BRIEF COMMUNICATION

# Unveiling the Nexus of Cognitive Impairment in Diabetes: Exploring the Enigmatic "Diabetic Melancholy"

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## ABSTRACT

Patients living with diabetes suffer from a spectrum of cognitive and mood disorders. To encompass the diverse neuropsychological aspects of diabetes, the authors herein propose the new construct of "diabetic melancholy", which stands for memory impairments, executive dysfunctions, language impairments, psychomotor retardation, low mood, and apathy. Authors have also described the underlying neural basis of cognitive dysfunction in diabetes.

**Keywords:** Diabetes, cognition, dementia, mood disorders

Diabetes mellitus, a chronic metabolic disorder characterized by hyperglycemia, has emerged as a global health concern, affecting over 400 million individuals worldwide[1]. Beyond its well-documented effects on systemic health, diabetes exerts a profound impact on cognitive function, presenting a complex interplay between metabolic dysregulation and neural vulnerability[2]. In recent years, the convergence of Alzheimer's disease (AD), vascular dementia (VaD), and cognitive impairment in diabetes has sparked intense scientific interest, prompting a re-evaluation of the neuropathological underpinnings and clinical manifestations of cognitive decline in this population[3].

## PATHOPHYSIOLOGY OF COGNITIVE IMPAIRMENTS IN DIABETES

The pathophysiology of cognitive impairments in diabetes is multifaceted, involving a constellation of interconnected mechanisms that span molecular, cellular, and system levels[4]. At the molecular level, insulin resistance, a hallmark feature of type 2 diabetes mellitus (T2DM), disrupts insulin signaling pathways within the brain, impairing glucose uptake and metabolism, and precipitating neuronal dysfunction[5]. Insulin, traditionally known for its role in glucose homeostasis, also serves as a neurotrophic factor, promoting neuronal survival, synaptic plasticity, and cognitive function[6]. Dysregulation of insulin signaling pathways, as observed in insulin resistance, compromises these neurotrophic effects, leading to synaptic loss, impaired neurotransmitter release, and cognitive decline[7].

Concurrently, chronic low-grade inflammation, fuelled by adipose tissue-derived cytokines and activated microglia, instigates neuroinflammatory cascades that exacerbate neuronal injury and synaptic loss[8]. Proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-$\alpha$), and interleukin-6 (IL-6) disrupt synaptic plasticity, impair neurotransmitter metabolism, and promote oxidative stress, further exacerbating neuronal dysfunction in diabetes[9,10].

Furthermore, the formation of advanced glycation end products (AGEs) and oxidative stress engender oxidative damage to cellular macromolecules, including proteins, lipids, and nucleic acids, precipitating neurodegenerative processes and compromising neuronal viability[11]. AGEs, formed through nonenzymatic glycation of proteins and lipids, accumulate in the brain parenchyma and cerebral vasculature, promoting neuronal apoptosis, blood-brain

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barrier dysfunction, and neurovascular uncoupling[10,11]. Oxidative stress, arising from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, further exacerbates neuronal injury, leading to mitochondrial dysfunction, DNA damage, and impaired synaptic transmission[12].

Moreover, dysregulation of sirtuins, a family of $NAD^+$-dependent deacetylases implicated in cellular homeostasis and longevity, and tau protein phosphorylation precipitates tau pathology, contributing to synaptic dysfunction and cognitive decline[13]. Sirtuins, particularly SIRT1 (silent information regulator sirtuin 1), regulate multiple cellular processes, including energy metabolism, DNA repair, and stress response, through deacetylation of target proteins such as histones, transcription factors, and metabolic enzymes[14]. Dysregulation of sirtuin activity, as observed in diabetes, disrupts mitochondrial function, promotes oxidative stress, and impairs synaptic plasticity, contributing to cognitive dysfunction[13]. Tau protein, a microtubule-associated protein implicated in microtubule stabilization and axonal transport, undergoes hyperphosphorylation in diabetes, leading to the formation of neurofibrillary tangles and synaptic loss[15]. Tau pathology, akin to that observed in AD, disrupts neuronal function, impairs synaptic transmission, and precipitates cognitive decline in diabetes[16].

## PATTERN OF COGNITIVE IMPAIRMENTS IN DIABETES

A nuanced understanding of the cognitive phenotype in diabetes necessitates a comprehensive evaluation of diverse cognitive domains, encompassing memory, executive function, attention, language, and visuospatial skills[17]. Memory impairments, ranging from deficits in working and immediate memory to impaired incidental memory, are pervasive in diabetes, reflecting disruptions in hippocampal and prefrontal cortical circuits. Executive dysfunctions, encompassing deficits in cognitive flexibility, inhibitory control, and task switching, further underscore the cognitive burden of diabetes[17-19]. Disruptions in attentional control, reflected in impaired sustained and divided attention, compromise cognitive performance and functional independence in diabetes. Moreover, language deficits, encompassing impaired verbal fluency, comprehension, and expressive language, impede communication and social interaction in diabetes. Visuospatial impairments, characterized by deficits in visuoconstruction, visual memory, and spatial orientation, further contribute to cognitive dysfunction and functional decline in diabetes. The heterogeneity of cognitive impairments in diabetes underscores the complex interplay between metabolic dysregulation, neural vulnerability, and individual differences in cognitive reserve and resilience[2,17].

## NEUROANATOMICAL SUBSTRATES INVOLVED IN DIABETES

The neuroanatomical correlates of cognitive impairments in diabetes are intricately woven into the fabric of neural circuits governing mood, memory, and executive function. Neuroimaging studies have revealed structural and functional alterations in regions such as the ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC), and hippocampus, implicated in mood regulation, attentional control, and episodic memory encoding[20]. Moreover, disruptions in neurotransmitter systems, particularly serotonin, have been implicated in the pathogenesis of mood disorders and cognitive impairments in diabetes[21]. Aberrant serotonergic signaling within the prefrontal-limbic circuitry may contribute to the development of depression and apathy, prevalent features among patients with diabetes.

## EXPLORING COGNITIVE FUNCTIONS

The intricate interplay between cognitive functions and neural substrates in diabetes unveils a complex tapestry of neurocognitive dysfunction, spanning diverse domains such as memory, attention, language, and executive function[22]. Memory circuits, encompassing the hippocampal formation and associated limbic structures, are vulnerable to the deleterious effects of hyperglycemia and insulin resistance, precipitating deficits in episodic memory and semantic memory retrieval[23]. Disruptions in attentional control, mediated by dysregulation of prefrontal cortical and thalamic circuits, compromise cognitive performance and functional independence in diabetes[24-26]. Moreover, language processing, a quintessential human faculty, is subserved by distributed neural networks encompassing the auditory cortex, Broca's area, and the anterior temporal lobe[27]. In diabetes, disruptions in syntactic processing and semantic retrieval may manifest as decreased verbal fluency and comprehension, reflecting underlying alterations in frontal-temporal connectivity. Executive dysfunctions, encompassing deficits in cognitive flexibility, planning, and problem-solving, underscore the cognitive burden of diabetes. Disruptions in dorsolateral prefrontal cortical (DLPFC) circuits, coupled with aberrant dopaminergic signaling within the mesocorticolimbic pathway may contribute to a deficit in reward processing and motivation observed in diabetes[28].

Information processing speed, a cardinal feature of cognitive efficiency, emerges as a sensitive marker of cognitive impairment in diabetes. Disruptions in frontal-subcortical networks, mediated by insulin resistance and neuroinflammation, contribute to slow cognitive processing and impaired attentional control, precipitating deficits in task-switching and inhibitory control[7]. Dysfunction within the prefrontal-striatal circuits impairs the ability to initiate and sustain goal-directed behavior, leading to deficits in cognitive flexibility and planning[29].

Moreover, alterations in the connectivity and function of the default mode network (DMN), a set of brain regions implicated in introspection and self-referential thought, may contribute to cognitive dysfunction in diabetes[30]. Dysfunctional DMN connectivity has been associated with rumination, excessive worry, and depressive symptoms, highlighting the potential role of maladaptive cognitive processes in the development and progression of "diabetic melancholy"[24,25,30].

## THE ENIGMA OF "DIABETIC MELANCHOLY"

Against the backdrop of cognitive impairments and mood alterations in diabetes[31], the concept of "diabetic melancholy" emerges as a unifying framework to elucidate the complex interplay between cognitive dysfunction and affective symptoms[32]. **M**emory impairment, **E**xecutive dysfunction, **LAN**guage deficit, psy**CHO**motor retardation, **L**ow mood, and Apath**Y** converge to define the heterogeneous phenotype of "diabetic melancholy" (Fig. 1).

This wide spectrum of cognitive dysfunctions and mood alterations in diabetes reflects the profound impact of metabolic dysregulation on neural circuits governing emotion regulation, reward processing, and stress response.

Moreover, the bidirectional relationship between cognitive impairment and mood disorders in diabetes underscores the need for integrated treatment approaches that target both cognitive and affective symptoms[33]. Pharmacological interventions, such as insulin sensitizers, anti-inflammatory agents, and neurotrophic factors, hold promise for mitigating neuronal injury and preserving cognitive function in diabetes. Psychosocial interventions, including cognitive-behavioral therapy, mindfulness-based interventions, and lifestyle modifications, may complement pharmacotherapy by addressing maladaptive cognitive and emotional patterns and promoting adaptive coping strategies[34,35].

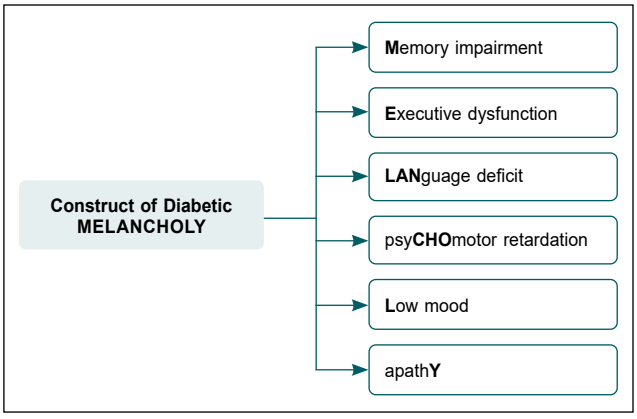


**Figure 1.** Components of "diabetic melancholy".

## CONCLUSION

The elucidation of "diabetic melancholy" heralds a paradigm shift in our understanding of the intricate interplay between metabolic dysregulation, neural vulnerability, and cognitive dysfunction in diabetes. By unraveling the neuropathological underpinnings and clinical manifestations of cognitive impairments in diabetes, we pave the way for targeted interventions and therapeutic breakthroughs aimed at mitigating the cognitive burden of this pervasive metabolic disorder. From molecular mechanisms to clinical phenotypes, the journey to unravel the enigmatic "diabetic melancholy" promises to yield insights that transcend disciplinary boundaries and transform the landscape of diabetes care. Integrating scientific knowledge with clinical expertise and patient-centered care will be essential for addressing the complex interplay between cognitive impairment, mood disorders, and metabolic dysregulation in diabetes.

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