct cortical atrophy patterns (insula, dlPFC, angular gyrus, hippocampus) and early disruptions in functional connectivity (Li et al., 2024). Compensatory hyperconnectivity may initially preserve function but fails as disease progresses (Yan et al., 2025). Non-motor symptoms, including depression and anxiety, further impair executive and memory functions. Subjective cognitive decline (SCD) is a key early indicator, with higher conversion to PD-MCI and PDD in PD versus normal aging (Ophey et al., 2022).

Despite progress, challenges remain. PD heterogeneity, limited longitudinal datasets, insufficient biological definition of the disease and multimodal integration difficulties constrain predictive model performance (Aarsland et al., 2021). ML approaches achieve high accuracy but face issues of data imbalance, interpretability, and clinical applicability (Hlavnička et al., 2025). Widely used tools like the MMSE lack sensitivity for early changes, underscoring the need for refined, disease-specific assessments. Future directions include multimodal data integration, protocol harmonization, and development of explainable AI models. Large-scale longitudinal studies are essential for validating predictive frameworks in real-world settings (Djiberou Mahamadou et al., 2025). Accurate early prediction of cognitive decline will enable personalized interventions, improve outcomes, and enhance clinical trial efficiency.

In conclusion, predicting cognitive decline in normal aging and PD requires integrative approaches combining biomarkers, neuroimaging, and advanced analytics. Despite mechanistic differences, convergence of multimodal data and ML offers a promising path toward accurate, clinically useful prediction models (Dennis & Strafella, 2024).

5.3 AI-based prediction of cognitive decline in PD

The application of ML techniques to predict cognitive decline in PD is an emerging field showing significant promise. Traditional research has primarily focused on explanatory models, aiming to understand the relationships between various clinical and biological variables and cognitive outcomes in PD. However, with the increasing availability of large,

multimodal datasets, predictive modeling using ML is gaining traction as a tool to identify individuals at high risk of cognitive deterioration, enabling timely interventions and personalized treatment strategies.

Current research utilizes a range of ML algorithms, including support vector machines (SVMs), random forests, and various neural network architectures, to forecast cognitive status or decline based on baseline clinical assessments, neuroimaging data, genetic markers, and other relevant features. These models often aim to predict conversion to MCI or PDD, or to estimate the rate of cognitive decline over a defined period. While many studies have shown encouraging results, challenges remain in terms of sample size limitations, feature selection, model interpretability, and the generalizability of findings across different PD cohorts. There is a growing need for models that integrate diverse data sources and provide clinically meaningful insights into the key drivers of cognitive decline in PD.

Addressing these challenges, a recent study utilized an explainable artificial neural network (XANN) to predict cognitive decline in a relatively large cohort of PD patients (N = 618) (Colautti et al., 2025). This research distinguishes itself through its focus on longitudinal prediction, training the ANN on baseline data from the CPP Integrated Parkinson's Database to forecast cognitive status three years later. The model achieved a high recall of 0.91 for identifying patients who developed cognitive decline at follow-up, indicating a strong ability to detect at-risk individuals.

Furthermore, the study emphasizes model interpretability by employing SHapley Additive exPlanations (SHAP) analysis, Group-Wise Feature Masking, and Brute-Force Combinatorial Masking. This rigorous approach consistently identified baseline Montreal Cognitive Assessment (MoCA) scores, memory performance, motor symptom severity, and anxiety levels as the most influential predictors of cognitive decline. The convergence of these findings across different explainability methods strengthens the confidence in these variables as potential targets for early identification and intervention. As AI models become more sophisticated, there are increasing concerns about the ethical implications of their use in healthcare, including potential biases, lack of transparency, and the risk of dehumanizing patients (Jobin et al., 2019). Applying AI-inspired analogies to understand CL in PD must be done cautiously, with careful consideration of the ethical ramifications.

6. Socially minded intelligence and human-AI collaboration

It is important to recognize that socially minded intelligence bridges individual and collective capabilities, enabling flexible collaboration between humans and AI agents in pursuit of shared goals, as illustrated by the deserted island scenario, where adaptive group dynamics become essential for survival (Bingley et al., 2026). Rather than treating intelligence as an isolated property, this perspective reframes it as an emergent, context-sensitive capacity that unfolds across interacting agents, offering a more precise and scalable way to analyze, design, and evaluate hybrid human-AI systems beyond the limits of traditional psychological and computational models.

7. Promising non-pharmacological strategies for mitigating cognitive load

Reducing CL by controlled breathing. Controlled breathing has emerged as a promising non-pharmacological strategy for mitigating CL – a state in which excessive mental demands impair information processing, performance, and decision-making. By consciously regulating respiratory patterns, controlled breathing engages a set of interconnected physiological and neural mechanisms that support cognitive function and resilience under stress (Zaccaro et al., 2018). At the physiological level, slow-paced breathing, typically around six breaths per minute, modulates the ANS by increasing vagal tone, thereby promoting parasympathetic dominance. This shift reduces stress-related cortisol release and enhances prefrontal regulation of attention and executive processes (Lehrer & Gevirtz, 2014). In parallel, controlled breathing influences key neurotransmitter systems, including GABA, glutamate, serotonin, and acetylcholine, which shape synaptic plasticity and large-scale network dynamics. Notably, inhibitory projections from limbic structures such as the amygdala to brainstem respiratory centers (e.g., the preBötzinger complex) link emotional regulation with the control of breathing rhythms (Feldman et al., 2013; Yackle et al., 2017). Controlled breathing also affects cerebral blood flow and oxygenation, particularly across respiratory phases, although its cognitive benefits appear to rely more strongly on neural entrainment mechanisms, i.e. the rhythmic component of the ongoing cortical activity (Heck et al., 2017; Boyadzhieva & Kayhan, 2021). Brainstem respiratory centers interact with cortical and limbic regions,

forming integrated circuits through which breathing can influence cognition and emotion. These interactions allow respiration to act as a coordinating signal for neuronal oscillations, thereby shaping attention, memory, and executive function (Kluger & Gross, 2021). At the neural level, controlled breathing synchronizes oscillatory activity across frequency bands such as delta, theta, and gamma, particularly in the PFC and hippocampus. This respiratory entrainment enhances attentional control and memory consolidation, with evidence showing that cognitive performance varies across phases of the breathing cycle (Heck et al., 2017; Tort et al., 2018). Nasal breathing, in particular, plays a critical role by entraining limbic and hippocampal rhythms, supporting memory and emotional discrimination, whereas oral breathing tends to disrupt these dynamics and reduce neural synchrony (Zelano et al., 2016). Core networks receiving interoceptive visceral signals involving the amygdala, hippocampus, insula, and brainstem adaptively coordinate breathing patterns during cognitive and emotional demands, further supporting regulation and performance (Critchley & Harrison, 2013). Empirical research supports the role of controlled breathing in reducing cognitive overload. Slow-paced breathing, such as in yogic breathing techniques, has been shown to improve WM, inhibitory control, and cognitive flexibility, with extended exhalation phases often enhancing these effects (Zaccaro et al., 2018; Laborde et al., 2022). These benefits are closely tied to enhanced autonomic regulation, reflected in increased heart rate variability and reduced sympathetic arousal, as well as neuroendocrine changes such as normalized cortisol levels (Lehrer & Gevirtz, 2014). Together, these effects contribute to improved executive function, emotional stability, and resilience under high CL. In practical terms, controlled breathing offers a simple and accessible tool for enhancing cognitive performance and managing stress across a range of contexts. Future research should aim to refine optimal breathing parameters, examine long-term cognitive and physiological outcomes, and develop personalized interventions based on real-time physiological markers such as heart rate variability or neural activity. Integrating controlled breathing with complementary approaches, such as mindfulness, physical activity, or neuromodulation techniques, may further enhance its effectiveness. Overall, controlled breathing represents a powerful mechanism for supporting cognitive function by modulating autonomic balance, neurochemical signaling, and large-scale brain network dynamics. Rather than acting through a single pathway, it operates as a multifaceted regulatory process that helps prevent cognitive overload and sustain adaptive performance.

Reducing CL by microbiota modulation. Microbiota composition does not directly determine CL, but modulates the biological efficiency of neural processing, thereby indirectly influencing the amount of cognitive effort required to perform a task. A favorable microbiota profile may improve neural efficiency and thereby lower CL through several mechanisms. First, by reducing neuroinflammation: chronic low-grade inflammation is known to impair attention, WM, and processing speed, and microbiota that promote anti-inflammatory signaling, such as via short-chain fatty acids like butyrate, can support more efficient cognition. Second, microbiota modulate neurotransmitter systems, including dopamine, serotonin, and GABA. Better-regulated neurotransmission can improve the signal-to-noise ratio in neural processing, meaning that the brain can perform the same task with less effort. Third, improved metabolic support plays a role: the brain is energetically demanding, and microbiota that optimize glucose metabolism and mitochondrial function can indirectly support sustained cognitive performance. Fourth, microbiota influence stress-axis regulation through the gut–brain axis (e.g., HPA axis modulation). Since stress increases perceived CL, a microbiota profile that reduces stress reactivity can make tasks feel less demanding (Zhang et al., 2025). Finally, through modulation of T lymphocytes, microbiota metabolites promote anti-inflammatory activity and resilience to stress-induced anxiety and depression (Westfall et al., 2020). Conversely, dysbiosis, or an imbalanced microbiota, may increase CL. Dysbiosis can promote neuroinflammation, disrupt dopaminergic signaling (relevant in conditions such as PD), and impair executive function and attention. These effects reduce neural processing efficiency, causing tasks to require more effort and thus higher CL. It is important to emphasize that microbiota do not directly "set" CL like a dial. Rather, they influence neural efficiency, which in turn determines the cognitive effort a task requires. Under optimal physiological conditions, a task may feel easier, whereas under inflammatory or dysregulated conditions, the same task may feel harder. Evidence supporting these ideas is mixed. There is strong evidence that microbiota affect cognition, mood, and brain function. Emerging evidence suggests links to processing efficiency and cognitive effort, but direct experimental studies measuring CL itself remain limited.

Reducing CL by plasma exchange. The ExPlas study protocol outlines a clinical trial to investigate the potential of plasma transfusions from exercise-trained donors to influence cognitive function in individuals with early AD or MCI (Tari et al., 2022). The research will evaluate the safety and tolerability of administering "exercised plasma" (ExPlas) and explore its

possible effects on various factors, including cognitive performance, physical fitness, vascular health, cerebral blood flow, brain structure, quality of life, and relevant biomarkers. The study design involves a double-blinded, randomized controlled trial comparing ExPlas to a control plasma product (Octaplasma – pooled, processed plasma collected from many donors and then treated to remove or inactivate viruses and standardize the levels of clotting factors, essentially a safer version of fresh frozen plasma [FFP] used in hospital settings) and a saline solution. Participants undergo regular plasma transfusions for over one year, with follow-up assessments planned for two and five years post-baseline. Cognitive function will be assessed through a battery of tests, such as the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word test, the MMSE, and the Trail-Making test. This research aims to provide data on whether ExPlas transfusions can potentially impact CL and improve cognitive outcomes in this patient population, while also examining the underlying mechanisms and safety considerations associated with this intervention. Additionally, the potential of using plasma transfusions from exercise-trained donors to mitigate the effects of AD is being tested in a rat model, with a particular focus on their impact on microglia and cytokine levels as key regulators of neuroinflammation, both of which play a central role in the progression of AD (Čuljak et al., 2020; Huuha et al., 2024). The core idea is to determine whether beneficial components present in the blood of physically active individuals can be transferred to those affected by AD to support brain health and cognitive function. The findings suggest that such transfusions are especially effective when applied at an early, pre-plaque stage of the disease, emphasizing the importance of timely intervention. Moreover, the use of exercise-conditioned plasma highlights that physical activity induces systemic changes in the blood that may have protective or restorative effects on the brain. At a cellular level, plasma from both exercise-trained and sedentary donors was found to alter microglial morphology, increasing the number and length of their branches, which may reflect functional changes. In parallel, the transfusions modified cytokine profiles, with exercised plasma potentially reducing pro-inflammatory signaling such as TNF-α activity (Huuha et al., 2024). Overall, the study indicates that plasma transfusions, particularly those derived from exercise-trained individuals, could represent a promising therapeutic strategy for reducing cognitive burden in early-stage AD by regulating inflammation and promoting adaptive microglial responses, although further research is necessary to validate these effects and clarify the mechanisms involved.

8. Conclusions

This review examines CL in the context of neurodegenerative diseases, focusing on PD, and proposes that cognitive decline can be better understood through the interplay of dopamine, PP, and analogies drawn from AI systems. Dopamine is positioned as a central modulator of CL, given its critical role in attention, WM, and cognitive control. Within PP, the brain minimizes CL by constructing generative models of the environment and selectively prioritizing prediction errors, with dopamine encoding the precision or salience of these errors. In PD, dopamine depletion disrupts frontostriatal circuits, thereby increasing CL and impairing efficient information processing. Parallels are drawn between neurocognitive constraints and AI systems with limited attention and context windows, supporting AI-based modeling of cognitive decline in PD. The integration of biomarkers and CR data may further improve prediction and extend toward socially minded intelligence in human-AI interaction as a basis for mitigating CL in aging and age-related neurodegenerative diseases. Finally, promising non-pharmacological interventions, including controlled breathing techniques, the maintenance of favorable microbiota profiles, and plasma exchange, are highlighted as potential means of reducing cognitive overload and supporting cognitive resilience.

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