Dissertation

A Prospective Cohort Study of Neurocognitive Function and Depression in Hypoparathyroidism

submitted by

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Graz, 10.02.2026 Adelina Tmava-Berisha, m.p.

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ABBREVIATIONS

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BDI-II	Beck Depression Inventory-II
BIPLONG	Bipolar Longitudinal Study
CaSR	Calcium-Sensing Receptor
CI	Confidence Interval
CNS	Central Nervous System
CVLT	California Verbal Learning Test
d	Cohen's d (effect size)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ESE	European Society of Endocrinology
FDR	False Discovery Rate
FWIT	Farbe-Wort-Interferenztest (Stroop Color-Word Interference Test)
HAMD	Hamilton Depression Rating Scale
HC	Healthy controls
HypoPT	Hypoparathyroidism
ICD-10	International Classification of Diseases, 10th Revision
IQ	Intelligence Quotient
MADRS	Montgomery-Åsberg Depression Rating Scale
M	Mean
MRI	Magnetic Resonance Imaging
MWT-B	Mehrfachwahl-Wortschatz-Intelligenztest
NMDA	N-Methyl-D-Aspartate
OR	Odds Ratio
PTH	Parathyroid Hormone
PTH1R	Parathyroid Hormone Type 1 Receptor
PTH2R	Parathyroid Hormone Type 2 Receptor
PTHrP	Parathyroid Hormone-Related Peptide
ρ	Spearman's Rho (correlation coefficient)
SD	Standard Deviation

SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TIP39	Tuberoinfundibular Peptide of 39 Residues
TMT	Trail Making Test
VLMT	Verbaler Lern- und Merkfähigkeitstest (German CVLT)
φ	Phi Coefficient
η^2	Eta-Squared
η^2p	Partial Eta-Squared

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I. ABSTRACT (GERMAN)

Hintergrund: Der chronische Hypoparathyreoidismus wird mit kognitiven Dysfunktionen und depressiver Symptomatik in Verbindung gebracht, wobei die genauen Hintergründe und Charakteristika derzeit noch nicht vollständig erforscht sind.

Zielsetzung: Ziel der Arbeit war die Charakterisierung kognitiver Funktionen und depressiver Symptomatik bei chronischem Hypoparathyreoidismus mittels umfassender neuropsychologischer Untersuchung und validierter Screening-Instrumente im Vergleich zu gematchten gesunden Kontrollpersonen.

Methoden: Es wurde eine prospektive Fall-Kontroll-Studie mit 30 Patient:innen mit chronischem Hypoparathyreoidismus (Erkrankungsdauer ≥6 Monate) und 30 nach Alter, Geschlecht, Bildungsgrad und Intelligenz gematchten gesunden Kontrollpersonen durchgeführt. Die Proband:innen absolvierten eine standardisierte Testbatterie zur Erfassung von Aufmerksamkeit/Verarbeitungsgeschwindigkeit (Trail Making Test A, Farbe-Wort-Interferenztest nach Stroop Bedingung 1 und 2: Farbbenennung und Wortlesen), verbalem Lernen/Gedächtnis (Verbaler Lern- und Merkfähigkeitstest) und exekutiven Funktionen (Trail Making Test B, Farbe-Wort-Interferenztest nach Stroop Bedingung 3: Interferenz).Die depressive Symptomatik wurde mittels Beck-Depressions-Inventar-II (BDI-II), Montgomery-Åsberg-Depressionsskala (MADRS) und Hamilton Depression Rating Scale (HAMD) erfasst. Kognitive Domänen-Composite-Scores wurden mittels Kovarianzanalyse unter statistischer Kontrolle des BDI-II verglichen. Die Prävalenz kognitiver Beeinträchtigungen (<25. Perzentile) wurde mittels exaktem Tests nach Fisher verglichen. Zusammenhänge zwischen Depression und Kognition wurden mittels Spearman-Korrelationen untersucht.

Ergebnisse: Nach statistischer Kontrolle für depressive Symptomatik zeigten Patient:innen signifikant niedrigere Leistungen im Bereich Aufmerksamkeit/Verarbeitungsgeschwindigkeit (p = .005, η^2p = 0.132), nicht jedoch im verbalen Gedächtnis (p = .159) oder in exekutiven Funktionen (p = .224). Die Prävalenz kognitiver Beeinträchtigungen war signifikant erhöht für Aufmerksamkeit/Verarbeitungsgeschwindigkeit (56.7% vs. 3.3%, p < .001, φ = 0.58) und exekutive Funktionen (60.0% vs. 16.7%, p = .001, φ = 0.45), jedoch nicht für verbales Lernen/Gedächtnis (46.7% vs. 23.3%, p = .103, φ = 0.24).Patient:innen berichteten signifikant höhere depressive Symptomschwere (BDI-II: 11.5 ± 8.4 vs. 4.5 ± 5.2, p < .001, d = 1.04), wobei

36.7% den klinisch relevanten Schwellenwert (BDI-II ≥14) überschritten gegenüber 6.7% der Kontrollpersonen (p = .010). Innerhalb der Patientengruppe zeigte die depressive Symptomschwere keine Korrelation mit Aufmerksamkeitsleistungen (ρ < 0.15), jedoch signifikante moderate negative Korrelationen mit verbalem Gedächtnis (ρ = -0,45 bis -0.46) und exekutiven Funktionen (ρ = -0.42 bis -0.45). Die blieben auch nach False-Discovery-Rate-Korrektur signifikant.

Schlussfolgerungen: Der chronische Hypoparathyreoidismus ist mit Defiziten in Aufmerksamkeit/ Verarbeitungsgeschwindigkeit assoziiert, die die Mehrheit der Patient:innen (56,7 %) betrifft und auch nach einer Kontrolle für depressive Symptomatik persistiert. Gedächtnis- und Exekutivdefizite zeigten moderate Korrelationen mit der depressiven Symptomschwere. Das domänenspezifische Muster legt nahe, dass verschiedene kognitive Domänen unterschiedliche Beziehungen zu krankheitsbezogenen Faktoren aufweisen könnten. Zukünftige Forschungsarbeiten sollten längsschnittliche Studiendesigns einsetzen, die neuropsychologische Testung mit bildgebenden Verfahren integrieren sowie Interventionsstudien zur Evaluation, ob PTH-Ersatztherapie neuropsychiatrische Manifestationen verbessern kann.

Schlüsselwörter: Hypoparathyreoidismus, kognitive Funktion, Depression, neuropsychologische Testung, Parathormon

II. ABSTRACT (ENGLISH)

Background: Chronic hypoparathyroidism has been associated with cognitive dysfunction and depressive symptoms. To date, systematic characterization using validated instruments with appropriate control groups remains limited.

Objective: To characterize cognitive function and depressive symptoms in chronic hypoparathyroidism using comprehensive neuropsychological assessment and validated screening instruments, with comparison to matched healthy controls.

Methods: This prospective case-control study investigated 30 patients with chronic hypoparathyroidism and 30 healthy controls matched on age, sex, education, and IQ. Participants completed standardized assessment of attention/processing speed (Trail Making Test A, Stroop Color-Word-Test, Conditions 1 and 2: Color Naming and Word Reading), verbal learning/memory (German Adaptation of the California Verbal Learning Test), and executive function (Trail Making Test B, Stroop Color-Word Test, Condition 3: Interference). Depressive symptoms were assessed via Beck Depression Inventory-II (BDI-II), Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAMD). Cognitive domain composite scores were compared using analysis of covariance, controlling for BDI-II. Impairment prevalence (<25th percentile) was compared using Fisher's exact tests. Spearman correlations examined depression-cognition relationships.

Results: After controlling for depressive symptoms, patients demonstrated significantly lower attention/processing speed ($p = .005$, $\eta^2p = .132$) but not verbal memory ($p = .159$) or executive function ($p = .224$). Impairment prevalence was markedly elevated for attention/processing speed (56.7% vs. 3.3%, $p < .001$, $\varphi = 0.58$) and executive function (60.0% vs. 16.7%, $p = .001$, $\varphi = 0.45$), but not for verbal learning/memory (46.7% vs. 23.3%, p = .103, φ = 0.24). Patients reported significantly higher depressive symptom severity (BDI-II: 11.5 ± 8.4 vs. 4.5 ± 5.2, $p < .001$, $d = 1.04$), with 36.7% exceeding clinically relevant threshold (BDI-II ≥14) versus 6.7% of controls ($p = .010$). Within patients, depressive symptom severity showed no correlation with attention ($\rho < .15$) but demonstrated significant moderate negative correlations with verbal memory (ρ = -.45 to -.46) and executive function (ρ = -.42 to -.45); all survived false discovery rate correction.

Conclusions: Chronic hypoparathyroidism is associated with attention/processing speed deficits affecting the majority of patients (56.7%), persisting after controlling for depressive symptoms. Memory and executive deficits showed moderate correlations with depressive symptom severity. The domain-specific pattern suggests different cognitive domains may have different relationships to disease-related factors. Future research should employ longitudinal designs integrating neuroimaging with neuropsychological assessment, as well as intervention studies evaluating whether PTH replacement therapy can improve neuropsychiatric manifestations.

Keywords: hypoparathyroidism, cognitive function, depression, neuropsychological assessment, parathyroid hormone

1 INTRODUCTION

Hypoparathyroidism has traditionally been regarded as a straightforward endocrine disorder characterized by deficient parathyroid hormone (PTH) secretion, resulting in hypocalcemia and hyperphosphatemia (Cipriani, C. et al., 2017). Accumulating evidence, however, indicates a more complex disease phenotype. Many patients experience persistent neuropsychiatric symptoms, including cognitive dysfunction and depressive symptoms, that are inadequately explained by serum calcium abnormalities alone and often persist despite apparently adequate conventional treatment (Sardella et al., 2021; Cusano and Bilezikian, 2018). These observations suggest that current pathophysiological models and management strategies may be insufficient to account for the central nervous system (CNS) consequences of chronic PTH deficiency.

This doctoral research systematically investigated neurocognitive function and depressive symptoms in patients with chronic hypoparathyroidism. The primary findings have been published (Tmava-Berisha et al., 2025), and this dissertation presents the complete study, including additional analyses and extended discussion.

1.1 Hypoparathyroidism: Definition and Epidemiology

1.1.1 Definition and Diagnostic Criteria

Hypoparathyroidism is characterized by insufficient PTH production, disrupting calcium-phosphorus homeostasis (Cipriani, C. et al., 2017). Diagnosis requires hypocalcemia with inappropriately low or normal intact PTH on at least two separate occasions separated by at least two weeks (Khan et al., 2022).

The definition of chronic postsurgical hypoparathyroidism has evolved based on systematic evidence regarding recovery trajectories. Recent international guidelines recommend defining chronic postsurgical hypoparathyroidism as persistence for at least 12 months following thyroid or parathyroid surgery, extending the previous 6-month threshold (Bollerslev et al., 2025; Bollerslev et al., 2022). This recent revision reflects systematic review evidence from 8,832 thyroid surgeries demonstrating that while 73.9% of patients with immediate postoperative hypoparathyroidism recovered by 6 months, an additional 7.4% recovered between months 6-12, with the final chronic hypoparathyroidism rate stabilizing at 6.3% of all operated patients (Bollerslev et al., 2025). For non-surgical cases, chronic hypoparathyroidism is defined from initial diagnosis, as spontaneous recovery is rare(Bollerslev et al., 2022).

The inconsistency in defining hypoparathyroidism across clinical studies represents a significant methodological challenge. A systematic review identified 89 articles employing 20 different definitions of hypoparathyroidism, resulting in reported incidence rates ranging from 0% to 20% (Cardoso et al., 2025). This heterogeneity reflects variability in diagnostic criteria (PTH thresholds, duration requirements, symptom consideration), assessment timing, and whether both biochemical and clinical criteria are required. The lack of standardized definitions complicates cross-study comparisons and meta-analyses, underscoring the importance of the recent consensus efforts to harmonize diagnostic criteria (Bollerslev et al., 2025; Tsourdi et al., 2025).

Primary Laboratory Findings:

- Hypocalcemia: corrected calcium typically <8.5 mg/dL (2.1 mmol/L) or ionized calcium <4.6 mg/dL (1.15 mmol/L)
- Inappropriately low or normal PTH: intact PTH <15 pg/mL or within normal reference range despite hypocalcemia—the hallmark diagnostic feature; however, the DACH consensus emphasizes that no universal PTH threshold should be applied diagnostically due to the existence of over 40 different PTH assays with varying reference ranges, recommending instead that clinical judgment incorporate the specific assay used and overall clinical context (Tsourdi et al., 2025)
- Hyperphosphatemia: typically, >4.5 mg/dL (1.45 mmol/L)

Secondary Laboratory Findings:

- Low or inappropriately normal 1,25-dihydroxyvitamin D levels
- 25-hydroxyvitamin D should be assessed to exclude vitamin D deficiency
- Serum magnesium measurement is essential, as hypomagnesemia can cause functional hypoparathyroidism reversible with magnesium repletion (Shoback et al., 2016)

Calcium measurements should be performed systematically at specific postoperative intervals (12-24 hours postoperatively, within 2 weeks, and every 3-6 months thereafter) to capture natural recovery trajectory and avoid premature classification as chronic disease (Tsourdi et al., 2025).

Differential Diagnosis includes vitamin D deficiency (low 25(OH)D with elevated PTH), chronic kidney disease (elevated creatinine with elevated PTH), pseudohypoparathyroidism

(elevated PTH despite hypocalcemia), and hypomagnesemia (can cause functional hypoparathyroidism) (Shoback et al., 2016; Clarke et al., 2016).

1.1.2 Epidemiology and Prevalence

Prevalence estimates vary substantially by geographic region and case ascertainment methodology: approximately 37 per 100,000 in the United States (Powers et al., 2013), 10–27 per 100,000 in Europe (Underbjerg et al., 2015; Cipriani, C. et al., 2017), 38.3 per 100,000 in Japan (Hasegawa et al., 2024), and 6.4 per 100,000 in Scotland (Vadiveloo et al., 2018). In Austria, analysis of 198 patients over 17 years revealed mean age 62.6 ± 18.7 years and 70.2% female distribution (Herteux et al., 2023). The disorder demonstrates consistent 3:1 female predominance across populations (Powers et al., 2013; Clarke et al., 2016).

1.1.3 Etiology

Postsurgical hypoparathyroidism accounts for 75–90% of cases, most commonly following total thyroidectomy, with inadvertent parathyroid gland removal, devascularization, or trauma during neck surgery (Bilezikian et al., 2011). Non-surgical causes include autoimmune hypoparathyroidism (isolated or as a component of autoimmune polyglandular syndrome type 1), genetic causes (mutations in genes encoding PTH, AIRE mutations, calcium-sensing receptor, or transcription factors regulating parathyroid development), infiltrative diseases (hemochromatosis, Wilson's disease, metastatic disease), radiation-induced damage, and severe hypomagnesemia (Mannstadt et al., 2017).

1.2 Physiological Principles

1.2.1 PTH and Calcium-Phosphate Homeostasis

Parathyroid Hormone Physiology. The parathyroid glands, typically four small endocrine organs located on the posterior thyroid surface, secrete PTH in response to decreases in serum calcium concentration detected by the calcium-sensing receptor (CaSR) (Ilahi et al., 2025). PTH is synthesized as preproPTH (115 amino acids) and processed to the biologically active 84-amino acid peptide. Normal serum PTH concentrations range from 15–65 pg/mL (Potts, 2005).

PTH Actions on Target Organs. PTH acts via the PTH/PTHrP type 1 receptor (PTH1R) in bone and kidney to restore calcium homeostasis (Goltzman et al., 2018). In bone, PTH stimulates osteoblast activity and promotes osteoclast-mediated bone resorption, releasing calcium into circulation. In kidney, PTH enhances distal tubular calcium reabsorption, reduces

proximal tubular phosphate reabsorption, and upregulates 1α-hydroxylase enzyme activity. The latter converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol), which enhances intestinal calcium absorption (Goltzman et al, 2018).

PTH in the Central Nervous System. Beyond classical actions on bone and kidney, PTH1R is expressed in brain regions, including hippocampus, prefrontal cortex, and limbic structures (Dettori et al., 2023). PTH-related peptides, including parathyroid hormone-related peptide (PTHrP) and tuberoinfundibular peptide of 39 residues (TIP39), are expressed in hippocampal and limbic regions. TIP39 activates PTH type 2 receptor (PTH2R) and modulates hypothalamic-pituitary-adrenal axis activity and affective behavior (Dobolyi et al., 2012). Preclinical studies demonstrate that PTH administration attenuates cognitive deficits in animal models (Chen et al., 2023), suggesting potential neuromodulatory functions beyond mineral metabolism.

1.2.2 Neurological Importance of Mineral Homeostasis

Calcium as Neuronal Second Messenger. Calcium serves as a ubiquitous intracellular second messenger in neurons, regulating neurotransmitter release, synaptic plasticity, and cell survival (Brini et al., 2013). Neurons maintain a steep calcium gradient from approximately 1.2 mM extracellular to approximately 100 nM resting cytosolic concentration. At presynaptic terminals, voltage-gated calcium channel opening triggers calcium influx that initiates neurotransmitter-filled vesicle fusion with the plasma membrane (Zamponi et al., 2015). Postsynaptically, calcium-dependent signaling cascades regulate long-term potentiation and depression—bidirectional forms of synaptic plasticity underlying learning and memory (Sanhueza and Lisman, 2013). Disruptions in calcium homeostasis impair these processes and have been implicated in neurodegenerative diseases (Wojda et al., 2008).

Phosphate and Energy Metabolism. Phosphate is critical for ATP production and cellular energy metabolism. Disturbances in phosphate homeostasis have been associated with cognitive impairment, with both hyperphosphatemia and hypophosphatemia linked to neurological dysfunction (Rroji et al., 2022; Park et al., 2017).

Vitamin D and Neuroprotection. The vitamin D receptor and biosynthetic enzymes are widely distributed in brain regions, including hippocampus, prefrontal cortex, and basal forebrain (Eyles et al., 2005). Active vitamin D (1,25-dihydroxyvitamin D) modulates neurotrophic factors, counters oxidative stress, and regulates inflammatory responses (Kesby

et al., 2011). Vitamin D deficiency represents a highly prevalent condition worldwide (approximately 40% of the European population has 25(OH)D <50 nmol/L) (Amrein et al., 2020) and has been associated with increased risk of cognitive impairment and depression (Annweiler et al., 2020).

Magnesium and Neuronal Function. Magnesium is required for normal PTH secretion; severe hypomagnesemia induces functional hypoparathyroidism (Shoback et al., 2016). Magnesium acts as a physiological antagonist at N-methyl-D-aspartate (NMDA) receptors, preventing excitotoxicity. Studies in animal models demonstrate that increasing brain magnesium enhances learning abilities and working memory (Slutsky et al., 2010).

1.3 Clinical Manifestations

The clinical phenotype of chronic hypoparathyroidism ranges from asymptomatic biochemical abnormalities to severe multisystem involvement. Symptom severity is influenced by the degree and speed of development of hypocalcemia, disease duration, and other individual patient factors (Bilezikian, 2020).

Acute Neuromuscular Manifestations. Hallmark features include perioral and acral paresthesias, muscle cramps, and carpopedal spasms reflecting increased neuromuscular excitability due to hypocalcemia (Shoback et al., 2016). Severe hypocalcemia may precipitate tetany, laryngospasm, and seizures (Underbjerg, L. et al., 2014). Chvostek's sign (facial muscle contraction elicited by tapping over facial nerve) and Trousseau's sign (carpopedal spasm induced by blood pressure cuff inflation) represent classic clinical indicators, though both demonstrate limited sensitivity and specificity (Bilezikian et al., 2011).

Cardiovascular Manifestations. Complications include QT interval prolongation on electrocardiography and impaired myocardial contractility, with increased risk of heart failure and arrhythmias documented in some, but not all epidemiological studies (Underbjerg et al., 2013).

Renal Complications. Conventional treatment with high-dose calcium and vitamin D analogs may induce hypercalciuria, contributing to nephrolithiasis (20–30% prevalence), nephrocalcinosis (up to 50%), and progressive decline in glomerular filtration rate (Underbjerg et al., 2013)Recent epidemiological data confirm substantially elevated hazard ratios for these complications (Bollerslev et al., 2025).

Other Manifestations. Chronic hypoparathyroidism is associated with posterior subcapsular cataracts (up to 50% with long-standing disease), dermatological changes including dry skin and brittle nails, dental abnormalities with enamel hypoplasia, and skeletal manifestations characterized by increased bone mineral density with abnormal microarchitecture reflecting low bone turnover (Bilezikian, 2020; Hejlesen et al., 2018)

Mortality and Systemic Complications. Systematic registry data reveal significantly elevated mortality risk (HR 1.8, 95% CI 1.49-2.17) compared to the general population (Bollerslev et al., 2025), attributed to cardiovascular events, infections, and other complications.

Neuropsychiatric Involvement. In addition to these systemic manifestations, patients frequently report cognitive difficulties and mood disturbances that persist despite apparently adequate biochemical control, suggesting mechanisms beyond hypocalcemia alone (Cusano and Bilezikian, 2018; Sardella et al., 2021). Recent expert consensus explicitly recognizes depression and anxiety as significant complications (Tsourdi et al., 2025).

The nature, prevalence, and pathophysiological basis of these neuropsychiatric symptoms are examined in Section 1.4.

1.4 Neuropsychiatric Manifestations

Chronic hypoparathyroidism is associated with diverse neuropsychiatric manifestations beyond classical neuromuscular symptoms. Seizures represent the most common neurological complication. They have been described in 25–70% of patients depending on disease duration and severity, with both generalized and focal presentations (Underbjerg, L. et al., 2014; Mannstadt et al., 2017). Movement disorders affect 5–15% of patients, typically associated with basal ganglia calcification, and include parkinsonism, dystonia, chorea, and athetosis (Goswami et al., 2012). Anxiety disorders appear to be very common, especially compared to general population rates, though systematic prevalence data remain limited (Mitchell et al., 2012). Less commonly, patients may experience psychotic symptoms, personality changes, irritability, and sleep disturbances (Sardella et al., 2021).

Among these manifestations, cognitive dysfunction and depressive symptoms have a substantial impact on quality of life and functional capacity yet remain inadequately characterized through systematic research (Cusano and Bilezikian, 2018; Pasieka et al., 2022). Unlike acute neuromuscular or seizure symptoms that typically correlate with hypocalcemia

severity, cognitive and affective disturbances often persist despite apparently adequate biochemical control, suggesting more complex underlying mechanisms (Mitchell et al., 2012). The current evidence base regarding these cognitive and affective manifestations is reviewed below.

1.4.1 Cognitive Dysfunction

Multiple convergent pathophysiological mechanisms may contribute to cognitive impairment in chronic hypoparathyroidism. Chronic hypocalcemia disrupts neuronal excitability and calcium-dependent neurotransmitter release, potentially impairing dopaminergic and serotonergic signaling in circuits regulating cognition (Potts, 2005; Schampel and Kuerten, 2017). Absence of PTH neuromodulatory signaling in hippocampal, prefrontal, and limbic brain regions may contribute to dysfunction independent of mineral abnormalities, as PTH1R is expressed in these regions and preclinical studies demonstrate cognitive improvements with PTH administration (Dettori *et al.,* 2023; Chen *et al.,* 2023). Chronic mineral dysregulation promotes neuroinflammation, with pro-inflammatory cytokines impairing synaptic function through multiple mechanisms, including reducing dendritic spine density and disrupting neurotransmitter synthesis (Yirmiya and Goshen, 2011; Miller and Raison, 2016). Vitamin D deficiency, highly prevalent in the general population and potentially exacerbated in hypoparathyroidism, may further contribute by upregulating pro-inflammatory pathways (Amrein et al., 2020; Knezevic et al., 2020). Intracranial calcifications, occurring in >50% of patients and characteristically affecting basal ganglia and hippocampus, may disrupt circuits critical for executive function, working memory, and memory consolidation (Aggarwal et al., 2013; Goswami et al., 2012).

Emerging evidence indicates patients experience deficits across multiple cognitive domains, though systematic characterization remains incomplete due to small sample sizes, heterogeneous assessment methods, and lack of appropriate control groups (Sardella et al., 2021).

Executive Function

Executive functions, mediated by prefrontal-striatal circuits with dopaminergic modulation, comprise inhibitory control, working memory, and cognitive flexibility that enable goal-directed behavior (Miyake et al., 2000). Disruption of these frontosubcortical circuits, particularly through basal ganglia calcification, may account for the executive deficits observed

in hypoparathyroidism. Patients demonstrate deficits in working memory and cognitive flexibility, manifesting as difficulties with multitasking, problem-solving, planning, and adaption strategies (Aggarwal et al., 2013). Performance on tasks requiring mental set-shifting and response inhibition appears particularly compromised (Sardella et al., 2021).

Attention and Processing Speed

Attention, mediated by distributed frontoparietal networks with dopaminergic and noradrenergic modulation, encompasses sustained attention (vigilance), selective attention (filtering distractors), and divided attention (processing multiple information streams) (Posner and Petersen, 1990). Processing speed, the fundamental rate at which cognitive operations are executed, depends critically on white matter integrity and subcortical dopaminergic function (Hedden and Gabrieli, 2004). Given the documented basal ganglia involvement in hypoparathyroidism, these dopamine-dependent processes may be particularly vulnerable. Patients demonstrate increased error rates and reaction time variability on sustained attention tasks, reduced target discrimination efficiency on selective attention tasks, and marked deficits dividing attention among concurrent information sources. Processing speed deficits become more pronounced with increasing task complexity (Nasreddine et al., 2005).

Memory Function

Verbal episodic memory, the capacity to encode, store, and retrieve verbally presented information such as word lists and narratives, depends critically on hippocampal-cortical networks for consolidation from temporary to long-term storage(Squire and Zola, 1996). The hippocampus appears particularly vulnerable in hypoparathyroidism through multiple mechanisms, including calcification and chronic hypocalcemia effects on calcium-dependent synaptic plasticity (Goswami et al., 2012). Patients demonstrate consistent verbal memory impairment characterized by a specific deficit pattern: relatively preserved immediate recall but accelerated forgetting over delays, suggesting hippocampal-dependent consolidation impairment rather than primary encoding or retrieval deficits (Sardella et al., 2021). While cognitive dysfunction represents one neuropsychiatric manifestation of chronic hypoparathyroidism, mood disturbances, particularly depressive symptoms, constitute another important clinical feature that may share pathophysiological mechanisms or interact with cognitive deficits (Cusano and Bilezikian, 2018).

1.4.2 **Depression**

Depression represents a significant clinical concern in chronic hypoparathyroidism, with prevalence substantially exceeding general population rates. Clinical presentation is complicated by overlap between depressive symptoms and somatic manifestations of the endocrine disorder, creating diagnostic challenges (Cusano and Bilezikian, 2018).

Prevalence

Depression prevalence in individuals with hypoparathyroidism estimates range from 25–60% depending on methodology, diagnostic criteria, and population characteristics (Cusano and Bilezikian, 2018). This wide range reflects methodological heterogeneity, with many studies relying on screening questionnaires rather than structured diagnostic interviews. Systematic assessment using validated instruments remains limited. The disorder demonstrates higher rates in women, consistent with general population patterns where women are diagnosed with depression at approximately twice the rate of men (Salk et al., 2017).

Clinical Presentation

Patients frequently present with prominent somatic symptoms, fatigue, sleep disturbances, subjective cognitive complaints, and reduced energy that may be attributed to inadequately controlled hypocalcemia rather than primary mood disorder (Mitchell et al., 2012). Some patients report mood symptoms fluctuating with calcium levels, while others experience persistent depression despite biochemical control, suggesting heterogeneous mechanisms.

Diagnostic Considerations

Depression diagnosis requires differentiation of primary mood disorder from endocrine disorder manifestations. DSM-5 and ICD-10 criteria require at least two core symptoms (depressed mood, anhedonia, reduced energy) persisting for a minimum of two weeks, plus additional features including impaired concentration, diminished self-esteem, guilt, pessimistic thinking, disturbed sleep, appetite changes, or suicidal ideation (Reed et al., 2019; Paykel, 2002). Application is complicated because many symptoms, particularly fatigue, sleep disturbance, and concentration difficulties, represent common features of both inadequately controlled hypoparathyroidism and major depression. Validated screening instruments, including Beck Depression Inventory-II (BDI-II) and Montgomery-Åsberg Depression Rating Scale (MADRS), provide standardized severity quantification useful for screening, but they do

not establish formal diagnoses, which require structured diagnostic interviews by qualified mental health professionals (Kessler and Ustün, 2004).

Relationship to Disease Pathophysiology

Elevated depression prevalence likely reflects the pathophysiological mechanisms outlined in Section 1.4.1, particularly disrupted neurotransmitter homeostasis in dopaminergic circuits, chronic neuroinflammation, and preferential basal ganglia involvement, structures critical for motivation, reward processing, and emotional regulation (Cusano and Bilezikian, 2018; Cummings, 1993). Vitamin D deficiency may be an additional contributor, as meta-analytic evidence shows that vitamin D supplementation reduces depressive symptoms in individuals with deficiency (Amrein et al., 2020).

1.4.3 Cognitive-Depression Relationships

The relationship between depressive symptoms and cognitive dysfunction is complex, with important implications for clinical assessment and therapeutic strategies (Kendler et al., 2020).

Shared Pathophysiological Substrates

The mechanisms described in Section 1.4.1 may contribute to both cognitive and affective symptoms, suggesting parallel or overlapping manifestations rather than independent processes (Pasieka et al., 2022). Basal ganglia calcification affecting dopaminergic circuits may simultaneously impair executive function and contribute to anhedonia and reduced motivation. Chronic neuroinflammation disrupts both cognitive processing and mood regulation. Hippocampal vulnerability may produce both memory consolidation deficits and mood dysregulation.

Depression-Associated Cognitive Impairment

Depression is associated with cognitive impairment even without primary neurological disease, characterized by deficits in executive function, processing speed, memory, and attention (Rock et al., 2014; Snyder, 2013). These effects primarily reflect motivational and emotional factors, including reduced effort allocation, impaired concentration secondary to rumination, psychomotor retardation, and cognitive load from persistent negative thoughts.

Cognition-Associated Affective Symptoms

Conversely, cognitive impairment may constitute a depression risk factor through multiple pathways (Jajodia and Borders, 2011). Awareness of cognitive decline can engender frustration,

embarrassment, and reduced self-efficacy, particularly when interfering with occupational or social functioning. Executive dysfunction may impair coping abilities and problem-solving skills needed to manage stressors, increasing vulnerability to depressive episodes (Alexopoulos et al., 2002). Memory impairments may interfere with medication adherence, potentially worsening both endocrine control and mood (DiMatteo et al., 2002).

Research Implications

Disentangling primary disease-related cognitive dysfunction from mood-related effects requires careful assessment of both domains using validated instruments, appropriate control groups, and statistical approaches examining independent and interactive effects (Porter et al., 2003).

1.5 Current Treatment Approaches

Conventional Therapy

Standard treatment comprises a calcium-rich diet, oral calcium supplementation (1,000–3,000 mg elemental calcium daily), native ((target level 30-60ng/ml) and active vitamin D analogs (i.e. calcitriol 0.25–2.0 μg daily or in some countries alfacalcidol) to maintain serum calcium in the low-normal range (8.0-9.0 mg/dL) (Brandi et al., 2016).

This approach aims to minimize hypocalcemic symptoms while avoiding hypercalciuria. Limitations include failure to replace PTH, calcium fluctuations despite therapy, frequent hypercalciuria with associated renal complications, and persistent symptoms despite achieving target calcium levels (Khan et al., 2022).

PTH Replacement Therapies

Recombinant human PTH (1-84) (rhPTH(1-84), (Natpara) received FDA approval in 2015 as the first PTH replacement therapy; however, the product experienced reduced market availability from 2019 onward due to manufacturing concerns and production was ultimately discontinued in 2024 (U.S. Food and Drug Administration, 2015; Takeda Pharmaceutical Company Limited, 2022).

Palopegteriparatide, a long-acting PTH analog, received FDA approval in August 2024 based on the PaTHway Trial, which demonstrated normocalcemia maintenance with reduced reliance

on conventional therapy (Clarke et al., 2016). Eneboparatide recently completed the Phase 3 CALYPSO trial (ClinicalTrials.gov, 2023).

Current guidelines identify specific indications for PTH replacement: persistent symptoms or hypocalcemia despite optimized conventional treatment, frequent calcium fluctuations, impaired quality of life, eGFR <60 mL/min/1.73m², hyperphosphatemia, and hypercalciuria exceeding sex-specific thresholds (Bollerslev et al., 2025).

PTH replacement addresses the underlying hormonal deficiency rather than merely treating biochemical consequences. However, evidence regarding neuropsychiatric outcomes remains limited, with clinical trials lacking comprehensive neuropsychological assessments as primary endpoints.

Management of Neuropsychiatric Symptoms

Depression management typically employs selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) as first-line pharmacotherapy (Cipriani, A. et al., 2018), with cognitive-behavioral therapy demonstrating efficacy (Cuijpers et al., 2013). Optimization of vitamin D status may represent an adjunctive approach (Amrein et al., 2020). However, systematic evidence regarding optimal management strategies for cognitive dysfunction and mood disorders in hypoparathyroidism remains limited, representing a critical area for future investigation.

1.6 Study Rationale and Objectives

1.6.1 Critical Knowledge Gaps

Despite increasing recognition of neuropsychiatric manifestations in chronic hypoparathyroidism, the evidence base remains fragmented and methodologically limited. A systematic review (Sardella et al., 2021) identified "extremely limited evidence, with only case reports and one cross-sectional controlled study available" examining cognitive function in this population. Recent international guidelines explicitly acknowledge depression and anxiety as significant complications (Bollerslev et al., 2025) and recommend routine quality-of-life assessment (Tsourdi et al., 2025), yet comprehensive neuropsychological characterization with validated instruments remains absent. Three critical knowledge gaps persist:

First, no studies have employed comprehensive neuropsychological assessment batteries with appropriate control groups matched on age, sex, educational level, and IQ. The latter is

particularly important because IQ correlates with cognitive reserve, which affects vulnerability to brain insults (Stern, 2012).

Second, while elevated depression rates have been reported, no studies have systematically included validated depression instruments (such as BDI-II, MADRS) as both outcome measures and statistical covariates in cognitive analyses. This precludes determination of whether cognitive deficits operate independently of mood symptoms or are substantially mood-mediated, a distinction with direct implications for screening protocols and treatment selection.

Third, the relationships between depressive symptom severity and specific cognitive domains remain unexplored. Existing studies have used global cognitive scores rather than domain-specific analyses, potentially obscuring differential relationships between mood symptoms and specific cognitive functions.

1.6.2 Study Aims and Hypotheses

Study Aim

To characterize cognitive function and depressive symptoms in patients with chronic hypoparathyroidism using validated neuropsychological and depression screening protocols, with comparison to matched healthy controls and normative data, and to examine relationships between depressive symptom severity and domain-specific cognitive performance.

Primary Hypotheses (Confirmatory):

Hypothesis 1a: Patients with chronic hypoparathyroidism will demonstrate significantly lower cognitive performance in attention/processing speed, verbal learning/memory, and executive function compared to matched HC.

Hypothesis 1b: Patients with chronic hypoparathyroidism will exhibit significantly higher prevalence of cognitive impairment (defined as performance <25th percentile on age-based normative reference values) compared to matched HC.

Secondary Hypotheses (Exploratory):

Hypothesis 2a: Patients with chronic hypoparathyroidism will demonstrate significantly higher prevalence of clinically relevant depressive symptoms (BDI-II ≥14) compared to matched healthy controls.

Hypothesis 2b: Depressive symptoms severity (BDI-II, MADRS) in patients with chronic hypoparathyroidism will demonstrate significant negative correlations with cognitive performance across attention/processing speed, verbal learning/memory, and executive function domains.

1.6.3 Expected Scientific Contributions

This study is expected to provide three key contributions:

Methodological Advancement. Comprehensive assessment protocols addressing prior methodological limitations, including matching on IQ, systematic mood assessment with validated instruments, and domain-specific cognitive analyses, will provide a template for future studies and advance evidence quality beyond the case reports and small uncontrolled series that currently dominate the literature.

Clinical Translation. Domain-specific impairment characterization will inform targeted screening protocols and clarify whether cognitive screening should be universal or targeted to specific patient subgroups. Examination of cognitive-mood relationships will determine whether cognitive deficits persist independently of depressive symptoms or are substantially mood-mediated, informing treatment selection between disease-specific interventions, mood-focused treatments, or combined approaches.

Theoretical Advancement. Systematic characterization of the neuropsychiatric phenotype using validated instruments will support recognition of hypoparathyroidism as a complex neuroendocrine condition with CNS manifestations requiring comprehensive multidisciplinary management, advancing understanding of PTH as a neuromodulator beyond classical mineral homeostasis functions.

2 METHODS

2.1 Study Design

This prospective case-control study compared cognitive performance and depressive symptoms between patients with chronic hypoparathyroidism and healthy controls matched on age, sex, education, and IQ. The study received ethics approval from the Institutional Review Board of the Medical University of Graz as part of the ongoing HypoPT cohort study (approval number: **29-062 ex 16/17**) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

2.1.1 Participants

2.1.1.1 ***Patient Recruitment***

Individuals with chronic hypoparathyroidism treated at the Clinical Department of Endocrinology and Diabetology of the Medical University Graz, Austria, were invited to participate in the study. The HypoPT study aims to identify and examine patients with hypoparathyroidism in Austria and to create a registry of this cohort.

Patients were diagnosed using the criteria from European Society of Endocrinology publications on the management of adult chronic hypoparathyroidism available at the time of recruitment (Bollerslev et al*.,* 2022). Chronic hypoparathyroidism was defined as disease duration of at least six months from initial diagnosis or following surgical parathyroid injury. The six-month threshold distinguishes chronic from transient hypoparathyroidism, as most cases of transient postsurgical hypoparathyroidism resolve within this timeframe (Bollerslev et al*.,* 2022).

Inclusion Criteria:

- Confirmed diagnosis of chronic hypoparathyroidism (≥6 months duration, regardless of etiology)
- Age 18–70 years
- Estimated IQ >80 (assessed via MWT-B)
- Fluent in German (required for neuropsychological testing)
- Capacity to provide informed consent

Exclusion Criteria:

- Neurological disorders (e.g., Parkinson's disease, Alzheimer's disease, stroke, traumatic brain injury, epilepsy unrelated to hypoparathyroidism, dementia)
- Current diagnosis of major psychiatric disorders (major depressive episode, mania, schizophrenia)
- Insufficient German language knowledge precluding valid test administration
- Severe uncorrected visual or auditory impairment precluding testing

All participants underwent comprehensive medical history review to identify significant comorbidities.

2.1.1.2 ***Control Recruitment***

For healthy controls, data were obtained from the ongoing study "BIPLONG-25-335 ex 12/13," which employed the same cognitive test battery. From the BIPLONG dataset (n=748), 30 healthy controls were individually matched to patients on age (±5 years), sex, education level (years of formal education ±2 years), and estimated IQ (MWT-B score ±10 points).

Inclusion Criteria:

- Age 18–70 years
- Fluent in German
- Capacity to provide informed consent
- Successfully matched to a patient participant

Exclusion Criteria:

- Any psychiatric disorder
- Medical history of brain injuries
- Medical history of thyroid or parathyroid disorders
- Current use of psychoactive drugs
- Severe uncorrected visual or auditory impairment

2.1.2 **Sample Size Determination**

Given the rarity of chronic hypoparathyroidism as an orphan disease with prevalence estimates of 8-10 per 100,000 in Europe (Powers et al., 2013; Underbjerg, Line et al., 2015), recruitment of large patient cohorts presents substantial challenges. The sample size of n=30 per group was determined pragmatically based on feasibility and consistency with prior neuropsychological

research in rare endocrine disorders, which have employed comparable sample sizes (n=19-59 patients) (Aggarwal et al., 2013; Rubin et al., 2022; Sikjaer et al., 2024; Saponaro et al., 2022).

This sample size enabled rigorous matching on critical confounding variables (age, sex, education, IQ) while providing adequate statistical power for detecting large effect sizes in primary between-group comparisons. Sample size limitations precluded detection of small-to-moderate effects and subgroup analyses, as discussed in Section 4.5.2

2.2 Procedures

2.2.1 Assessment Session

All participants completed a single comprehensive assessment session lasting approximately 2.5–3 hours, conducted by trained neuropsychologists. The session comprised:

- Informed consent and demographic questionnaire
- Clinical interview and medical history
- Neuropsychological assessment battery
- Depression screening instruments
- Debriefing

Furthermore, current medication regimens (calcium supplementation dose, vitamin D analog type and dose, PTH replacement therapy if applicable) were documented.

2.2.2 Demographic and Clinical Variables

Demographic Variables:

- Age (years)
- Sex (male/female)
- Education (years of formal schooling)

Clinical Variables (Patients Only):

- Disease duration
- Etiology (postsurgical vs. non-surgical)
- Current medications (calcium, vitamin D analog type and dose)

2.3 Neuropsychological Assessment

The cognitive performance of participants was assessed using a standardized cognitive test battery that included the Trail Making Test (TMT) Part A/B (Reitan, 1958), the Color-Word

Interference Test (Farbe-Wort-Interferenztest, FWIT) by J.R. Stroop (Bäumler, 1985), and the California Verbal Learning Test (CVLT; German adaptation: Verbaler Lern- und Merkfähigkeitstest, VLMT) (Helmstaedter et al., 2001). All tests were administered in German by trained investigators following standardized procedures.

2.3.1 Intelligence Estimation

2.3.1.1 ***Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B)***

The MWT-B estimates baseline verbal intelligence through a 37-item multiple-choice vocabulary recognition task. Participants identify the single real word among four orthographically similar non-words (Lehr, 2005) Vocabulary knowledge demonstrates high resistance to cognitive decline and correlates strongly with premorbid intellectual functioning (Lezak et al., 2012). The MWT-B provides age-corrected IQ estimates (M = 100, SD = 15) based on German normative data.

Administration: Participants read each row of five letter strings and indicate the real German word. No time limit is imposed.

Scoring: Total correct responses convert to age-corrected IQ estimates via published normative tables.

2.3.2 Cognitive Assessment

2.3.2.1 ***Trail Making Test (TMT)***

The TMT assesses psychomotor speed, visual scanning, attention, and cognitive flexibility through two timed conditions (Reitan, 1958).

TMT-A: Participants connect 25 numbered circles in ascending sequence as quickly as possible. Performance primarily reflects psychomotor speed and visual scanning.

TMT-B: Participants alternate between numbered (1–13) and lettered (A–L) circles in ascending sequence (1-A-2-B-3-C...). Performance requires cognitive flexibility and working memory in addition to basic processing speed.

Administration: Participants complete a practice trial before each condition. Time to completion (seconds) is recorded

Scoring: Completion time in seconds. Longer times indicate poorer performance.

2.3.2.2 ***Farbe-Wort-Interferenztest (FWIT)***

The German adaptation of the Stroop Color-Word Interference Test assesses processing speed, selective attention, and response inhibition through three conditions presented on separate sheets (Bäumler, 1985).

Condition 1 (Color Naming): Participants name the color of 72 color patches (red, blue, green, yellow) arranged in 6 rows as quickly as possible.

Condition 2 (Word Reading): Participants read 72 color words (red, blue, green, yellow) printed in black ink, arranged in 6 rows, as quickly as possible.

Condition 3 (Interference): Participants name the ink color of 72 color words where word and ink color are incongruent (e.g., the word "red" printed in blue ink), arranged in 6 rows. This condition requires inhibiting the prepotent reading response.

Administration: Each condition is timed. Practice items precede each condition. Self-corrections are allowed; uncorrected errors are recorded but do not stop timing.

Scoring: Completion time in seconds for each condition. Longer times indicate poorer performance.

2.3.2.3 ***Verbaler Lern- und Merkfähigkeitstest (VLMT)***

The German adaptation of the Rey Auditory Verbal Learning Test (California Verbal Learning Test in English) assesses verbal episodic memory across encoding, consolidation, and retrieval phases (Helmstaedter et al., 2001).

Structure:

Immediate Learning (Trials 1–5): The examiner reads a 15-word list (List A) at one-second intervals. Participants immediately recall words in any order. This procedure repeats five times with the same word list. The total number of words recalled across all five trials provides an index of learning capacity.

Interference List: A different 15-word list (List B) is presented once, with immediate recall. This assesses vulnerability to proactive interference.

Short Delay Free Recall: Without additional presentation, participants recall the original list (List A).

Short Delay Cued Recall: Participants recall List A words with semantic category cues.

Long Delay (30 minutes): After a filled delay period with non-verbal tasks, participants complete:

- Long Delay Free Recall of List A
- Long Delay Cued Recall of List A with semantic category cues

Recognition: Participants identify the 15 target words (List A) among 50 words presented (15 List A words, 15 List B words, 20 phonologically and semantically similar foils).

Administration: Standard procedures per manual. Words are read at consistent pace. No feedback on performance is provided during testing. The 30-minute delay is filled with non-verbal tasks from other cognitive domains.

Scoring: Number of correctly recalled words for each trial. Recognition trial scored as number of correctly identified target words minus false positives.

2.3.3 Composite Score Construction

To facilitate domain-level analyses and reduce multiple comparisons, composite scores were calculated for each cognitive domain following established procedures.

Procedure:

- **Score Inversion:** Raw scores for tests where higher values indicate worse performance (TMT-A, TMT-B, all FWIT conditions) were inverted, so that higher scores consistently indicated better performance across all measures.
- **Z-Transformation:** All individual test raw scores were converted to Z-scores using the sample mean and standard deviation: $Z = (X - M) / SD$. This standardization places all tests on a common metric.
- **Domain Composite Calculation:** Domain composite scores were calculated by summing relevant Z-scores:
  - **Attention/Processing Speed Composite:**

TMT-A (inverted and Z-transformed)
FWIT Condition 1 - Color Naming (inverted and Z-transformed)
FWIT Condition 2 - Word Reading (inverted and Z-transformed)

  - **Verbal Learning/Memory Composite:**

VLMT Trials 1–5 Total (Z-transformed)
VLMT Short Delay Free Recall (Z-transformed)

VLMT Long Delay Free Recall (Z-transformed)

- **Executive Function Composite:**

TMT-B (inverted and Z-transformed)

FWIT Condition 3 - Interference (inverted and Z-transformed)

- **Rankit Transformation:** Since Shapiro-Wilk tests indicated departure from normal distribution for domain composite scores ($p < .05$ for attention and executive domains), Rankit transformation using Blom's formula (Blom, 1958) was applied to normalize distributions for parametric analyses. Following transformation, all variables demonstrated acceptable distributional properties for ANCOVA (Shapiro-Wilk $p > .05$; skewness and kurtosis within ±1.0).

2.3.4 Cognitive Impairment Classification

For each cognitive domain, participants were classified as impaired or unimpaired based on performance relative to age-based normative reference values from test manuals (Tombaugh, 2004; Van der Elst et al., 2006; Helmstaedter et al., 2001).

Impairment Criterion: Performance below the 25th percentile, consistent with test manual guidelines for identifying clinically significant impairment (Lezak et al., 2012; Heaton, 2004). This threshold represents performance worse than 75% of the age-matched normative population.

Domain-Specific Criteria:

- **Memory Deficit:** Performance below 25th percentile in at least 3 of 5 VLMT subtests (Trials 1-5 Total, Short Delay Free Recall, Short Delay Cued Recall, Long Delay Free Recall, Long Delay Cued Recall)
- **Attention Deficit:** Performance below 25th percentile in at least 2 of 3 attention tasks (TMT-A, FWIT Color Naming, FWIT Word Reading)
- **Executive Function Deficit:** Performance below 25th percentile in at least 1 of 2 executive function tasks (TMT-B, FWIT Interference)

These criteria require consistent impairment across multiple measures within a domain rather than impairment on a single test, thereby reducing false-positive classifications while maintaining clinical sensitivity.

2.4 Depression Assessment

2.4.1 Beck Depression Inventory-II (BDI-II)

The BDI-II is a 21-item self-report questionnaire assessing depressive symptom severity over the preceding two weeks. Items assess cognitive (e.g., pessimism, self-criticism), affective (e.g., sadness, loss of pleasure), and somatic (e.g., fatigue, sleep disturbance) symptoms of depression (Beck et al., 1961).

Administration: Participants rate each item on a 0–3 scale reflecting increasing symptom severity. The questionnaire is self-administered with instructions provided by the examiner.

Scoring: Total score (range 0–63) calculated by summing all items.

Interpretation:

- 0–13: Minimal depressive symptoms
- 14–19: Mild depressive symptoms
- 20–28: Moderate depressive symptoms
- 29–63: Severe depressive symptoms

Important Note: The BDI-II is a screening instrument that assesses symptom severity and identifies individuals reporting clinically relevant symptom levels warranting further evaluation. It does not establish formal psychiatric diagnoses, which require structured clinical interviews conducted by qualified mental health professionals (Kessler and Ustün, 2004).

Psychometric Properties: The German version (Hautzinger, Keller and Kühner, 2006) demonstrates good internal consistency (Cronbach's α = .89–.93) and validity comparable to the English version.

Methodological Note on Cut-off Selection:

In our prior publication using this dataset (Tmava-Berisha et al*.,* 2025), BDI-II was included solely as a covariate in cognitive analyses, with the threshold of BDI-II >18 mentioned descriptively but not statistically tested. For the current dissertation, we conduct new exploratory analyses (Hypothesis 2a, 2b) examining depressive symptoms as a primary outcome.

We selected BDI-II ≥14 as the threshold for these exploratory hypothesis tests because:

(1) It represents the established threshold for clinically relevant symptoms requiring further evaluation, as defined in the BDI-II manual (Beck et al., 1961) and validated in medical populations (Kung et al., 2013; Arnau et al., 2001);

(2) It maximizes sensitivity for identifying individuals who may benefit from screening and further evaluation;

(3) It allows examination of mild-to-moderate symptoms, which is clinically relevant even if below the moderate severity threshold (≥18);

(4) The convergence with clinician-rated MADRS findings (reported in this dissertation) supports that elevated BDI-II scores reflect genuine mood symptoms rather than somatic symptom overlap.

2.4.2 **Montgomery-Åsberg Depression Rating Scale (MADRS)**

The MADRS is a 10-item clinician-rated scale designed to assess depressive symptom severity. Unlike self-report measures, clinician-rated scales may reduce bias from somatic symptom overlap with endocrine disorder manifestations (Montgomery and Asberg, 1979).

Items Assessed: The MADRS evaluates apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item is rated on a 0–6 scale based on symptom severity.

Administration: A trained clinician conducts a semi-structured interview lasting approximately 15–20 minutes. Ratings are based on symptoms during the past week. The clinician integrates information from the patient's verbal report, observed behavior, and clinical judgment.

Scoring: Total score ranges 0–60, calculated by summing all 10 items.

Interpretation:

- 0–6: No depression
- 7–19: Mild depression
- 20–34: Moderate depression
- ≥35: Severe depression

Psychometric Properties: The MADRS demonstrates good inter-rater reliability (r = .89–.97) and internal consistency (Cronbach's α = .84). It shows high correlation with other depression measures including BDI (r = .60–.75).

2.4.3 Hamilton Depression Rating Scale (HAMD)

The Hamilton Depression Rating Scale (HAMD) is a clinician-administered interview assessing depressive symptom severity (Hamilton, 1960). The HAMD was employed for assessment of healthy control participants as part of the BIPLONG study protocol from which control data were obtained.

Structure: The HAMD comprises 17 items assessing depressed mood, feelings of guilt, suicide ideation, insomnia (initial, middle, and late), work and activities, psychomotor retardation, agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, loss of weight, and insight. Each item is rated on either a 3-point (0–2) or 5-point (0–4) scale based on symptom severity and frequency.

Administration: A trained clinician conducts a semi-structured interview typically lasting 15–20 minutes. Items are rated based on the patient's symptoms over the past week.

Scoring: Total score ranges 0–52 (for the 17-item version), calculated by summing all items.

Interpretation:

- 0–7: No depression
- 8–13: Mild depression
- 14–18: Moderate depression
- 19–22: Severe depression
- ≥23: Very severe depression

Psychometric Properties: The HAMD demonstrates good inter-rater reliability (r = .80–.98) and internal consistency (Cronbach's α = .70–.85). It correlates highly with other depression measures including MADRS (r = .70–.85) and BDI (r = .60–.75).

Note on Study Design: While patient participants were investigated with both BDI-II and MADRS as part of the hypoparathyroidism study protocol, healthy control participants from the BIPLONG dataset were assessed using BDI-II and HAMD as the primary depression screening measure according to that study's protocol. This difference in depression screening assessment instruments between groups reflects the use of existing control data from a separate

study and represents a methodological consideration. However, all three instruments (BDI-II, MADRS, HAMD) are well-validated measures of depressive symptom severity with established convergent validity, supporting comparability of depression screening results across groups for identifying presence versus absence of clinically relevant symptoms.

2.5 Statistical Analysis

All statistical analyses were conducted using IBM SPSS version 28.0 (IBM Corp., Armonk, NY). Two-tailed tests were employed throughout, with alpha set at .05 unless otherwise specified. Effect sizes are reported for all analyses following established conventions.

2.5.1 Preliminary Analyses

Data Screening: Data were examined for univariate and multivariate outliers using boxplots and Mahalanobis distance. No outliers exceeding 3 standard deviations were identified. Normality was assessed via Shapiro-Wilk tests, histograms, Q-Q plots, and skewness/kurtosis values (acceptable range: ±2.0 for skewness, ±3.0 for kurtosis). Homogeneity of variance was evaluated using Levene's test.

Matching Verification: Independent-samples t-tests (continuous variables) and chi-square tests (categorical variables) confirmed successful matching on age, sex, education, and IQ.

Missing Data: Of 34 patients initially enrolled, four were excluded due to incomplete assessment data. Three patients did not complete all required neuropsychological measures (missing Stroop test or incomplete VLMT subtests), and one patient discontinued the assessment session prematurely due to excessive cognitive fatigue and distress. These exclusions resulted in a final sample of 30 patients with complete data across all neuropsychological and mood assessment measures. Complete data were also obtained for all 30 matched healthy controls. All analyses were conducted using complete case analysis with no imputation.

2.5.2 Confirmatory Analyses (Primary Hypotheses)

2.5.2.1 Group Differences in Cognitive Performance

Domain-specific group differences were evaluated using three separate one-way analyses of covariance (ANCOVAs), with Group (patients vs. controls) as the independent variable, cognitive domain composite score (attention/processing speed, verbal learning/memory, executive function) as the dependent variable, and BDI-II total score as covariate.

Rationale for Covariate: ANCOVA was selected to statistically control for potential confounding effects of depressive symptoms on cognitive performance, given the well-documented relationship between depression and cognition in the literature and the observed group difference in BDI-II scores.

Assumptions Verification: For each ANCOVA, the following assumptions were tested:

- **Normality of residuals:** Assessed via Shapiro-Wilk test on standardized residuals (criterion: $p > .05$)
- **Homogeneity of variance:** Assessed via Levene's test (criterion: $p > .05$)
- **Homogeneity of regression slopes:** Assessed via Group × BDI-II interaction term (criterion: $p > .05$ indicates assumption satisfied)
- **Linear relationship between covariate and dependent variable:** Assessed via scatterplots and correlation analysis
- **Independence of covariate and independent variable:** Assessed via independent-samples t-test comparing BDI-II scores between groups (significant difference observed, noted as limitation)

All assumptions were satisfied for all three ANCOVAs, supporting the validity of the analyses.

Effect Sizes: Partial eta-squared (η^2p) quantified effect magnitude using Cohen's (Cohen, 1988) criteria: .01 = small, .06 = medium, .14 = large effect.

*2.5.2.2 **Prevalence of Cognitive Impairment***

For each cognitive domain, participants were classified as impaired or unimpaired based on performance relative to age-based normative reference values from test manuals. Fisher's exact tests were conducted to compare the frequency of cognitive impairment between groups for each domain.

Effect Sizes: Phi coefficient (φ) quantified effect magnitude for 2×2 contingency tables using Cohen's (Cohen, 1988) criteria: .10 = small, .30 = medium, .50 = large effect.

2.5.3 Exploratory Analyses (Secondary Hypotheses)

The following analyses were exploratory in nature, examining relationships suggested by prior literature but not pre-specified as primary confirmatory hypotheses.

2.5.3.1 ***Prevalence and Severity of Depressive Symptoms***

Continuous Measures: Independent-samples t-test compared groups on BDI-II total score. Welch correction was applied when Levene's test indicated unequal variances ($p < .05$).

Categorical Distribution: Chi-square test examined the overall distribution of participants across BDI-II severity categories (minimal, mild, moderate, severe). Fisher's exact test compared groups on prevalence of clinically relevant depressive symptoms (BDI-II ≥14).

2.5.3.2 ***Correlations Between Depressive Symptoms and Cognitive Performance***

Within the patient group (n=30), Spearman rank-order correlations examined relationships between depressive symptom severity (BDI-II total, MADRS total) and cognitive domain composite scores (attention/processing speed, verbal learning/memory, executive function).

Rationale for Spearman Correlations: Spearman correlations were selected over Pearson correlations for two reasons: (1) Shapiro-Wilk tests indicated departures from normality, and (2) Spearman correlations are more robust to outliers and do not assume linear relationships.

Partial Correlations: Age and education were included as control variables in partial correlation analyses, as both variables are known to influence cognitive performance. The correlation between depressive symptom severity and cognition was calculated while holding age and education constant.

Correlation Magnitude Interpretation: Following Cohen (Cohen, 1988) conventions, correlation magnitude was interpreted as small ($|\rho| = .10–.29$), moderate ($|\rho| = .30–.49$), or large ($|\rho| \geq .50$).

Multiple Comparison Correction: False Discovery Rate (FDR) correction using the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was applied to the family of six correlation tests (3 cognitive domains × 2 depression measures) to control Type I error rate while maintaining statistical power for exploratory analyses. This procedure controls the expected proportion of false positives among rejected null hypotheses. Both uncorrected p-values and FDR-adjusted p-values are reported to allow evaluation of results under different Type I error control strategies.

2.5.4 **Hypothesis Testing Framework**

Confirmatory hypotheses (H1a, H1b) were pre-specified primary hypotheses tested using planned statistical approaches. No adjustment for multiple comparisons was applied to the three

domain-specific comparisons (attention, memory, executive function) as these represented distinct a priori hypotheses testing different cognitive constructs rather than post-hoc data exploration. This approach follows recommendations for planned comparisons testing specific hypotheses (Rothman, 1990).

Exploratory hypotheses (H2a, H2b) were secondary analyses examining relationships informed by prior literature but not pre-specified as primary outcomes. While these analyses provide valuable information, findings should be considered preliminary and requiring replication. For exploratory correlation analyses (H2b), FDR correction was applied to balance Type I and Type II error risks, as recommended for exploratory hypothesis generation (Benjamini and Hochberg, 1995).

3 RESULTS

3.1 Participant Characteristics

The final sample comprised 30 patients with chronic hypoparathyroidism with complete data and 30 matched healthy controls who completed the full study protocol. Table 1 presents demographic and clinical characteristics for the final sample.

Table 1: Participant demographic and clinical characteristics

Variable	Patients (n = 30)	Healthy controls (n = 30)	Statistics
Sex n (%)			χ^2 (1) = .111; p = .739
Women	24 (80.0)	25 (83.3)	
Men	6 (20.0)	5 (16.7)	
Age, mean ± SD	44.5 ± 13.1	44.0 ± 12.8	t (58) = 0.038; p = .882
Education, years, M ± SD	13.6 ± 2.2	13.4 ± 2.2	t (55) = 0.450; p = .655
BDI-II, M ± SD, points	11.5 ± 8.4	4.5 ± 5.2	t (48.3) = 4.054; ***p* < .001**
IQ, M ± SD, points	105.3 ± 13.5	112.3 ± 15.5	t (56) = -1.840; p = .071
Clinical characteristics			
Duration of disease (years)	8.7 ± 5.3	-	
Etiology			
Postsurgical	27 (90.0)	-	
Idiopathic	2 (6.7)	-	
Autoimmune	1 (3.3)	-	
Treatment			
Standard therapy	24 (80)	-	
PTH 1-84	6 (20)		

Note: M = mean, SD = standard deviation, BDI-II = Beck Depression Inventory-II, IQ = intelligence quotient, PTH = parathyroid hormone. Data previously published in Tmava-Berisha et al. (2025), doi:10.1210/clinem/dgae800.

No significant differences were observed between groups regarding age, sex distribution, years of education, or IQ, confirming successful matching on key demographic variables.

Disease etiology was predominantly postsurgical (90%), with a mean disease duration of 8.7 ± 5.3 years. Patients demonstrated significantly higher BDI-II scores than controls, though the patient mean fell below the threshold for mild depressive symptoms.

3.2 Primary Outcomes

3.2.1 Group Differences in Cognitive Performance

Patients with hypoparathyroidism demonstrated significantly lower performance on TMT-A, Stroop color naming, Stroop interference, and all CVLT subtests. No significant differences were observed for Stroop color-word reading, TMT-B, or TMT B-A. Table 2 presents cognitive raw scores for individual neuropsychological tests in patients and controls.

Table 2: Cognitive raw scores in patients and controls

Cognitive variables (M ± SD)	**Patients (*n* = 30)**	**Healthy controls (*n* = 30)**	**Test statistic (F)**	***p* - value**	***η²***
TMT-A (s)	35.6 ± 16.9	28.1 ± 8.8	4.625	**.036**	0.074
TMT-B (s)	80.6 ± 38.4	66.88 ± 18.7	3.085	.084	0.050
TMT-B- TMT-A (s)	47.4 ± 34.6	38.8 ± 14.4	1.581	.214	0.068
Stroop color-word reading (s)	46.4 ± 10.9	46.1 ± 10.4	0.012	.912	0.000
Stroop color naming (s)	70.0 ± 27.1	32.9 ± 9.6	49.920	**<.001**	0.463
Stroop interference (s)	108.6 ± 38.8	73.1 ± 14.4	21.999	**<.001**	0.275
CVLT trial 1-5	48.4 ± 15.4	59.3 ± 9.1	11.188	**.001**	0.162
CVLT short delay free recall	10.0 ± 3.9	12.3 ± 3.1	6.087	**.017**	0.095
CVLT short delay cued recall	11.5 ± 3.3	13.2 ± 2.4	5.369	**.024**	0.085
CVLT long delay free recall	10.8 ± 3.4	12.8 ± 2.6	6.528	**.013**	0.101
CVLT long delay cued recall	11.9 ± 3.4	13.5 ± 2.5	4.243	**.044**	0.068
CVLT recognition	14.2 ± 1.4	14.8 ± 0.6	4.374	**.041**	0.070

Note: Statistics from independent samples t-tests. Abbreviations: CVLT, California Verbal Learning Test; M, mean; s, seconds; TMT, Trail Making Test. Data previously published in Tmava-Berisha et al. (2025), doi:10.1210/clinem/dgae800.

Domain Composite Score Analysis

Given the significant difference in BDI-II scores between groups, analyses of covariance (ANCOVAs) were conducted to compare patients and controls on cognitive domain composite scores, controlling for BDI-II as a covariate.

Table 3: Cognitive domain composite scores by group

Cognitive domain scores	**Patients (*n* = 30) *M* ± *SD***	**Healthy controls (*n* = 30) *M* ± *SD***	***F***	***p-value***	***η²p***
Attention and processing speed	-0.90 ± 2.54	0.90 ± 1.52	8.64	**.005**	0.132
Verbal learning and memory	-1.83 ± 5.87	1.83 ± 3.95	2.04	.159	0.035

Cognitive domain scores	Patients (n = 30) $M \pm SD$	Healthy controls (n = 30) $M \pm SD$	F	p-value	η^2p
Executive function	-0.90 ± 3.22	0.91 ± 2.61	1.512	.224	0.026

Note: Results from one-way ANCOVA controlling for BDI-II scores. η^2p = partial eta squared. Data previously published in Tmava-Berisha et al. (2025), doi:10.1210/clinem/dgae800.

After controlling for BDI-II scores via ANCOVA, groups differed significantly only in attention/processing speed, with a large effect size approaching the conventional threshold [$F(1,57) = 8.64$, $p = .005$, $\eta^2p = .132$], with patients showing lower performance ($M = -0.90 \pm 2.54$) compared to controls ($M = 0.90 \pm 1.52$). Verbal memory and executive function differences did not reach significance after covariate adjustment, despite numerically lower patient performance.

3.2.2 Prevalence of Cognitive Impairment

Impairment prevalence was significantly elevated in patients for attention/processing speed (56.7% vs. 3.3%) and executive function (60.0% vs. 16.7%), both with large effects (Table 4). Verbal memory impairment showed elevated prevalence in patients (46.7% vs. 23.3%), which did not reach statistical significance.

Table 4: Prevalence of Cognitive Impairment by Domain

Deficit domain	Patients (n= 30)	Healthy controls (n = 30)	p-value	φ
Attention and processing speed *(%)*	17 (56.7)	1 (3.3)	**<.001**	0.58
Verbal learning and memory *(%)*	14 (46.7)	7 (23.3)	.103	0.24
Executive function *(%)*	18 (60.0)	5 (16.7)	**.001**	0.45

Note: HC = healthy controls. Fisher's exact test used due to expected cell frequencies <5. φ = phi coefficient. Data previously published in Tmava-Berisha et al. (2025), doi:10.1210/clinem/dgae800.

3.3 Secondary Outcomes

3.3.1 Depressive Symptoms

Table 5 presents depression assessment results. Patients completed BDI-II and MADRS; controls completed BDI-II and HAMD per BIPLONG protocol. Different instruments preclude direct MADRS-HAMD comparison.

Table 5: Depression Measures and Severity Distribution

Measure	Patients (*n*=30)	Healthy controls (*n*=30)	Statistics
Continuous Measures			
BDI-II Total Score, *M (SD)*	11.5 (8.4)	4.5 (5.2)	t (48.3) = 4.05, ***p* < .001**, d = 1.04
MADRS Total Score, *M (SD)*	10.5 (9.3)	-	-
HAMD Total Score, *M (SD)*	-	0.9 (1.7)	-
BDI-II Severity Categories, *n (%)*			χ^2 (3) = 10.03, ***p* = .018**
Minimal (0-13)	19 (63.3)	28 (93.3)	
Mild (14-19)	4 (13.3)	1 (3.3)	
Moderate (20-28)	7 (23.3)	1 (3.3)	
Severe (29-63)	0 (0.0)	0 (0.0)	
Clinically Relevant Symptoms			
BDI-II ≥14, n *(%)*	11 (36.7)	2 (6.7)	***p* = .010** (Fisher's exact)

Note: BDI-II = Beck Depression Inventory-II; MADRS = Montgomery-Åsberg Depression Rating Scale; HAMD = Hamilton Depression Rating Scale. Different instruments reflect separate study protocols. t-test with Welch correction (Levene's $p = .007$). d = Cohen's d.

Patients demonstrated significantly higher BDI-II scores than controls, with a large effect size (Table 5). Over one-third of patients (36.7%) exceeded the clinically relevant threshold (BDI-II ≥14) compared to 6.7% of controls (p = .010, Fisher's exact test).

BDI-II severity distribution differed significantly between groups, χ^2 (3) = 10.03, p = .018. The majority of patients (63.3%) reported minimal symptoms, with 13.3% mild, 23.3% moderate, and no severe symptoms. In contrast, 93.3% of controls reported minimal symptoms. In addition, Patient mean MADRS score (10.5 ± 9.33) fell in the mild depression range (7-19); the HC mean HAMD score (0.90 ± 1.67) fell in the no depression range (0-7).

3.3.2 Depressive Symptoms-Cognition Correlations

Table 6 presents Spearman partial correlations (controlling for age and education) between depression measures and cognitive domain scores within the patient group (n = 30).

Table 6: Correlations between depressive symptoms and cognitive performance

Depression Scale	Cognitive Domain	*ρ*	*p*	*FDR-adjusted p*
BDI-II				
	Attention/Processing Speed	-.137	.486	.572
	Verbal Learning/Memory	-.453	**.016**	**.032**

Depression Scale	Cognitive Domain	*ρ*	*p*	*FDR-adjusted p*
MADRS	Executive Function	-.448	**.017**	**.032**
	Attention/Processing Speed	-.111	.572	.572
	Verbal Learning/Memory	-.463	**.013**	**.026**
	Executive Function	-.425	**.028**	**.042**

Note: ρ = Spearman partial correlation. Negative values = higher depression associated with lower cognition. FDR = False Discovery Rate correction (6 tests).

For attention and processing speed, no significant correlations were observed with either BDI-II or MADRS. In contrast, for verbal learning and memory, significant moderate negative correlations were observed with both BDI-II (ρ = -.453, p = .016, FDR-adjusted p = .032) and MADRS (ρ = -.463, p = .013, FDR-adjusted p = .026). Similarly, for executive function, significant moderate negative correlations were observed with both BDI-II (ρ = -.448, p = .017, FDR-adjusted p = .032) and MADRS (ρ = -.425, p = .028, FDR-adjusted p = .042). All correlations with memory and executive function survived FDR correction for multiple comparisons, indicating robust associations independent of multiple testing considerations.

4 DISCUSSION

4.1 Summary of Principal Findings

This prospective case-control study examined cognitive function and depressive symptoms in chronic hypoparathyroidism using a comprehensive neuropsychological assessment with rigorous matching on age, sex, education, and baseline verbal intelligence.

Confirmatory Findings (Primary Hypotheses):

After controlling for depressive symptoms (BDI-II), patients demonstrated significantly lower performance in attention/processing speed compared to matched controls. In contrast, group differences in verbal learning/memory and executive function did not reach statistical significance after covariate adjustment.

Cognitive impairment prevalence was markedly elevated in patients for attention/processing speed and executive function, with large effect sizes. Verbal memory impairment showed elevated prevalence that did not reach statistical significance.

Exploratory Findings (Secondary Hypotheses):

Patients reported significantly higher depressive symptom severity with a large effects, and over one-third exceeded the threshold for clinically relevant symptoms compared to controls.

Domain-specific patterns emerged in cognition-depression relationships. Depressive symptom severity showed no correlation with attention/processing speed but demonstrated significant moderate negative correlations with verbal learning/memory and executive function.

4.1.1 Attention and Processing Speed Deficits

Attention/processing speed represented the most consistently impaired cognitive domain, with three convergent lines of evidence supporting this as a disease-related deficit relatively independent of depressive symptoms:

First, the deficit persisted after statistically controlling for depressive symptoms, demonstrating a large effect size. Second, neither self-report nor clinician-rated depressive symptom severity correlated with attention/processing speed performance, indicating minimal linear association. Third, impairment magnitude was substantial, with over half of patients demonstrating clinically significant deficits compared to few controls.

These findings are consistent with the pathophysiological mechanisms outlined in Section 1.4.1. Specifically, in prior studies basal ganglia calcification has been documented in >50% of patients and shows associations with dopamine-dependent processing speed measures (Goswami et al., 2012; Aggarwal et al., 2013). In addition, chronic hypocalcemia has been experimentally associated with altered neuronal excitability in animal models (Potts, 2005; Schampel and Kuerten, 2017).

However, our study did not directly measure these factors, and these remain plausible hypotheses requiring empirical testing through studies integrating neuroimaging and biochemical monitoring with cognitive assessment.

Our findings align with the pilot study by Rubin et al. 2022 (n=19), which reported slower processing speed in hypoparathyroid adults. Our study extends these findings through a matched control group, larger sample, and systematic control for depressive symptoms. The consistency across independent samples strengthens evidence that attention/processing speed deficits represent a genuine disease feature.

Furthermore, processing speed represents a fundamental cognitive capacity that correlates with performance across higher-order domains and predicts real-world outcomes including work productivity and instrumental activities of daily living in diverse patient populations (John and DeLuca, 2007; Callahan and Terry, 2015). The observed deficits may therefore have functional implications, consistent with epidemiological evidence documenting increased utilization of social security benefits in hypoparathyroidism(Astor et al*.,* 2016). However, the direct relationship between cognitive test performance and real-world occupational functioning has not been empirically assessed in hypoparathyroidism and remains an inference requiring validation.

4.1.2 **Memory and Executive Function**

Memory and executive function demonstrated a more complex pattern. While deficits were evident in unadjusted analyses, they did not remain statistically significant after controlling for depressive symptoms. Specifically, depressive symptom severity (BDI-II and MADRS) showed statistical associations with both domains, indicating shared variance between mood symptoms and cognitive performance.

However, impairment prevalence analyses revealed a statistically significant difference in executive function deficits patients compared to controls, despite the non-significant ANCOVA result for continuous scores.

This apparent discrepancy between continuous (ANCOVA) and categorical (prevalence) analyses has three plausible explanations, which are not mutually exclusive:

Distributional differences: Dichotomous impairment classification may detect group differences with different statistical properties than continuous scores, potentially providing greater sensitivity at the lower end of the performance spectrum.

Variance partitioning: ANCOVA adjustment removes variance that is shared between mood symptoms and cognitive performance. This shared variance may reflect:

- Depression temporally preceding cognitive deficits (Mechanism A, Section 4.1.5)
- Cognitive deficits temporally preceding depression (Mechanism B, Section 4.1.5)
- Both reflecting common disease mechanisms (Mechanism C, Section 4.1.5)
- Bidirectional relationships (Mechanism D, Section 4.1.5)

ANCOVA cannot distinguish these scenarios. If Mechanism C is correct, covariate adjustment removes disease-related variance, potentially obscuring true group differences.

Statistical power: Limited power for detecting small-to-moderate effects after covariate adjustment may have resulted in Type II errors for continuous analyses, while the categorical approach with larger effect sizes retained adequate power.

These possibilities require larger samples and longitudinal designs for resolution.

4.1.3 Elevated Depressive Symptoms

Patients reported significantly higher depressive symptom severity with a large effect size, though the mean patient score remained below the threshold for mild depressive symptoms. Over one-third exceeded the threshold for clinically relevant symptoms warranting further evaluation.

Methodological Considerations

Several methodological considerations warrant emphasis. First, screening instruments assess symptom severity and identify individuals who may warrant further evaluation but do not

establish formal psychiatric diagnoses. Diagnosis requires structured clinical interviews conducted by qualified mental health professionals (Kessler and Ustün, 2004).

Second, the BDI-II includes somatic symptoms (fatigue, sleep disturbance) that may overlap with manifestations of the underlying endocrine disorder, potentially inflating scores independent of mood disturbance. However, the convergence of self-report (BDI-II) and clinician-rated (MADRS) measures provides some support for genuine elevated symptoms rather than mere somatic symptom reporting. Mean MADRS score (10.5 ± 9.3) fell in the mild depression range (7-19), consistent with BDI-II findings.

Third, control participants from the BIPLONG study were assessed using HAMD rather than MADRS, precluding direct statistical comparison of clinician-rated depression scales between groups. While all three instruments (BDI-II, MADRS, HAMD) assess depressive symptoms with established convergent validity, differences in item content and rating procedures limit direct comparability.

4.1.4 **Domain-Specific Depression Symptoms-Cognition Relationships**

Correlation analyses revealed a domain-specific pattern: depressive symptom severity showed no correlation with attention/processing speed but demonstrated significant moderate negative correlations with verbal memory and executive function. This pattern was consistent across both self-report and clinician-rated measures and remained significant after correction for multiple comparisons.

However, several methodological considerations affect interpretation. First, the sample size (n=30 patients) provided 80% power to detect correlations of $|\rho| \geq 0.48$, indicating adequate power for the moderate correlations observed but limited power for small effects. Second, correlations were conducted within the patient group only, where range restriction in depression scores (compared to the full population distribution) may have attenuated correlation coefficients. Third, the use of partial correlations controlling for age and education is an appropriate analytic strategy, but it further reduces statistical power.

4.1.5 **Interpreting Cognition- Depressive Symptoms Relationships: Mechanistic Hypothesis**

The following mechanistic hypotheses are speculative models compatible with our observed cross-sectional correlations but not established by our data. Cross-sectional correlations cannot distinguish between these alternatives; they are equally compatible with forward

causation, reverse causation, shared underlying mechanisms, or bidirectional relationships. Each hypothesis makes distinct predictions testable only through longitudinal or experimental research designs. We present four mechanistic hypotheses below:

HYPOTHESIS A: Depression Temporally Precedes and Influences Cognition

Proposed model: Depressive symptoms develop first (due to chronic illness burden, biochemical alterations, or other factors) and are subsequently associated with reduced cognitive performance.

Plausible mechanisms :

- Reduced cognitive effort during testing (motivation deficit)
- Rumination consuming cognitive resources
- Psychomotor slowing
- Sleep disturbance affecting consolidation

Testable predictions:

- In longitudinal data: Depression onset temporally precedes cognitive decline
- In intervention studies: Depression treatment is followed by cognitive improvement
- Depression severity predicts cognitive change over time

HYPOTHESIS B: Cognitive Deficits Temporally Precede and Influence Depression

Proposed model: Memory and executive deficits develop first (due to disease-related brain changes) and are subsequently associated with the development of depressive symptoms.

Plausible mechanisms:

- Subjective awareness of cognitive decline
- Functional limitations in daily activities
- Reduced work capacity
- Loss of independence

Testable predictions:

- In longitudinal data: Cognitive decline temporally precedes depression onset
- In intervention studies: Cognitive interventions are followed by mood improvement
- Cognitive impairment severity predicts subsequent depression development

HYPOTHESIS C: Shared Pathophysiology Without Direct Causal Relationship

Proposed model: Both cognitive deficits and depressive symptoms reflect common pathophysiological substrates without direct causal relationships between symptoms.

Plausible mechanisms:

- Chronic hypocalcemia associated with neurotransmitter alterations
- Basal ganglia calcification associated with dopaminergic dysfunction
- Neuroinflammation associated with cognitive and mood changes
- PTH deficiency associated with neuromodulatory alterations

Testable predictions:

- Disease severity biomarkers correlate with both cognition and mood independently
- Treating depression does not improve cognition (or vice versa)
- Disease-modifying treatments are associated with simultaneous improvement in both domains
- Mediation analysis: Depression does not mediate the disease→cognition relationship

HYPOTHESIS D: Bidirectional Relationships and Feedback Loops

Proposed model: Cognitive difficulties and depressive symptoms maintain statistical associations through mutually reinforcing relationships over time, as documented in general population studies (da Silva et al., 2013).

Plausible mechanisms :

- Initial cognitive changes associated with psychological distress
- Depression associated with reduced cognitive engagement
- Cognitive avoidance associated with increased impairment
- Demoralization associated with reduced compensatory effort

Testable predictions:

- Cross-lagged panel models: Each predicts change in the other over time
- Intervention studies: Combined interventions show greater effects than single interventions
- Time-series analysis: Daily mood fluctuations correlate with daily cognitive performance

4.1.6 **Comparison with Prior Literature**

Sardella et al. 2021 concluded evidence linking chronic hypoparathyroidism to cognitive impairment was "extremely limited, with only case reports and one cross-sectional controlled study available." Our study addresses four critical methodological limitations identified in prior research: (a) a matched control group with rigorous individual matching (prior studies lacked matched controls or used convenience samples); (b) matching on baseline verbal intelligence, a critical variable not addressed in any prior studies, which controls for cognitive reserve affecting vulnerability to disease-related impairment (Stern, 2012); (c) comprehensive domain-specific assessment (prior studies used global screening instruments with limited construct validity); and (d) systematic mood assessment with validated instruments employed both as outcomes and as statistical covariates, enabling distinction between mood-independent and mood-related cognitive deficits.

A recent Danish study (Sikjaer et al*.,* 2024) provides complementary evidence through a different methodological approach: combining neuropsychological testing, quality-of-life assessment, and structural MRI. Key findings included poorer cognitive performance in patients, particularly in long-term memory, with structural imaging revealing smaller hippocampal volumes correlating inversely with cognitive impairment severity. Importantly, they identified specific correlations between regional brain volumes and distinct cognitive domains: thalamus volume correlated with auditory memory, caudate volume with executive functions, and left putamen volume with processing speed. Disease duration was associated with thalamus volume specifically in postsurgical patients, suggesting progressive structural changes in this subgroup. Additionally, reduced quality of life was associated with both cognitive deficits and structural brain changes. The convergence between our behavioral findings and their neuroimaging data strengthens the evidence that cognitive deficits are associated with structural brain pathology. However, causal directionality (whether structural changes temporally precede cognitive decline, whether cognitive decline temporally precedes structural changes, or whether both reflect common mechanisms) cannot be established from cross-sectional studies.

Case reports have documented both reversible cognitive presentations with prompt intervention (Kumar et al*.,* 2013) and irreversible presentations with chronic disease (Terada et al*.,* 2015; Adorni et al*.,* 2005; Dos Santos et al*.,* 2016). While these observations suggest possible time-dependent windows for intervention, systematic longitudinal data establishing whether early

treatment prevents cognitive decline are lacking. The reversibility question remains empirically unresolved.

The consistency of findings across independent studies (Rubin et al., 2022; Saponaro et al., 2022; Sikjaer et al., 2024; Aggarwal et al., 2013), including the present investigation, provides converging evidence from multiple methodological approaches (matched case-control, neuroimaging, epidemiological) that cognitive dysfunction represents a common feature of chronic hypoparathyroidism. However, three critical limitations constrain confident conclusions:

Prevalence uncertainty: Estimates range from 30-70% depending on assessment method and impairment definition, reflecting methodological heterogeneity rather than true population variability being established.

Determinant ambiguity: The relative contributions of calcification, biochemical instability, PTH deficiency, and mood symptoms remain undetermined due to lack of studies systematically measuring all factors.

Clinical significance unclear: The relationship between documented cognitive deficits and real-world functional outcomes (work capacity, independent living, medication adherence) has not been directly assessed.

Possible Contributing Factors from Prior Literature

The following discussion synthesizes evidence from prior studies regarding factors that might contribute to the cognitive deficits documented in our sample and others. Our study did not measure these factors directly. These represent hypotheses for future investigation derived from literature review, not conclusions from our data.

Structural Correlates

Basal ganglia calcification has been documented in over 50% of patients in prior imaging studies, with prevalence increasing with disease duration (Goswami et al., 2012; Illum and Dupont, 1985). Zavatta et al. 2021 demonstrated associations between calcification burden and both local brain metabolic alterations and systemic phosphate levels. The basal ganglia play established roles in processing speed and sustained attention in neuroanatomical models (Callahan and Terry, 2015). Processing speed correlates with white matter volume in healthy populations (Magistro et al., 2015). These observations, combined with the region-specific

structure-function correlations documented by Sikjaer et al. 2024 linking putamen volume with processing speed, suggest that structural pathology might contribute to the attention deficits observed in the present study. However, without individual neuroimaging data, we cannot determine which patients in our sample harbor these structural changes or test direct structure-function relationships in our cohort.

Hippocampal structural changes may be relevant to memory deficits, as demonstrated by the correlation between hippocampal volumes and memory performance documented by Sikjaer et al. 2024. Our finding that memory deficits did not persist after controlling for depressive symptoms complicates interpretation. Possible explanations include: (1) structural changes are present but their cognitive effects are mediated by mood symptoms, (2) structural changes are present in only a subset of patients, (3) mood symptoms and structural changes independently contribute to memory deficits, or (4) ANCOVA overcorrection removed disease-related variance (see Section 4.1.2). These alternatives cannot be distinguished without individual neuroimaging data in our sample.

Biochemical Factors

Saponaro et al. 2022 demonstrated correlations between serum calcium levels and cognitive performance, even within "controlled" ranges, suggesting that biochemical factors influence cognition. Calcium plays critical roles in neuronal signaling and enables astrocytes to support information processing (John and DeLuca, 2007). Astrocytes use calcium signaling to modulate neuronal activity and synaptic transmission, contributing to information integration across neural networks. Chronic hypocalcemia in hypoparathyroidism may disrupt these astrocyte-mediated processes, potentially contributing to processing speed deficits.

Rubin (Rubin, 2023) highlighted that "calcium crashes"—rapid fluctuations despite adequate average control—may contribute to intermittent symptoms not captured by routine monitoring. Our single-timepoint calcium measurement does not capture variability that may contribute to symptoms.

Hormonal Mechanisms

PTH receptors are expressed in brain regions including hippocampus and limbic structures (Dettori et al., 2023), suggesting PTH may serve neuromodulatory functions. Loss of PTH signaling might contribute to symptoms independent of calcium levels, potentially explaining persistent complaints despite apparent biochemical control (Hadker et al*.,* 2014).

Furthermore, recent evidence suggests that PTH2R and its endogenous ligand, tuber infundibular peptide of 39 residues (TIP39), are concentrated in endocrine, viscerosensory, and auditory brain regions (Bagó et al*.,* 2009). This PTH2R-TIP39 system may be involved in nociceptive information processing, regulation of hypothalamic neurons, and modulation of emotional processes. The absence of PTH in hypoparathyroidism disrupts not only direct PTH signaling but potentially also the PTH2R-TIP39 system, which could contribute to both cognitive and mood-related symptoms. However, this mechanism remains speculative and requires investigation through studies measuring PTH2R expression and TIP39 levels in hypoparathyroid patients. We did not examine PTH replacement effects systematically (only 20% of patients received PTH). These hormonal hypotheses require randomized controlled trials comparing PTH replacement to conventional therapy with neuropsychological endpoints.

Disease Duration as Integrating Factor

The evidence reviewed above converges to suggest that disease duration may be a determining factor in cognitive dysfunction severity. The correlation between longer disease duration and greater cognitive impairment (Sikjaer et al., 2024), the association between disease duration and thalamus volume in postsurgical patients (Sikjaer et al., 2024), and evidence of progressive calcification over time (Goswami et al., 2012; Zavatta et al., 2021), all point toward cumulative pathological changes. This temporal pattern may explain variability in cognitive outcomes across studies with different mean disease durations and supports the importance of early diagnosis and optimal biochemical control to potentially limit progressive brain changes. However, whether early intervention actually prevents cognitive decline remains to be established through longitudinal studies.

4.2 Methodological Considerations

4.2.1 Strengths

IQ Matching: To our knowledge, this represents the first study employing rigorous matching on IQ, a critical variable affecting cognitive performance and reserve capacity (Stern, 2012). This strengthens inferences regarding disease-associated differences.

Systematic Mood Assessment: Prior studies either omitted mood assessment or did not incorporate it into statistical models (Sardella et al., 2021). Dual assessment (self-report and clinician-rated) with systematic covariate adjustment distinguished mood-independent from mood-related cognitive deficits. The domain-specific pattern that emerged would have remained obscured without this approach.

Domain-Specific Assessment: Comprehensive assessment with composite score construction offers increased reliability, construct validity through convergent evidence, and clinically interpretable profiles (Lezak et al., 2012). The dissociation between domains constrains mechanistic hypotheses.

Standardized Instruments: All measures represent well-validated instruments with established psychometric properties and normative data, enabling comparison and replication.

4.2.2 Limitations

Cross-Sectional Design: The cross-sectional design documents associations but cannot establish causality, temporal precedence, or directionality of relationships. We cannot determine whether depressive symptoms precedes, follows, or develops concurrently with cognitive deficits. We cannot determine whether cognitive impairment is stable, progressive, or fluctuating over time. We cannot assess whether relationships between variables reflect causal mechanisms versus shared underlying factors. Longitudinal studies with repeated assessment from the time of diagnosis would be required to address these questions.

Attrition and Missing Data: Four of 34 initially enrolled patients (11.8%) were excluded due to incomplete assessment data (three with missing neuropsychological tests, one premature discontinuation due to fatigue). This may introduce selection bias by preferentially excluding patients with more severe cognitive impairment or psychological distress unable to tolerate the comprehensive assessment, potentially underestimating impairment severity. Complete case

analysis ensures data integrity but limits generalizability to the full spectrum of disease severity.

Sample Size: No formal a priori power analysis was conducted given the pragmatic constraints of recruiting patients with this rare orphan disease. While the sample (n=30 per group) is comparable to or larger than prior neuropsychological studies in hypoparathyroidism (Aggarwal et al., 2013; Rubin et al., 2022; Sikjaer et al., 2024; Saponaro et al., 2022), it provided limited power for detecting small-to-moderate correlations and precluded subgroup analyses. Post-hoc power analysis indicated adequate power (>80%) for detecting the large effect sizes ($d \geq 0.8$) observed in primary outcomes (attention/processing speed) but underpowered for smaller effects. Larger samples would enable examination of disease heterogeneity (e.g., postsurgical vs. non-surgical etiologies, disease duration effects) and detection of more subtle cognitive-mood relationships.

Absence of Individual Neuroimaging: We did not obtain neuroimaging for participants. While basal ganglia calcification and hippocampal atrophy are documented in this population, we cannot determine which patients in our sample have these findings or test structure-function relationships. Discussion of structural factors relies on extrapolation from prior literature rather than demonstration in our participants.

Biochemical Assessment Limitations: Single-timepoint calcium measurement does not capture variability that may contribute to symptoms (Rubin, 2023). Our design cannot address whether calcium levels, fluctuations, or other biochemical parameters correlate with cognitive performance.

Generalizability: The predominantly postsurgical (90.0%), female (80.0%), conventionally-treated (80.0%) sample may not generalize to patients with severe disease, non-surgical etiologies, or PTH replacement therapy. Recruitment through a single center may introduce selection bias.

Depression Assessment: Screening instruments identify symptoms warranting evaluation but do not establish diagnoses (Kessler and Ustün, 2004). Structured interviews would enable precise diagnostic characterization.

Treatment Heterogeneity: Varied treatment regimens and a subset receiving PTH replacement represent potential moderating variables our sample size precluded examining.

4.3 Clinical Implications

4.3.1 Recognition of Cognitive Dysfunction

The present findings suggest that cognitive difficulties, particularly in attention/processing speed, may be common in chronic hypoparathyroidism. Recognition of these potential difficulties has several clinical implications, though optimal management approaches remain to be established:

Work Capacity Assessment: Processing speed and executive function have been shown to predict work productivity and occupational functioning in other patient populations (John and DeLuca, 2007). Observed deficits may therefore be relevant for work capacity evaluations, workplace accommodation decisions, and disability benefit determinations. Objective neuropsychological assessment may provide useful data beyond self-report and routine biochemical monitoring for these purposes. However, the relationship between cognitive test performance and real-world occupational functioning was not directly assessed in the present study and requires investigation.

Quality of Life: The objective demonstration of cognitive deficits may validate patient-reported subjective complaints of "brain fog" and cognitive difficulties (Hadker et al., 2014) and align with quality-of-life impairments (Kontogeorgos et al., 2022). Recognition that complaints may reflect genuine measurable deficits rather than "functional" or "psychosomatic" symptoms could improve patient-provider relationships and treatment satisfaction. However, whether such recognition actually improves patient outcomes requires empirical testing.

Medical Decision-Making: Cognitive deficits, particularly executive dysfunction, may affect capacity for informed consent and treatment adherence.

4.3.2 Screening Considerations

The question "Should cognitive screening be routinely implemented?" cannot be answered definitively with current evidence. We propose a conditional recommendation:

Current evidence does not support universal cognitive screening in chronic hypoparathyroidism because:

Uncertain natural history: We do not know whether deficits are stable, progressive, or fluctuating;

Lack of validated interventions: Cognitive rehabilitation has demonstrated efficacy in other neurological conditions such as multiple sclerosis (Rayegani et al., 2024) and traumatic brain injury (Cicerone et al., 2019), with meta-analyses showing small to medium effect sizes for improvements in attention, memory, and executive function. However, no studies have evaluated such interventions in hypoparathyroidism.

Unknown predictive validity: The relationship between test performance and patient-important outcomes is unestablished;

Resource intensity: Comprehensive assessment requires specialized expertise not widely available.

However, targeted screening may be justified in high-risk subgroups pending validation studies:

Potential indicators for selective assessment include:

- Disease duration >10 years (Goswami et al., 2012; Zavatta et al., 2021)
- Subjective cognitive complaints interfering with daily functioning
- Documented basal ganglia calcification on clinical imaging
- Occupational performance decline
- Elevated depressive symptom scores (moderate correlation with executive/memory deficits)

Need for Validation Studies: Prospective studies are needed to establish: (1) optimal screening instruments for this population, (2) appropriate cutoff scores, (3) sensitivity/specificity of screening approaches, (4) availability of effective interventions, and (5) cost-effectiveness of screening programs.

4.3.3 Management of Depressive Symptoms

The moderate correlations observed between depressive symptom severity and memory/executive function raise the possibility that treatment of mood symptoms might improve cognitive performance in these domains. However, this hypothesis requires testing through intervention studies and cannot be inferred from cross-sectional correlational data. Conversely, it is possible that cognitive deficits contribute to mood symptoms, in which case depression treatment alone might be insufficient to improve cognition. Standard evidence-based treatments for depression (pharmacotherapy, psychotherapy) (Cipriani, A. et al., 2018; Cuijpers et al., 2013) have well-established efficacy

in other populations and may be beneficial for patients with hypoparathyroidism and comorbid mood symptoms. However, treatment trials specifically in this population have not been conducted, and potential interactions between antidepressant medications and calcium/PTH metabolism are unknown.

Recommendation:

Depression treatment should be considered for patients with clinically significant mood symptoms (BDI-II ≥14) based on general psychiatric evidence, not based on assumptions about cognitive benefits. Cognitive effects of depression treatment in hypoparathyroidism require empirical testing through randomized controlled trials with cognitive outcomes as prespecified endpoints.

4.3.4 Implications for PTH Replacement Therapy

The present findings documenting substantial cognitive dysfunction and elevated depressive symptoms support the inclusion of comprehensive neuropsychiatric endpoints (cognitive performance, mood symptoms, quality of life) in clinical trials of PTH replacement therapies. However, neuropsychiatric outcomes have not been systematically evaluated as primary or secondary endpoints in most PTH replacement trials to date (Meola et al., 2018). Future trials should employ validated neuropsychological and psychiatric assessment instruments to determine whether PTH replacement offers neuropsychiatric advantages beyond improvements in biochemical control. The present study included a subset of patients (20%) receiving PTH replacement therapy (Natpara), but the sample size precluded meaningful comparison with conventionally treated patients. Larger observational studies and randomized controlled trials are needed to definitively assess neuropsychiatric effects of PTH replacement.

4.4 Future Research Directions

Section 4.1.5 outlined four mechanistic hypotheses with testable predictions. The following research priorities would address fundamental limitations of the present study and advance toward evidence-based interventions.

4.4.1 Longitudinal Studies

Prospective studies following patients from diagnosis are essential for establishing temporal relationships and natural history. Such studies would test the competing mechanistic hypotheses (A-D, Section 4.1.5) by determining whether depression precedes cognitive decline, cognitive

decline precedes depression, both emerge simultaneously, or bidirectional influences exist. Repeated comprehensive assessment (neuropsychological, psychiatric, biochemical, neuroimaging) would establish whether cognitive deficits are stable, progressive, or fluctuating, and identify predictors of cognitive trajectory including etiology, disease duration, and biochemical control quality.

4.4.2 Neuroimaging Integration

Multimodal imaging integrated with neuropsychological assessment would test structure-function relationships discussed in Section 4.1.6. Key questions include whether basal ganglia calcification correlates with attention deficits, whether hippocampal volume correlates with memory performance independent of mood, whether white matter integrity predicts processing speed, and critically, whether structural changes precede, parallel, or follow cognitive changes in longitudinal designs.

4.4.3 Intervention Studies

Experimental interventions provide the strongest evidence for causality and therapeutic efficacy:

Depression treatment trials would test whether reducing depressive symptom severity improves cognitive performance, distinguishing between Hypothesis A (depression causes cognitive deficits) and Hypothesis C (shared mechanisms without direct causation) from Section 4.1.5. Randomized controlled trials with comprehensive neuropsychological assessment as prespecified endpoints are needed.

PTH replacement trials should incorporate neuropsychiatric endpoints (cognitive performance, mood symptoms, quality of life) to determine whether PTH offers advantages beyond biochemical control. The hormonal mechanisms outlined in Section 4.1.6 suggest potential neuropsychiatric benefits requiring empirical testing.

Cognitive rehabilitation interventions demonstrating efficacy in other neurological conditions warrant testing in hypoparathyroidism. Domain-specific training and compensatory strategies might improve functional outcomes even if underlying deficits persist.

Calcium optimization studies with intensive monitoring would test whether minimizing calcium variability improves cognitive stability beyond effects of mean calcium levels.

4.4.4 **Mechanistic Studies**

Studies correlating biochemical parameters (calcium levels and variability, phosphate, magnesium) with cognitive performance, examining neuroinflammatory biomarkers, testing genetic vulnerability factors, and employing preclinical models to investigate PTH neuromodulatory functions would advance understanding of pathophysiology and identify therapeutic targets.

4.5 Conclusions

This prospective case-control study provides a comprehensive neuropsychological characterization of chronic hypoparathyroidism using validated instruments, systematic depression screening assessment, and rigorous matching on IQ.

Principal Findings:

- Attention/processing speed deficits persisted after controlling for depressive symptoms, with over half of patients demonstrating clinically significant impairment compared to controls. This represents the most robust disease-related cognitive deficit.
- Memory and executive deficits demonstrated a more complex pattern: Deficits were evident in unadjusted analyses and impairment prevalence but did not remain statistically significant in continuous measures after controlling for mood symptoms. The interpretation of this discrepancy between categorical and continuous analyses remains uncertain and requires investigation in larger samples.
- Elevated depressive symptoms in patients with hypoparathyroidism is common, with over one-third reporting clinically relevant depressive symptoms warranting further evaluation.
- The domain-specific pattern of findings—attention deficits showing no association with depressive symptoms versus memory/executive deficits showing moderate correlations with depressive symptoms— suggests potential differences in underlying mechanisms, though alternative explanations cannot be excluded.

Integration with Literature:

Our findings converge with, though extend methodologically beyond, recent independent studies (Rubin et al., 2022; Saponaro et al., 2022; Sikjaer et al., 2024). The accumulated evidence across multiple methodological approaches (case-control, neuroimaging, epidemiological) supports the conclusion that cognitive dysfunction represents a common

feature of chronic hypoparathyroidism. However, critical uncertainties persist regarding prevalence (30-70% depending on methods), determinants (relative contributions of structural vs. biochemical vs. hormonal factors), and clinical significance (relationship to functional outcomes).

Clinical Relevance:

The documentation of cognitive difficulties—particularly attention/processing speed deficits affecting >50% of patients—has potential implications for clinical management, though optimal approaches to screening, assessment, and treatment remain to be established through intervention research. Importantly, this study documents associations but does not establish whether cognitive deficits are: (1) stable vs. progressive; (2) reversible with treatment; or (3) predictive of functional impairment in daily life. These questions require longitudinal and interventional research designs.

Future Directions:

Longitudinal studies are needed to establish temporal relationships and natural history. Integration of neuroimaging with neuropsychological assessment would test structure-function relationships. Intervention studies examining PTH replacement, depression treatment, and cognitive rehabilitation would determine whether outcomes can be improved.

Final Perspective:

The present study provides evidence that neuropsychiatric aspects of chronic hypoparathyroidism warrant greater clinical and research attention. While methodological limitations constrain causal inference, the documentation of cognitive difficulties in a substantial proportion of patients has potential implications for comprehensive patient care. Further research is needed to establish optimal approaches to recognition, assessment, and management of neuropsychiatric manifestations in this rare endocrine disorder, and to determine whether interventions can meaningfully improve patient outcomes.

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