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"MULTIMODAL PHYSIOLOGICAL BIOMARKERS OF COGNITIVE DYSFUNCTION IN MAJOR DEPRESSIVE DISORDER: FROM NEUROPHYSIOLOGY TO AUTONOMIC AND PERIPHERAL BIOMARKERS".

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ABSTRACT:
Major Depressive Disorder (MDD) and early neurocognitive disorders (such as mild cognitive impairment, or MCI) present massive global public health challenges, particularly among aging populations. Cognitive dysfunction represents a core, highly debilitating dimension of these conditions, persisting even during clinical remission. Traditional diagnostic strategies rely heavily on subjective screening tools and clinical interviews. However, a profound "subjective-objective paradox" exists: subjective memory complaints (SMCs) often reflect acute psychosocial distress, anxiety, and current depressive symptom severity rather than objective neural or memory decline. There is an urgent clinical need to transition from subjective proxies to objective, non-invasive brain-body biotypes that span multiple physiological systems to achieve early risk stratification and precise therapeutic monitoring.
Objective: This review synthesizes recent evidence to establish a systems-based, multimodal physiological framework for mapping cognitive homeostasis and autonomic dyshomeostasis. By integrating neuroelectrophysiological, cardiac, endocrine, and neuromuscular markers, we outline a definitive roadmap for predicting clinical transitions (such as MDD-to-MCI conversion) and characterizing central-autonomic-peripheral communication in older adults.
Methods A comprehensive synthesis was performed across 38 recent clinical trials, prospective cohort studies, neuroimaging datasets, systematic reviews, and Mendelian randomization (MR) analyses. This review systematically evaluates: (1) neuroelectrophysiological indices of cognitive processing (event-related potentials [ERPs] such as the P300, N170, and LRP); (2) cardiac autonomic biomarkers (resting and task-reactive heart rate variability [HRV] and respiratory oscillations); (3) neuroendocrine markers (hypothalamic-pituitary-adrenal [HPA] axis dynamics and cortisol diurnal profiles); and (4) peripheral somatic indicators (isometrically measured handgrip strength, sarcopenia indices, and segmental bioelectrical impedance analysis [BIA]).
Results & Synthesis: 1.Neurophysiological Processing (The P300 Paradigm): ERP studies establish the P300 wave as an objective indicator of cognitive resource allocation (P3b amplitude) and information processing speed (P3b latency). Active depression is robustly characterised by significantly reduced P300 amplitude and prolonged latency, correlating with impaired verbal memory and executive dysfunction in older adults [8]. Conversely, a history of MDD is associated with a hyper-reactive novelty P3 (P3a) and accelerated target P3 (P3b) latency, suggesting persistent sensory distractibility even after clinical remission [9].
2.Cardiac-Autonomic Dysregulation: While resting HRV (e.g., RMSSD, HF, LF, and non-linear SD1) is widely used to index parasympathetic (vagal) tone, large-scale umbrella reviews indicate that while reduced HRV is highly suggestive in dementia, PTSD, and schizophrenia, evidence for overall HRV reduction in adult MDD is weaker [4]. However, task-reactive HRV assessments reveal that depression disrupts the normal physiological coupling between autonomic vagal tone and executive performance (e.g., inhibitory control during continuous performance tests) [5].
3.The Non-Linear Compensation Paradigm: In early-stage mild neurocognitive disorder (mNCD), resting vagally-mediated HRV (specifically HF-HRV) exhibits a paradoxical compensatory increase due to prefrontal and anterior cingulate cortex (ACC) hyperactivation [10]. This compensatory mechanism becomes exhausted as neurodegeneration progresses, leading to a profound decline in total and parasympathetic resting HRV in frank dementia [15].
4.Stress-Induced Neuroendocrine cascades: Chronic stress induces HPA axis hyperactivity and glucocorticoid receptor (GR) desensitisation (glucocorticoid resistance) in 40–60% of MDD patients. Chronic hypercortisolemia flattens diurnal cortisol rhythms, triggers neuroinflammation via hippocampal microglial activation, suppresses adult neurogenesis, and impairs synaptic plasticity (attenuating BDNF signaling), culminating in irreversible hippocampal and prefrontal dendritic atrophy [39].
5.Peripheral Neuromuscular & Body Composition Biomarkers: Handgrip strength (HGS) and sarcopenia indices (such as appendicular lean mass [ALM] and gait speed) exhibit a robust, bidirectional causal relationship with general cognitive function, heavily mediated by moderate-to-vigorous physical activity and regional gray matter volume (GMV) within the subcortical nuclei and temporal cortices [44]. Furthermore, segmental BIA demonstrates that early cognitive decline (MCI and AD dementia) is characterized by reduced reactance and phase angle in the lower extremities,

reflecting diminished body cell mass, compromised cell membrane strength, and abnormal cellular fluid distribution [43].

6.Humoral and Network Dyshomeostasis: Adipomyokine network mapping in poorly managed hypertension (PMHTN) reveals systemic homeostatic collapse: the positive, neuroprotective coupling between adiponectin and verbal delayed memory, as well as IGF-1/IGFBP-3 and cognitive activity, is completely severed [51]. Elevated vaspin levels correlate with cognitive inefficiency (poorer MMSE and Trail Making Test Part B scores) and physical frailty [52].

Conclusions & Clinical Implications

Single-channel physiological variables are fundamentally insufficient for capturing the complex, bidirectional brain-heart-body interactions that govern cognitive homeostasis. Integrating electrophysiological, autonomic, neuroendocrine, and somatic markers into advanced machine learning and sensor-fusion models (such as combining video-based facial expressiveness with rPPG-derived HRV and quantitative EEG) significantly enhances diagnostic and prognostic accuracy. A validated multi-channel biotype predicts subsequent cognitive decline and MCI transition with up to 80.6% precision. Incorporating non-pharmacological interventions (such as resistance training, hatha yoga, and HRV biofeedback) offers a definitive clinical roadmap to actively restore HPA axis equilibrium, expand grey matter volume, enhance neurogenesis, and preserve cognitive autonomy in older adults.

KEYWORDS: Major Depressive Disorder; Mild Cognitive Impairment; Cognitive Dysfunction; Neurocognitive Disorders; P300; Event-Related Potentials; Heart Rate Variability; Autonomic Dysfunction; HPA Axis; Cortisol; Handgrip Strength; Sarcopenia; Bioelectrical Impedance Analysis; Brain-Heart-Body Interaction; Multimodal Biomarkers; Cognitive Decline; Precision Medicine; Machine Learning.

INTRODUCTION

Major Depressive Disorder (MDD) represents an incapacitating global public health and healthcare crisis with annual prevalence of approximately 4% to 6%, with lifetime prevalence estimates reaching up to 20% depending on the country and demographic factors. According to the World Health Organization (WHO), depression was ranked as the third leading cause of the global burden of disease in 2020 and is projected to become the primary cause of disease burden globally by 2030.

Beyond the profound deterioration of individual quality of life, MDD imposes a staggering socioeconomic toll. The global economic impact of depression, driven by direct medical treatment costs and indirect costs such as absenteeism and loss of productivity, is estimated at trillions of dollars annually. Critically, individuals suffering from depression face a significantly higher risk of all-cause mortality and suicide compared to the general population, with the severity of depressive symptoms positively correlating with mortality rates. This elevated risk is further compounded by autonomic nervous system (ANS) dysregulation, which serves as a biological link to increased cardiovascular mortality in depressed cohorts [1,2,6].

2. Cognitive Dysfunction in MDD

While traditionally conceptualized as a primary emotional or mood disorder, cognitive dysfunction is increasingly recognized as a core clinical dimension and a major determinant of overall health outcomes in MDD. Research indicates that up to 94% of patients suffer from cognitive deficits during an active depressive episode, and these impairments frequently persist as residual symptoms even during periods of clinical remission, contributing significantly to long-term functional disability and elevated relapse risk [3,6].

Cognitive dysfunction in MDD spans multiple distinct domains, including attention, processing speed, memory, learning, and executive function. In the domain of executive control, depressed individuals exhibit pronounced deficits in planning, initiating, and completing goal-directed tasks, as well as impairments in cognitive flexibility, set-shifting, decision-making, and inhibitory control [16].

Electrophysiological and neuroimaging evidence demonstrates that these deficits stem from a broad impairment of neural networks, particularly prefrontal cortical structures and the central autonomic network [1,2]. For instance, event-related potential (ERP) studies using Simon conflict tasks show that depressed patients exhibit specific conflict control dysfunctions at the early response-execution stage—marked by reduced lateralized readiness potential (R-LRP) amplitudes—rather than the initial perceptual encoding phase. Furthermore, neuroendocrine hyperactivity driven by hypothalamic-pituitary-adrenal (HPA) axis dysregulation leads to chronic cortisol excess, which induces neurotoxic effects, reduced neurogenesis, and structural atrophy in the hippocampus, directly impairing verbal and working memory [2,3,8].

3. Why Conventional Clinical Assessment May Be Insufficient

Traditional clinical evaluations of depression and its associated cognitive impairments have historically relied on subjective self-report questionnaires, such as the Geriatric Depression Scale (GDS), and clinician-led diagnostic interviews. However, these conventional assessment modalities exhibit significant limitations that can lead to diagnostic inaccuracies.

In clinical settings, subjective memory complaints (SMCs) are frequently utilized as a primary proxy for assessing cognitive decline, yet extensive empirical studies reveal that SMCs do not significantly correlate with objective neuropsychological memory performance, diagnostic ratings, or neurophysiological indicators. Furthermore, cognitive impairments themselves can severely compromise a patient's self-awareness; individuals with neurocognitive disorders or severe depression often lack insight into their deficits (anosognosia), leading to the complete denial or underreporting of cognitive symptoms. Conversely, standard psychiatric scales like the GDS can be highly misleading in older or medically ill populations, frequently misclassifying cognitively impaired but non-depressed adults as clinically depressed due to symptom overlap.

4. Need for Objective Biomarkers

To overcome the diagnostic limitations of subjective questionnaires and capture cognitive decline before it progresses to irreversible stages, there is an urgent need to establish objective, non-invasive, and reliable physiological biomarkers [8]. Electroencephalography (EEG) and event-related potentials (ERPs) serve as highly sensitive, dynamic tools that record the real-time postsynaptic potentials of cortical neurons during cognitive tasks, bypassing subjective bias. Specifically, the P300 ERP component—a positive wave reflecting attentional allocation and working memory updating—has demonstrated strong clinical utility [9].

Studies show that while subjective cognitive complaints fail to track objective deficits, P300 amplitude is significantly associated with objective verbal memory recall and clinical diagnostic ratings [9]. Furthermore, a prolonged P300 latency serves as a stable neurophysiological marker of delayed cognitive processing speed, and combining P300 latency with objective serum markers (such as brain-derived neurotrophic factor, or BDNF) provides a highly accurate, clinically validated model for predicting the transition from depression to mild cognitive impairment (MCI) [17].

Similarly, autonomic markers such as vagally-mediated heart rate variability (HRV) offer a practical, non-invasive window into the functional state of the parasympathetic nervous system [1]. By utilizing objective physiological and neurophysiological markers, clinicians can complement routine subjective clinical assessments and achieve early, precise risk stratification.

5. Rationale for Multimodal Physiological Assessment

Because cognitive dysfunction in MDD is a multifaceted pathology involving complex interactions between the central nervous system (CNS) and the autonomic nervous system (ANS), relying on any single biological marker is fundamentally insufficient[1]. The CNS and ANS are structurally and functionally interrelated through the Central Autonomic Network (CAN); the brain regions responsible for cognitive control and emotional regulation (such as the prefrontal cortex and anterior cingulate cortex) also govern peripheral cardiac and respiratory rhythms via preganglionic autonomic pathways. Consequently, a multimodal physiological assessment that integrates neuroelectrophysiological measures (like ERPs and quantitative EEG) with peripheral autonomic indicators (like HRV and respiration) provides a far more complete and accurate representation of the patient's functional status.

Empirical studies confirm that neurophysiological measurements and neuropsychological tests assess distinct aspects of cognitive processing and cannot substitute for one another; rather, they serve as essential, complementary tools. Furthermore, single autonomic variables often exhibit high overlap across different mental disorders, rendering them non-specific when analyzed in isolation[2].

However, evaluating overall multimodal physiological profiles—such as combining continuous HRV variables, EEG spectral power, skin temperature, and neurocognitive performance—reveals highly unique, disease-specific signatures that can distinguish depression from other neurodegenerative and psychiatric conditions. This integrated body-mind approach allows clinicians to capture the full spectrum of a patient's emotional, autonomic, and cognitive dysregulation, paving the way for personalized, objective, and highly effective therapeutic monitoring[3].

Cognitive dysfunction in MDD

1)Attention

Attentional dysfunction is a core feature of Major Depressive Disorder (MDD), involving abnormalities in electrophysiological processing and autonomic regulation. ERP studies show altered P300 responses in individuals with a history of MDD, characterized by increased P3a amplitude, indicating heightened involuntary attentional shifting and distractibility, and reduced P3b latency, suggesting altered voluntary attentional processing. Depressed patients also demonstrate impaired signal detection during continuous performance tasks and disrupted associations between resting HRV parameters (SDNN, lnLF, and lnHF) and cognitive performance, indicating impaired autonomic–cognitive integration[4]. Reduced frontal beta activity during working-memory processing, together with its relationship to vagal HRV, further supports altered central–autonomic coordination. Importantly, attentional deficits are also evident in subthreshold depression, with impaired sustained attention, reduced RVP discriminability, and increased reaction-time variability. Overall, these findings suggest that attentional impairment occurs across the depressive spectrum and involves altered cortical processing, sustained attention, and central–autonomic integration[4].

Processing Speed

Processing speed is a key cognitive domain affected in Major Depressive Disorder (MDD), with slower information processing and psychomotor speed frequently reported as core neuropsychological features. According to the general slowing theory, reduced processing speed is a sensitive indicator of cognitive aging and acts as a bottleneck contributing to deficits in executive function and working memory. It is also considered the clinical and neurobiological correlate of psychomotor retardation, a cardinal feature of depression. Electrophysiologically, impaired processing speed is reflected by prolonged P300, mismatch negativity (MMN), and N200 latencies, with delayed P300 latency particularly indicating slower cognitive information processing, stimulus evaluation, and decision-making[5]. Common neuropsychological measures include the Digit Symbol Substitution Test (DSST) and Trail Making Test-A (TMT-A), on which depressed individuals show fewer correct responses and prolonged reaction times. Importantly, persistent subthreshold depression is also associated with prolonged DSST response times and fewer correct responses, suggesting that processing-speed deficits may serve as early objective markers of emerging cognitive decline.

2)Executive Function

Executive dysfunction is a major cognitive dimension of Major Depressive Disorder (MDD), affecting planning, initiation, organization, goal-directed behavior, inhibitory control, task-switching, verbal fluency, and cognitive flexibility. Electrophysiological studies using Simon conflict tasks indicate impaired cognitive conflict resolution in MDD, specifically during response execution, reflected by reduced response-locked lateralized readiness potential (R-LRP) amplitudes, suggesting impaired suppression of incorrect prepotent responses and activation of appropriate

actions. Continuous performance testing shows reduced detectability despite normal reaction times, indicating that impaired inhibitory control is not simply a speed–accuracy trade-off but reflects broader prefrontal network dysfunction, consistent with the neurovisceral integration model. Standardized assessments further demonstrate impaired executive function, with increased total and perseverative errors and failures to maintain cognitive set on the Wisconsin Card Sorting Test (WCST), along with prolonged Trail Making Test-B (TMT-B) completion times indicating impaired set-shifting and visuomotor switching. These deficits are further aggravated in comorbid alcohol dependence and MDD, with markedly impaired inhibitory control and loss of the Stroop interference effect. Even in subthreshold depression, early selective executive deficits are evident as fewer DSST correct responses and impaired planning and strategizing.

3)Memory

Memory deficits are common in Major Depressive Disorder (MDD), particularly affecting verbal learning, working memory, and delayed recall. These impairments are closely linked to HPA-axis dysregulation, in which chronic stress-induced hypercortisolemia causes glucocorticoid receptor desensitisation/resistance and hippocampal vulnerability. Given the hippocampus's high glucocorticoid receptor density, prolonged cortisol exposure can suppress neurogenesis, cause dendritic spine atrophy, and reduce BDNF, contributing to impaired verbal and visual memory and hippocampal-dependent learning. Working memory is also reflected by the P300 component, which indexes context updating, stimulus discrimination, and memory retrieval[6]. Depressed individuals show reduced P300 amplitude, with lower baseline amplitude predicting poorer working-memory performance and delayed verbal recall. EEG studies further demonstrate reduced relative beta power during working-memory tasks, with HRV measures showing negative associations with beta and positive associations with delta power, suggesting autonomic–cortical coupling in working-memory and attentional efficiency. Notably, subjective memory complaints (SMCs) show little relationship with objective memory performance or P300 amplitude and are more strongly associated with perceived stress, anxiety, and depressive severity, indicating a distinction between subjective and objective cognitive impairment[6].

4)Persistence After Remission

The traditional "pseudodementia" model considered cognitive impairment in depression to be fully reversible following remission of mood symptoms. However, contemporary evidence indicates that cognitive dysfunction is a persistent and trait-like feature of MDD, affecting up to 94% of patients during acute episodes and often continuing despite clinical remission. Deficits in attention, processing speed, episodic learning, memory, and executive function may persist after affective symptoms improve. This residual dysfunction is associated with neurobiological alterations including cortical thinning, reduced cerebral blood flow, and prefrontal–hippocampal atrophy. Clinical trials with paroxetine and nortriptyline demonstrate significant improvement in depressive symptoms without normalization of cognitive performance, while selective serotonergic agents such as citalopram and escitalopram show limited cognitive benefits; citalopram may even worsen processing speed and verbal learning in non-responders. Thus, residual cognitive impairment is a major barrier to functional recovery and may increase vulnerability to subsequent mild cognitive impairment and dementia, highlighting the need for targeted cognitive remediation even after depressive remission.

Neurophysiological Biomarkers of Cognitive Dysfunction in Major Depressive Disorder

1. The P300 Event-Related Potential

The P300 event-related potential (ERP) is a non-invasive, objective EEG marker of central cognitive information processing with millisecond temporal resolution[17]. It is typically elicited using auditory or visual oddball paradigms, in which infrequent target stimuli are detected among standard distractors. The P300 comprises two functionally distinct components:

- P3a (Novelty-related P3): A frontally distributed, early component reflecting involuntary orienting attention to unexpected stimuli, involving hippocampal and prefrontal regions.
- P3b (Target-related P3): A centroparietally distributed component reflecting voluntary attention, conscious stimulus evaluation, context updating, and working-memory processing.

In active Major Depressive Disorder (MDD), P300 abnormalities are prominent, particularly reduced amplitude, indicating impaired cognitive resource allocation, and prolonged latency, reflecting slower stimulus perception, discrimination, and classification[18].

Correlation with Objective Cognitive Domains

In depressed older adults, particularly those with comorbid Mild Cognitive Impairment (MCI), P300 parameters correlate significantly with objective neuropsychological performance:

- Working Memory: Parietal P300 amplitude shows a significant negative correlation with computerized Letter-n-Back performance, suggesting that reduced neural resources for context updating are associated with impaired information storage and manipulation[19].
- Complex Cognition: P300 latency demonstrates a significant negative correlation with Verbal Reasoning Test performance, indicating that prolonged latency is associated with slower processing speed and reduced verbal fluency during complex cognitive tasks [17,18].

Predictive Value for Mild Cognitive Impairment (MCI) Transition

Longitudinal evidence suggests that P300 latency may predict subsequent MCI development in depressed patients. After one year, individuals who developed MCI showed significantly longer baseline P300, MMN, and N200 latencies than cognitively stable patients. Stepwise logistic regression demonstrated that combining baseline P300 latency with synapse-associated serum biomarkers BDNF and FGF22 provided strong predictive performance, with sensitivity of 0.795, specificity of 0.821, and overall accuracy of 0.806. Integrating P300 latency with FGF22 and BDNF may therefore improve early detection by capturing both electrophysiological processing deficits and biochemical alterations in synaptic function[19].

The Trait Marker Paradox: Lifetime MDD and Twin Studies

Although active MDD is associated with reduced P300 amplitude, studies of young adult twins with a lifetime history of MDD demonstrate a distinct neurophysiological pattern. After controlling for familial factors, genetics, alcohol abuse, and smoking, individuals with lifetime MDD showed increased novelty-related P3a amplitude and reduced (accelerated) target-related P3b latency. This pattern suggests heightened attentional sensitivity and involuntary distractibility that may persist beyond depressive episodes, indicating that some neurophysiological abnormalities may represent stable, trait-like vulnerabilities rather than solely state-dependent effects [13].

2. Other EEG and ERP Measures

Other ERPs and quantitative EEG measures complement P300 by capturing different stages of automatic, cognitive, motor, and elaborative processing in MDD.

N200 (N2) and Cognitive Conflict Resolution

The N200 (N2) is a frontally distributed negative potential peaking at approximately 250–350 ms, reflecting conflict monitoring, mismatch detection, and response inhibition. In healthy individuals, its amplitude is modulated during interpersonal processing, with greater absolute amplitude under "negative other" conditions in the Extrinsic Affective Simon Task (EAST), reflecting conflict with a default positive other-schema. In MDD, this schema-related N200 modulation is absent, suggesting impaired early automatic processing of social and emotional cues. Prolonged baseline N200 latency is also associated with subsequent objective cognitive decline and MCI development [23,24].

Lateralized Readiness Potential (LRP) and Motor Execution

The Lateralized Readiness Potential (LRP) reflects pre-motor preparation and response execution. Using Simon conflict tasks and Residue Iteration Decomposition (RIDE), LRP components can distinguish perceptual coding from response execution:

- Perceptual Coding (S-LRP): No significant abnormalities in amplitude or latency, indicating preserved early visual and stimulus-processing mechanisms.
- Stimulus-Response Translation (P300-C): Stable amplitudes indicate preserved translation of perceptual information into appropriate action.
- Response Execution (R-LRP): Significantly reduced amplitudes under both congruent and incongruent conditions indicate impaired response execution.

Thus, executive dysfunction in MDD appears to arise primarily from a selective deficit in early motor regulation and response execution, affecting suppression of incorrect prepotent responses and activation of appropriate responses rather than perceptual processing.

Late Positive Potential (LPP) and Elaborative Processing

The Late Positive Potential (LPP) is a centroparietal potential occurring after 600 ms, reflecting conscious, top-down elaborative processing of emotional stimuli through prefrontal–anterior cingulate networks. In EAST paradigms, MDD patients show significantly reduced LPP amplitude specifically for "positive self-words." This suggests that abnormalities in self-referential processing emerge predominantly at a late elaborative stage, with impaired processing and consolidation of positive self-related information despite relatively preserved early N200 and P300 responses [23,24,25].

N170 and Early Face Processing

The N170 is a face-specific ERP reflecting structural face encoding in the occipitotemporal cortex. In patients with depression and obstructive sleep apnea (OSAHS), emotional-face paradigms demonstrate significantly prolonged N170 latency. This delay correlates with daytime sleepiness, slow-wave sleep deprivation, and cognitive decline (MoCA scores), suggesting that N170 may serve as an early objective marker of impaired automatic face-processing speed in depressed, sleep-deprived individuals [23,24,25].

3. Limitations of Neurophysiological Biomarkers

Although neurophysiological biomarkers provide valuable millisecond-level insights into cognitive dysfunction, several limitations restrict their current clinical utility and generalizability:

- High Overlap and Lack of Etiological Specificity: Abnormal ERP parameters, particularly prolonged P300 latency and reduced amplitude, are not specific to MDD and occur in various neurological, psychiatric, and metabolic disorders, including Alzheimer's disease, dementia, Parkinson's disease, schizophrenia, epilepsy, vestibular disorders, and diabetic neuropathy. Therefore, P300 or N170 abnormalities alone have limited diagnostic specificity.
- Sample Size Constraints and Demographic Bias: Neurophysiological studies often involve small, convenience-based samples with restricted or unequal demographic representation. Studies limited to males to avoid menstrual hormonal variability reduce generalizability to females, while cohorts with disproportionate female representation may introduce sex-related confounding.
- Active Medication and Substance Comorbidities: Psychotropic medications, particularly SSRIs, can alter ERP parameters and complicate interpretation of electrophysiological findings. Smoking and alcohol use, both common in MDD, can independently and differentially affect P300 amplitude and latency and are often inadequately controlled.
- Spatial Resolution and Methodological Divergence: Conventional EEG has limited spatial resolution, and studies using only a few electrodes may fail to capture complex topographical network dynamics. Although techniques such as RIDE and ICA improve ERP component analysis, their long-term test–retest reliability and internal consistency in psychiatric populations remain insufficiently established.
- High Cost and Implementation Barriers: Multimodal approaches combining high-density EEG, polysomnography, fMRI, and biochemical markers are costly and logistically demanding. Distinguishing subtle

cognitive abnormalities from normal aging or transient stress requires adequately powered, standardized, longitudinal studies, limiting their routine clinical applicability.

Autonomic Biomarkers of Cognitive and Emotional Dysregulation

1. Heart Rate Variability (HRV)

Heart rate variability (HRV), the natural variation in consecutive R–R intervals, is a non-invasive marker of autonomic nervous system (ANS) regulation. It reflects the activity of the Central Autonomic Network (CAN), comprising the prefrontal cortex, anterior cingulate cortex (ACC), insula, and amygdala, and therefore provides a physiological index of central–peripheral autonomic integration [1].

HRV is assessed using time-domain, frequency-domain, and non-linear measures:

- Time-Domain Indices: SDNN reflects overall HRV and combined autonomic influences, while RMSSD measures short-term beat-to-beat variability and is a predominantly vagally mediated index of parasympathetic activity.
- Frequency-Domain Indices: HF (0.15–0.40 Hz) reflects respiratory sinus arrhythmia and vagal parasympathetic modulation. LF (0.04–0.15 Hz) represents combined sympathetic and parasympathetic influences and, at rest, is strongly influenced by cardiac baroreflexes rather than serving as a pure measure of sympathetic activity. The LF/HF ratio is conventionally used to represent sympathovagal balance.
- Non-Linear Poincaré Plot Parameters: SD1 reflects instantaneous beat-to-beat variability and correlates with parasympathetic activity, whereas SD2 represents longer-term HRV.

Large systematic and umbrella reviews consistently indicate reduced resting HRV in psychiatric and neurocognitive disorders, suggesting impaired autonomic flexibility and adaptive capacity. An umbrella review of 21 systematic reviews involving 34,625 participants found suggestive evidence of reduced resting HRV in dementia, PTSD, somatic symptom disorders, and schizophrenia, while evidence for reduced overall HRV and vagal tone in adult MDD was weaker (class IV) [4,8].

2. Sympathetic/Parasympathetic Dysfunction

The association between MDD and cognitive impairment is strongly linked to autonomic imbalance, characterised by sympathetic hyperactivation and reduced parasympathetic (vagal) tone. Chronic stress and HPA-axis overactivation contribute to reduced vagal output and cardiorespiratory and neuroendocrine instability [5].

Neurovisceral Decoupling and Executive Dysfunction

The neurovisceral integration model proposes that cardiac vagal tone (vm-HRV) reflects the integrity of prefrontal–subcortical inhibitory circuits involved in attentional regulation and cognitive flexibility. In healthy individuals, higher resting SDNN, LF, and HF are associated with better inhibitory control (IC) and faster visual reaction times. In MDD, this central–peripheral relationship is disrupted [8,10].

During the Conners Continuous Performance Test-II (CCPT-II), healthy individuals show an association between parasympathetic lnHF and inhibitory control (detectability,), whereas MDD patients demonstrate lower detectability and a complete decoupling between autonomic indices and cognitive performance, suggesting impaired prefrontal network functioning[10,14].

Altered Central-Peripheral Autonomic Coupling

Combined neuroimaging and ECG studies demonstrate abnormal coupling between the Central Autonomic Network (CAN) and peripheral autonomic activity in MDD:

- Negative Insular/Prefrontal Coupling: Resting HRV intermediate-frequency activity (IM; 0.12–0.18 Hz) is linked to insular and prefrontal BOLD activity. Healthy individuals show positive coupling during cognitive reappraisal in the right insula and right vlPFC, whereas MDD shows reversed negative coupling, indicating prefrontal deactivation and impaired top-down autonomic regulation [14].
- Aberrant vmPFC Reactivity: During longitudinal neurofeedback, healthy controls demonstrate stable inverse vmPFC-HRV coupling, while MDD patients show unstable and fluctuating coupling.
- Effortful Respiratory Regulation: During cognitive emotion regulation, MDD patients exhibit widespread positive coupling of respiratory IM activity with the ACC, hippocampus, insula, and dmPFC, suggesting more effortful and compensatory, but less efficient, central regulation of autonomic homeostasis.

The Developmental Pathway of Childhood Trauma

Early-life stress contributes substantially to adult autonomic and depressive pathology. Adults with depression and early adverse life events (EALs) or childhood trauma show significantly lower resting LF, HF, SDNN, and RMSSD than healthy controls. Mediation analyses indicate that LF-HRV partially mediates the relationship between childhood trauma and adult depressive severity [22,29].

Two potential mechanisms are proposed: (1) childhood adversity may impair recruitment of prefrontal executive networks, reducing top-down emotional control and vagal output; or (2) trauma may disrupt ANS development, resulting in inadequate vagal maturation and reduced autonomic feedback required for normal prefrontal development, thereby increasing vulnerability to adult depression and cognitive decline.

The Non-Linear Compensation Paradigm in Cognitive Decline

Although parasympathetic activity generally declines with advancing neurocognitive pathology, early mild neurocognitive disorder (mNCD) may show a paradoxical compensatory increase in resting HF-HRV (normalized units). Older adults with biomarker-supported mNCD demonstrate higher HF-HRV than healthy older adults, potentially reflecting compensatory hyperactivation of CAN regions such as the ACC to preserve cognitive function. With progression to dementia, this compensatory capacity may become exhausted, resulting in the characteristic decline of total and parasympathetic resting HRV[16].

3. Limitations of Autonomic Biomarkers

Despite the clinical potential of HRV and peripheral autonomic measures, several limitations restrict their translation into routine diagnostic tools:

- Lack of Etiological and Diagnostic Specificity: Autonomic dysregulation is a transdiagnostic feature shared across dementia, PTSD, somatic symptom disorders, schizophrenia, GAD, and panic disorder. Similar reductions in vagal measures such as RMSSD and HF therefore prevent isolated HRV indices from distinguishing specific psychiatric disorders.
- Vast Methodological Heterogeneity: Studies differ substantially in ECG/PPG recording duration (from 5-minute resting assessments to 24-hour monitoring) and HRV calculation methods, including absolute power (ms^2), logarithmic transformation, and normalized units (n.u.), contributing to inconsistent findings.
- The Confound of Baseline Anticipatory Stress: Short-term resting HRV is sensitive to measurement context. While continuous ambulatory monitoring in subthreshold depression detects reduced LF power, 2-minute recordings immediately before cognitive testing may show no group differences because anticipatory stress suppresses parasympathetic activity, particularly in healthy controls.
- Significant Demographic and Lifestyle Confounders: HRV is influenced by age, gender, BMI, physical fitness, physical activity, and education, which are often inadequately controlled. For example, greater physical activity can substantially increase resting HRV and confound studies of early cognitive decline.
- The Influence of Active Medications and Substances: SSRIs and beta-blockers can independently alter heart rate and HRV, while alcohol consumption and tobacco smoking affect sympathovagal regulation, complicating identification of depression-specific autonomic patterns.
- High Risk of Methodological Bias in Existing Reviews: The quality of the existing literature is variable. In an umbrella review of HRV in mental disorders, only 5 of 21 systematic reviews met the high-quality standards of the AMSTAR 2 tool, raising concerns about the robustness and generalizability of reported effects.
- Controversial Physiological Interpretation of Low Frequency (LF) and LF/HF Ratio: The LF/HF ratio, traditionally viewed as an index of sympathovagal balance, has increasingly been questioned because LF does not reliably represent sympathetic cardiac activity and is substantially influenced by parasympathetic-mediated baroreflex mechanisms, making its physiological interpretation ambiguous.

Neuroendocrine Biomarkers

1)HPA Axis

The hypothalamic-pituitary-adrenal (HPA) axis is a major neuroendocrine pathway regulating the stress response. Stress stimulates hypothalamic CRH release, which triggers pituitary ACTH secretion and subsequent glucocorticoid, primarily cortisol, release from the adrenal cortex. Cortisol normally provides negative feedback to the hypothalamus and pituitary. In MDD, approximately 40–60% of patients exhibit hypercortisolemia or HPA-axis dysregulation, driven partly by glucocorticoid receptor (GR) desensitization and down-regulation, resulting in glucocorticoid resistance and impaired negative feedback [33,36]. Co-secreted arginine vasopressin (AVP) synergistically enhances ACTH release, further promoting HPA-axis hyperactivity.

2)Cortisol

Cortisol, a cholesterol-derived glucocorticoid, regulates glucose metabolism, inflammation, and basal homeostasis. It normally follows a diurnal rhythm, peaking 30–45 minutes after awakening and declining toward evening. In MDD, this rhythm is often flattened or chronically elevated. Although acute cortisol responses are adaptive, persistent hypercortisolemia can compromise the blood–brain barrier, activate microglia and neuroinflammation, increase reactive oxygen species (ROS), and cause structural damage, particularly in the prefrontal cortex (PFC) and hippocampus.

Relationship with Cognition

HPA-axis hyperactivity and elevated cortisol are associated with objective cognitive deficits in MDD. The hippocampus, which has a high density of corticosteroid receptors, is particularly vulnerable to chronic glucocorticoid exposure. Prolonged cortisol excess suppresses hippocampal neurogenesis, causes dendritic retraction, and reduces dendritic spine density in CA1 and CA3 pyramidal neurons, contributing to impaired verbal memory, spatial learning, and working memory. Cortisol also disrupts BDNF signaling, impairing synaptic plasticity and cognitive flexibility. Additionally, glucocorticoid excess and pro-inflammatory cytokines enhance tryptophan degradation through the kynurenine pathway, reducing serotonin availability and increasing neurotoxic metabolites such as quinolinic acid, thereby contributing to excitotoxicity, executive dysfunction, and memory impairment. Neuroimaging further demonstrates inverse amygdala–vmPFC coupling during negative-affect regulation, which predicts altered diurnal cortisol patterns and links central cognitive-emotional networks with peripheral endocrine rhythms[40].

Peripheral Physiological Markers of Cognitive Dysfunction

1. Handgrip Strength

Handgrip strength (HGS), measured isometrically using a hydraulic dynamometer, is a validated, simple peripheral marker of neuromuscular health and functional capacity and is associated with cognitive decline, psychiatric illness, and neurodegeneration in older adults. Population studies show that greater HGS is associated with better fluid intelligence, processing speed, memory, and executive function, as well as fewer anxiety and depressive symptoms. These associations may be stronger in females than males[7].

Prospective nine-year data indicate that lower baseline HGS predicts subsequent decline in fluid intelligence, prospective memory, reaction time, and visual memory, whereas baseline cognitive impairment is a substantially weaker predictor of later muscle-strength decline. Conversely, higher neuroticism, lower health satisfaction, and poorer financial satisfaction predict subsequent reductions in HGS[44].

Neurobiological and Subcortical Correlates

Brain-wide structural studies demonstrate that greater HGS is associated with increased grey matter volume (GMV), particularly in subcortical regions such as the ventral striatum, thalamus, putamen, pallidum, and brainstem, and limbic-temporal regions including the hippocampus, amygdala, parahippocampal gyrus, temporal pole, and temporal fusiform cortex. GMV in these regions partially mediates the relationship between HGS and cognitive performance, explaining up to 21.83% of variance in numeric/working memory and approximately 15% in symbol-digit substitution[45].

Geriatric Rehabilitation and Multi-Dimensional Staging

In geriatric rehabilitation, HGS provides an indicator of physical, nutritional, cognitive, and psychological vulnerability. In a pilot study of 80 older adults (mean age 69.6 years), greater digital HGS was associated with better Rapid Cognitive Screen performance, improved nutritional status, and lower physical frailty. Among older women, higher HGS was associated with better Mini Nutritional Assessment (MNA) scores, marital status, and cognitive performance, and lower frailty and depressive symptoms.

Causal Triangulation and Physical Activity Mediation

Two-sample Mendelian Randomization (MR) studies support a direct, genetically predicted causal relationship between HGS and general cognitive function. MR mediation analyses further indicate that moderate-to-vigorous physical activity (MVPA) during leisure time mediates 10.6% of the total causal effect of HGS on cognition. Clinical trials also show that resistance training improving muscular fitness can enhance global cognition in older adults with cognitive impairment. Genetically predicted higher HGS additionally appears to provide causal protection against falls, physical frailty, clinical depression, and ischemic stroke[41,47].

2. Bioimpedance Parameters

Bioelectrical impedance analysis (BIA) is an inexpensive, non-invasive, and reproducible technique that measures tissue resistance (R) and reactance (Xc) to assess body composition, muscle quality, and cellular water compartments. Although whole-body measures such as BMI and total fat-free mass may not distinguish cognitively normal (CN) individuals from those with Mild Cognitive Impairment (MCI), segmental multi-frequency BIA identifies localized cellular and fluid abnormalities, particularly in the lower extremities [48].

Electrophysiological Markers of Cellular Integrity

At 50 kHz, reactance and phase angle (PA) reflect cell membrane integrity, cellular strength, and body cell mass. Reactance represents the ability of cell membranes to store electrical charge, while PA is a sensitive marker of cellular health, inflammation, and malnutrition. Older adults with MCI and early Alzheimer's disease (AD) show significantly reduced lower-extremity reactance and PA.

Abnormal Cellular Hydration and Fluid Shifts

Reduced lower-extremity reactance and resistance are associated with abnormal cellular water distribution, involving a shift from intracellular water (ICW) to extracellular water (ECW), reduced cell volume, and localized overhydration of lean tissue. Segmental multi-frequency BIA shows that lower-extremity segmental water (SW_lower) and segmental lean mass (SL_lower) are positively associated with MCI, indicating lower-limb overhydration. These associations are particularly significant in women, with lower-extremity resistance and reactance showing high sensitivity to cognitive decline[48].

Staging the AD Continuum via Vector Analysis

Bioelectrical Impedance Vector Analysis (BIVA), which plots height-normalized resistance and reactance on an RXc graph, demonstrates progressive downward and rightward displacement of 95% confidence ellipses from CN to MCI and AD dementia. This pattern reflects progressive loss of body cell mass, impaired membrane integrity, and lower-limb overhydration. Changes are greatest during the CN-to-MCI transition and slower from MCI to AD dementia, suggesting that impaired cellular integrity and fluid homeostasis are early manifestations of AD pathology and supporting lower-extremity BIA measures as cost-effective biomarkers for early and progressive cognitive decline [49].

3. Metabolic and Inflammatory Markers

Cognitive dysfunction in depression is closely linked to chronic low-grade inflammation, metabolic dysregulation, and neuroinflammation. Chronic psychological, environmental, or early-life stress activates the HPA axis and sympathetic system, increasing circulating catecholamines, glucocorticoids, and pro-inflammatory cytokines [36].

Neuroinflammatory Cascades and Blood-Brain Barrier Breakdown

MDD is associated with elevated IL-1β, IL-6, TNF-α, and hs-CRP. Intestinal dysbiosis and increased gut permeability may facilitate translocation of lipopolysaccharides (LPS) and microbial antigens, promoting systemic inflammation. Cytokines such as IL-1β and TNF-α reduce BBB tight-junction proteins, increasing BBB permeability and allowing inflammatory signals to activate microglia and astrocytes. This promotes ROS and excitotoxic glutamate release, suppresses BDNF, impairs hippocampal neurogenesis and synaptic integrity (including reduced synaptophysin), and promotes neuronal apoptosis, contributing to executive and memory deficits [35].

The Tryptophan-Kynurenine Bypass

Inflammatory cytokines (IL-6, TNF-α) and cortisol increase IDO and TDO activity, diverting tryptophan from serotonin synthesis toward the kynurenine pathway. Reduced serotonin availability is accompanied by accumulation of neurotoxic metabolites, particularly quinolinic acid, in the hippocampus and prefrontal cortex. Quinolinic acid induces NMDA-mediated excitotoxicity and oxidative stress, contributing to prefrontal–hippocampal atrophy and impairments in attention, processing speed, and cognitive flexibility [50].

Adipokines, Myokines, and Network Dyshomeostasis

In older adults, adipose and muscle tissues act as endocrine organs through adipokines and myokines, influencing cognition and cardiovascular function[51]. In poorly managed hypertension (PMHTN), network analyses demonstrate disrupted relationships among cognitive reserve, physical performance, and metabolic biomarkers:

- Adiponectin: Normally promotes hippocampal plasticity and neurogenesis and correlates positively with MoCA delayed recall; this relationship is lost in PMHTN[51].
- Vaspin: Higher levels, associated with greater body fat/BMI, correlate with poorer MMSE and TMT-B performance, indicating cognitive inefficiency and physical frailty [52].
- Visfatin: Positively associated with mean and systolic BP in normotensive individuals but negatively associated with mobility and gait speed (Timed Up and Go) in hypertensive older adults [52].
- IGF-1 & IGFBP-3: Their positive association with cognitive activity in healthy controls is lost in PMHTN, suggesting a metabolic pathway contributing to accelerated cognitive vulnerability[53].

Multimodal Physiological Biomarker Models

1. The Paradigm Shift: From Single-Channel to Multimodal Predictive Analytics

Traditional psychiatric assessment relies heavily on isolated biomarkers and subjective clinical scales. However, cognitive impairment in MDD involves interacting abnormalities in synaptic function, HPA-axis activity, autonomic regulation, and cellular-fluid homeostasis, limiting the sensitivity and specificity of single markers. Multimodal models therefore integrate independent physiological domains to provide a systemic representation of cognitive and affective dysfunction. Systems-based network medicine further demonstrates interconnected abnormalities across cognition, autonomic function, blood pressure, and trophic factors, particularly in comorbid cardiovascular and affective disorders.

2. Electrophysiological-Serological Synergistic Models

Combining central electrophysiology with peripheral markers of synaptic integrity can improve prediction of cognitive deterioration. A validated model combining P300 latency (information-processing speed) with serum BDNF and FGF22 (synaptic formation and plasticity markers) predicts transition from depression to MCI.

Stepwise logistic regression produced 80.6% accuracy, 79.5% sensitivity, and 82.1% specificity, compared with only 62.5% accuracy for P300 latency alone. MoCA scores correlate positively with baseline BDNF and FGF22 and negatively with P300 latency, supporting the superior value of combining electrophysiological and biochemical markers to reflect synaptic dysfunction[55].

3. Central-Peripheral Autonomic fMRI Coupling Models

Multimodal fMRI–ECG–respiration approaches characterize interactions within the Central Autonomic Network (CAN) by linking cerebral BOLD activity with peripheral HRV and respiratory intermediate-frequency (IM; 0.12–0.18 Hz) oscillations [32].

During cognitive-emotional regulation, MDD demonstrates reversed negative HRV-IM coupling with the right insula and right vlPFC, indicating impaired top-down emotional regulation, together with widespread hyperactive respiratory-IM coupling involving the ACC, hippocampus, bilateral insula, and dmPFC [34]. This pattern suggests inefficient, compensatory CNS recruitment to maintain autonomic homeostasis. Incorporating early adverse life events further indicates that childhood trauma disrupts prefrontal executive control, promotes amygdala/insula hyperactivation, and reduces vagal output (RMSSD) during cognitive-emotional regulation [28].

4. Contactless Digital Biomarker Fusion

To reduce the cost and burden of conventional neuroimaging and multi-lead ECG, contactless multimodal systems combine automated facial expression analysis (AFEA), remote photoplethysmography (rPPG)-derived HRV, and wireless EEG for continuous real-world monitoring.

- AFEA + Heart Rate (HR): Video-based facial features combined with rPPG-derived HR achieve 75.8% classification accuracy for cognitive-affective engagement, outperforming facial analysis alone [56].
- AFEA + EEG: Fusion of facial expressiveness with frontal EEG spectral features, including theta and alpha power, improves classification of emotional processing and cognitive status[57].

These systems integrate observable facial behaviour with cortical and autonomic signals, offering an unobtrusive approach for continuous monitoring of early cognitive decline and late-onset depression.

5. Integrated Somatic-Cognitive (BIA-NBT) Models

Combining segmental multi-frequency BIA with standardized neuropsychological test batteries (NBT) may improve early cognitive screening by capturing systemic changes in cellular integrity and fluid distribution. Lower-extremity reactance and resistance, reflecting reduced body cell mass, impaired membrane capacitance, and overhydration, combined with cognitive measures such as MMSE, improve MCI detection compared with cognitive screening alone [3].

Adding digital handgrip strength assessment (e.g., Squegg™) and brief depression measures such as GDS-15 enables rapid, low-cost multidimensional assessment integrating muscle strength, physical frailty, cellular health, depression, and cognitive decline.

Current Gaps and Limitations in Multimodal Physiological Biomarker Research

1. Methodological Heterogeneity and Standardisation Barriers

Clinical translation is limited by substantial methodological heterogeneity. HRV studies range from 2–5-minute resting recordings to 24-hour ambulatory monitoring, with inconsistent use of absolute power, logarithmic values, and normalised units, producing contradictory results. Measurement context also matters; anticipatory stress before cognitive tasks can suppress parasympathetic activity and obscure group differences. EEG/ERP studies similarly vary in stimuli, task demands, electrode configurations, and signal-processing methods such as RIDE, while the test–retest reliability and psychometric properties of decomposed ERP components remain insufficiently established.

2. Confounding Variables and Lack of Etiological Specificity

Most physiological biomarkers are transdiagnostic rather than disease-specific. Prolonged/reduced P300 parameters occur in MDD, schizophrenia, bipolar disorder, Alzheimer's disease, vascular dementia, and vestibular disorders, while reduced HRV occurs across PTSD, GAD, somatic symptom disorders, and schizophrenia.

Interpretation is further affected by:

- Active Medications: SSRIs such as fluoxetine and citalopram can alter P200/P300 parameters and cardiac autonomic activity.
- Comorbidities: Alcohol use, smoking, and anxiety can independently and sometimes oppositely influence neuroendocrine and neurophysiological measures.
- Demographics: Age, sex, BMI, fitness, and education influence muscle mass, fluid distribution, and autonomic tone and require careful matching or adjustment.

3. The Challenge of Causality in Cross-Sectional Designs

Most studies linking HPA-axis activity, HRV, somatic measures, and cognition are cross-sectional and therefore cannot establish temporal or causal relationships. For example, associations between HGS, autonomic function, and brain structure cannot determine whether physical/autonomic dysfunction causes neurodegeneration, results from depression, or reflects shared pathology [10] . Mendelian Randomization (MR) provides preliminary causal evidence linking HGS with cognition, but requires prospective clinical validation. Similarly, longitudinal BIA studies are scarce, with BIVA largely limited to cross-sectional dementia research, leaving its utility for early cognitive change and prodromal MDD unclear [8,11,15,41].

4. Subtype and Population Heterogeneity

Aggregating biologically heterogeneous disorders can obscure meaningful effects. HPA-axis hyperactivity and hypercortisolemia are more characteristic of severe, melancholic, and psychotic depression and may be absent in atypical depression [. Similarly, mNCD studies rarely distinguish Alzheimer's disease, Lewy body dementia, frontotemporal degeneration, and vascular etiologies, limiting subtype-specific brain–heart research.

Generalizability is further restricted by small convenience samples and demographic imbalance, including male-only cohorts or over-representation of highly educated and affluent populations, with inadequate representation of diverse and clinically complex groups.

5. Technological and Analytical Gaps in Multimodal Integration

Despite strong rationale, true brain–heart–body integration remains limited, with ERPs, HRV, cortisol, and BIA traditionally studied in separate disciplines. Simultaneous multimodal datasets are rare, and systems combining AFEA, rPPG, and EEG have largely been evaluated in small healthy samples rather than psychiatric or geriatric populations.

Advanced approaches such as machine learning and systems-based network medicine remain underused. Large-scale, clinically validated algorithms capable of modelling non-linear interactions across multiple biomarkers are needed to distinguish subtle cognitive decline from normal aging and transient affective changes.

6. Data Privacy, Governance, and Real-World Feasibility

Continuous digital monitoring through smartphones, wearables, video, and passive sensors generates highly sensitive information about emotional state, motor behavior, and cognitive performance. Robust frameworks for data governance, informed consent, privacy protection, and algorithmic-bias prevention remain limited.

Clinical implementation is additionally constrained by technology acceptance among older adults, equipment and infrastructure costs, and insufficient multidisciplinary training required to interpret complex multimodal physiological data.

Future Directions in Multimodal Physiological Biomarker Research

1. Integrating the Gut-Microbiota-HPA-Brain Axis

Future research should integrate the HPA axis and gut-brain axis (GBA), as chronic stress-related HPA hyperactivity can promote gut dysbiosis, increased intestinal permeability, systemic inflammation, and neuroinflammation. Longitudinal trials should evaluate precision psychobiotics, prebiotics, personalized diets, and fecal microbiota transplantation (FMT) to determine whether microbiome restoration can reduce inflammatory cytokines, normalize diurnal cortisol, support serotonin synthesis, and preserve hippocampal neurogenesis and synaptic plasticity.

2. Contactless Multimodal Sensor Fusion and Real-World Digital Phenotyping

Future psychiatric monitoring should move toward continuous, passive, real-world assessment using contactless technologies. Combining Automated Facial Expression Analysis (AFEA), remote photoplethysmography (rPPG)-derived HRV, and wearable EEG/fNIRS could enable unobtrusive monitoring of cognitive and affective changes. These systems should be validated against gold-standard ECG and neuroimaging across diverse cognitive and social stressors and tested in homes, nursing facilities, and residential settings. Robust data governance, consent, privacy, and ethical frameworks will be essential.

3. Longitudinal Cohort Designs and Causal Triangulation

Future studies should replace predominantly cross-sectional designs with multi-year prospective cohorts tracking progression from healthy states through subthreshold depression (StD), MDD, and mild neurocognitive disorder (mNCD). Combining longitudinal data with two-sample Mendelian Randomization (MR) can clarify causal relationships between peripheral markers—including appendicular lean mass, BIA-derived phase angle, and HGS—and cognitive function, determining whether frailty and sarcopenia are causal risk factors or consequences of shared neurodegenerative pathways.

4. Subgroup-Specific and Transdiagnostic Biotyping

Rather than binary diagnostic categories, future research should use multimodal biomarker profiles to identify biologically meaningful depression subtypes. Large transdiagnostic datasets analyzed using machine/deep learning could integrate high-density ERP measures, including R-LRP deficits, with BIA/BIVA-derived cellular and hydration profiles. Such biotyping may distinguish prodromal neurodegenerative frontal-autonomic compensation from the parasympathetic withdrawal and neurovisceral decoupling characteristic of primary adult MDD.

5. Biomarker-Guided Autonomic and Cognitive Remediation Trials

Randomized clinical trials should evaluate targeted, non-pharmacological interventions including HRV biofeedback, mindfulness, progressive resistance training, and structured yoga-diet programs. Repeated P300 measurements and continuous HRV monitoring should provide objective markers of neuroplastic and autonomic recovery. Using these physiological measures as treatment endpoints, alongside subjective scales, could improve treatment dosing, response monitoring, and personalized psychiatric rehabilitation.

CONCLUSION

The clinical characterization of cognitive dysfunction in Major Depressive Disorder (MDD) has reached a critical evolutionary junction, transitioning from a localized, subjective diagnostic framework to an objective, systems-based neurobiological paradigm. Historically categorized as a state-dependent "pseudo-dementia" expected to resolve completely upon the alleviation of mood symptoms, modern clinical and longitudinal evidence establishes that cognitive deficits frequently persist as disabling, trait-like remnants during remission. This review systematically integrates diverse neurobiological channels to demonstrate that cognitive impairment in MDD is a systemic brain-body pathology, wherein central neurocognitive degradation is tightly coupled with autonomic withdrawal, neuroendocrine hyperdrive, peripheral neuromuscular weakness, and cellular-fluid dyshomeostasis.

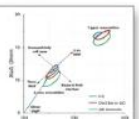
A critical analysis of the existing literature reveals several profound methodological and conceptual gaps that currently restrict the clinical translation of these physiological biomarkers. First, the vast majority of biomarker studies rely on cross-sectional designs, which fail to establish temporal cascades or provide definitive causal evidence. While advanced genetic techniques like Mendelian Randomization have begun to map causal pathways between peripheral metrics—such as handgrip strength—and global cognition, these causal networks require rigorous, long-term prospective validation in clinical cohorts. Second, extensive methodological heterogeneity in data collection—especially in short-term heart rate variability (HRV) recording lengths, quantitative EEG configurations, and bioimpedance parameters—introduces substantial experimental noise, compounding the "anticipatory stress" of active testing environments. Third, isolated physiological parameters exhibit a stark lack of diagnostic specificity. Alterations such as reduced P300 amplitudes or diminished vagally-mediated HRV represent general transdiagnostic markers of general psychopathology and autonomic dysregulation, shared across PTSD, anxiety, schizophrenia, and primary dementias, rather than MDD-specific signatures. Finally, study designs are heavily confounded by the active use of psychotropic medications, patient-selection biases, small sample sizes of convenience, and gender-restricted samples.

The primary importance of this review lies in its timely, multidimensional synthesis, which directly dismantles clinical siloes to introduce an integrated, systems-based network medicine framework. By contrasting the stark subjective-objective paradox—wherein Subjective Memory Complaints (SMCs) serve as indicators of acute psychosocial distress and current affective severity rather than actual neural or objective memory decline—this review underscores the clinical danger of utilizing subjective proxy scales as diagnostic criteria for Mild Neurocognitive Disorder (mNCD). Crucially, this review demonstrates that while single-channel variables are insufficient, multimodal predictive analytics and sensor-fusion models significantly enhance diagnostic and prognostic precision. Combining electrophysiological markers of information processing speed (P300 latency) with serological markers of synaptic plasticity (BDNF and FGF22) yields a clinically validated model capable of predicting subsequent Mild Cognitive Impairment (MCI) transition in depressed patients with a high accuracy of 80.6%. Ultimately, by outlining how targeted interventions like resistance training, yoga, and HRV biofeedback can actively restore HPA-axis equilibrium and vagal tone, this review provides a definitive clinical roadmap to utilize objective brain-body biotypes for personalized risk stratification, therapeutic monitoring, and comprehensive psychiatric care

SYSTEMIC BIOMARKERS OF COGNITIVE DECLINE AND DEPRESSION.

SYSTEM MODALITY	SPECIFIC BIOMARKER	TARGET CONDITION	SHIFT	CLINICAL SIGNIFICANCE & MECHANISM		CONTEXT / NUANCE
Autonomic & Behavioral	Vagally Mediated HRV (RMSSD)	Depression / Stress Response	↓ (Low HRV)	High HRV acts as a physiological shield, neutralizing the adverse depressive effects of expressive suppression.	●	Evaluated in spousal bereavement and older adults.
Neurophysiological (EEG/ERPs)	P300, MMN, & N200 Latencies	Depression transitioning to MCI	↑ (Prolonged)	Early markers of synaptic damage. P300 latency independently predicts MCI onset in depressed patients; reflects slowed cognitive processing.	●	Measurable before clinical onset of MCI.
Bioelectrical Impedance (BIA)	Lower Extremity Reactance (Xc) & Phase Angle (PA)	MCI / Alzheimer's Disease (AD)	↓ (Decreased)	Indicates reduced body cell mass and weakened cell membrane capacitance. Strong link to MCI/AD.	●	Most pronounced in females.
Bioelectrical Impedance (BIA)	Lower Extremity Resistance (R)	MCI / AD	↓ (Decreased)	Indicates fluid shifts and overhydration (↑ Extracellular Water) in lean mass.	◑	Specifically localized to lower extremities in cognitive decline.
Biochemical & Endocrine	Serum BDNF, FGF22 & Cortisol	Depression / Chronic Stress	BDNF/FGF22 ↓ Cortisol ↑	Elevated cortisol drives hippocampal atrophy. Depleted BDNF/FGF22 halts excitatory synapse formation.	●	Evaluated in longitudinal serum studies.

The Predictive Triad: Combining BDNF, FGF22, and P300 latency yields highly accurate predictive models (AUC = 0.790) for MCI in depression.

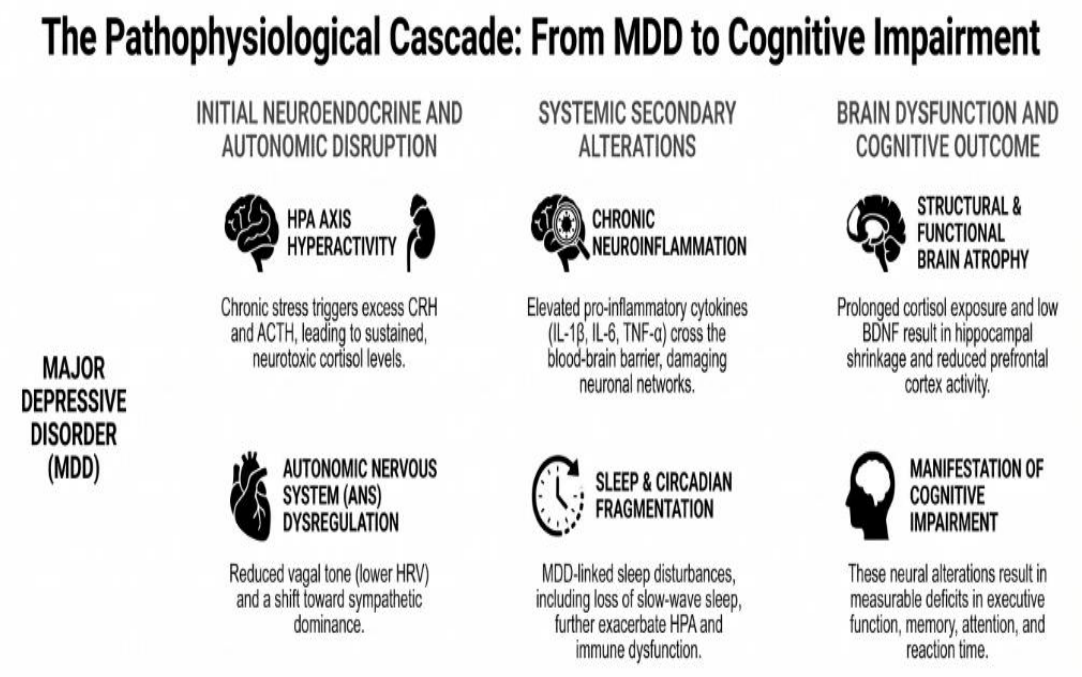


Data Extraction Table:

Physiological Marker	Measurement Methodology	Cognitive Domain	Depression Severity Correlation	Brain Region Association (Inferred)	Clinical Outcome/Review Perspective
P300 (Event-Related Potential)	EEG (Auditory/Visual Oddball Paradigm); Latency (ms) and Amplitude (μV)	Attention, working memory, information processing speed, and stimulus evaluation	Negative correlation; reduced amplitude and prolonged latency correlate with higher severity and cognitive slowing	Parietal cortex, Frontal-limbic circuits, Temporoparietal junction, and Anterior Cingulate Cortex (ACC)	Objective electrophysiological biomarker for monitoring cognitive resource allocation; latency is often more sensitive than amplitude in early MDD
EEG (Spectral Power & Rhythms)	Quantitative EEG; Spectral analysis (Alpha, Theta, Delta, Beta power)	Executive function, working memory, and internal concentration	Frontal alpha asymmetry and slow-frequency (theta/delta) power correlate with severity and cognitive deficits	Prefrontal Cortex (PFC), Hippocampus, and Frontal-occipital networks	Multimodal EEG features provide high sensitivity for MDD cognitive phenotypes; beta wave changes act as gatekeepers for information retention
Heart Rate Variability (HRV)	ECG/PPG analysis; Time-domain (RMSSD, SDNN) and Frequency-domain (HF, LF, LF/HF ratio)	Executive function, emotion regulation, inhibitory control, and attention	Reduced HRV (low parasympathetic tone) correlates with higher severity, cognitive rigidity, and impaired top-down control	Ventromedial Prefrontal Cortex (VMPFC), Amygdala, Insula, and Central Autonomic Network (CAN)	Reflects autonomic dysregulation and impaired neurovisceral integration; serves as a proxy for the brain-heart axis integrity
Cortisol / HPA Axis Markers	Salivary, Serum, Urine, or Hair Cortisol Concentration (HCC); GR sensitivity assays	Working memory, verbal memory, and executive function	Hypercortisolemia and HPA axis hyperreactivity positively correlate with cognitive impairment and symptom severity	Hippocampus (volume reduction), Prefrontal Cortex (atrophy), and Hypothalamus	Chronic excess cortisol triggers dendritic atrophy and neuroinflammation, underpinning treatment resistance and cognitive decline
Neuroendocrine Markers (DHEA, AVP, CRH, ACTH)	Serum/Plasma biochemical assays; Hormonal co-secretion analysis	Executive functions, emotional regulation, and stress coping	Elevated DHEAS and AVP/CRH activity correlate with impaired hippocampal function and memory deficits	Paraventricular Nucleus (PVN), Hippocampus, and Dorsolateral Prefrontal Cortex (DLPFC)	Neurosteroids and V1B receptor antagonists represent potential therapeutic targets for normalizing the stress response
Hand Grip Strength	Handheld Dynamometry (Isometric assessment in kg)	Processing speed, memory, executive function, and fluid reasoning	Lower grip strength correlates with increased depression severity and higher risk of cognitive decline (frailty)	Motor cortex, Basal ganglia, Hippocampus, and global white matter integrity	Reliable peripheral marker of neuromuscular health and cognitive resilience; physical activity mediates this relationship

Lateralized Readiness Potential (LRP)	EEG (C3/C4 electrodes); Stimulus-locked (S-LRP) and Response-locked (R-LRP)	Executive function, conflict resolution, and motor execution	Significantly reduced R-LRP amplitudes in MDD; indicates impaired activation of correct responses	Primary motor cortex and Midbrain limbic (dopaminergic) pathways	Suggests MDD conflict control deficits occur at the execution stage rather than the perceptual encoding stage
N170 / N200 / N450 (ERPs)	Visual/Auditory ERP recording; latency and amplitude	Emotion processing, conflict detection, and sensory gating	Prolonged N170/N200 latencies and reduced N450 amplitudes correlate with depressive mood and executive deficits	Parieto-occipital lobe, Anterior Cingulate Cortex (ACC), and Prefrontal Cortex	Markers of early automatic processing and evaluative cognitive control; deficits often persist during clinical remission
Brain-Derived Neurotrophic Factor (BDNF)	Serum/Plasma protein expression (ELISA)	Hippocampal-dependent memory and neuronal plasticity	Inverse correlation; low BDNF levels are associated with high severity and hippocampal atrophy	Hippocampus (Dentate Gyrus)	Mediates the relationship between stress-induced HPA overactivation and cognitive adaptation deficits
Respiration IM Band	Pneumatic respiratory belt; Frequency-domain analysis ($0.12–0.18$ Hz)	Emotion regulation and cognitive reappraisal	MDD patients exhibit more effortful autonomic regulation and altered coupling during tasks	ACC, Insula, and Dorsomedial Prefrontal Cortex (dmPFC)	Stronger positive coupling between respiratory oscillations and emotion-regulation areas compared to healthy controls

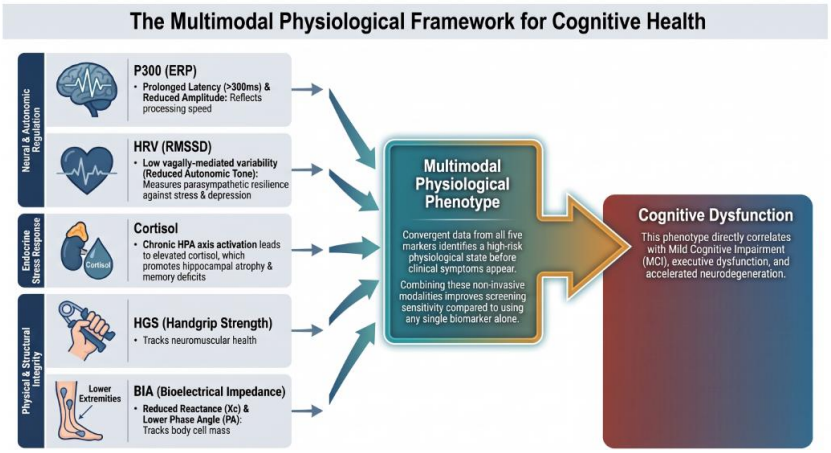
Figure1.Pathophysiology Of Cognitive Dysfunction In Mdd



COMPARISON OF AUTONOMIC AND SEROLOGICAL MARKERS IN MDD-RELATED IMPAIRMENT (vs. Healthy)

Marker Category	Observed Change in MDD	Impact on Cognition
Heart Rate Variability (HRV)	Significantly Lower lnHF/RMSSD	Reduced inhibitory control and flexible adaptation
Brain-Derived Neurotrophic Factor	Lower Baseline Serum BDNF	Impaired neuroplasticity and hippocampal neurogenesis
ERP Indices (P300 Latency)	Prolonged/Higher Latency	Delayed information processing and attention deficits

Figure 2. Multimodal physiological framework for cognitive health



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