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Clinical Research Article

A Pilot Study of Cognition Among Hypoparathyroid Adults

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Abstract

Purpose: Hypoparathyroid patients describe cognitive deficits, yet data regarding objective assessment of cognitive function are limited. We assessed cognition in a pilot study of hypoparathyroid patients using the National Institutes of Health Toolbox® Adult Cognitive Battery (NIHTB-CB). We also sought to determine whether cognition relates to emotion, quality of life, and hypoparathyroidism-related biochemistries.

Methods: Nineteen hypoparathyroid patients were studied. Objective cognition was assessed with NIHTB-CB. Impairment was defined as fully demographically adjusted T-score < 1.5 SD in at least 1 cognitive domain or < 1 SD in 2 or more domains.

Results: Of the 19 participants (17 women; median age 49; 18 postsurgical), impaired demographically adjusted NIHTB-CB cognition scores were observed in 13 subjects (68%). Cognition scores correlated with self-reported perception of general health. Processing speed was the most commonly impaired cognitive domain, with T-scores that were ≤2 SD in 6 subjects (32%). Processing speed correlated with serum calcium ($r = 0.53$, $P = 0.023$) and inversely with serum phosphate ($r = -0.48$, $P = 0.042$) levels.

Conclusions: Impaired cognition using the NIHTB-CB was common in this small pilot cohort of hypoparathyroid patients. Slower processing speed was present and associated with lower serum calcium and higher serum phosphate levels. Larger controlled studies with additional neuropsychological testing are needed to investigate cognitive function in hypoparathyroidism.

Key Words: hypoparathyroidism, cognition, NIH Toolbox, PTH

Hypoparathyroidism is a rare endocrine disorder that leads to hypocalcemia, hypercalciuria, and hyperphosphatemia [1]. Cognitive deficits are frequently reported by hypoparathyroid patients. A common complaint is "brain fog," with slowed thinking and an inability to perform day-to-day tasks [2]. Yet data regarding objective assessments of cognitive function in hypoparathyroidism are scarce. Most of the available reports have used the Short Form Health Survey (SF-36) scale [3-10], which is a self-report of impaired quality of life (QoL). It is thus unclear to what extent objective, performance-based, and clinically meaningful measures of cognitive function are abnormal in hypoparathyroidism.

The National Institutes of Health (NIH) Toolbox® Cognition Battery (NIHTB-CB) is a validated and reliable method for objective assessment of cognitive function [11-14]. This instrument assesses the cognitive domains of language, episodic memory, executive function, attention, working memory, and processing speed. It has been validated with the item response theory method and is considered to have comparable precision with traditional neuropsychological measures [15,16]. It generates cognitive outcomes that are adjusted for age, sex, race, ethnicity, and education based on normative data collected in a large US nationally representative sample. We hypothesized that the NIHTB-CB would provide preliminary data regarding cognition in a pilot cohort of hypoparathyroid individuals.

Given that depression and anxiety are increased in hypoparathyroidism [17-19], we also questioned whether cognitive abilities relate to emotional function. The NIH Toolbox® Emotion Battery (NIHTB-EB), also normed on large US nationally representative samples, was created to assess emotional functioning [20,21]. We anticipated that the NIHTB-EB would reveal psychological symptoms that would relate to cognition and to QoL as measured by the SF-36.

We also considered that serum calcium levels relate to neurological findings in hypoparathyroidism, with hypocalcemia causing neuromuscular irritability [1]. We therefore further hypothesized that cognition as a continuous construct would be associated with hypoparathyroidism-related biochemical abnormalities.

Methods

Patient Sample

Patients who were consecutively seen for clinical care of their hypoparathyroidism at the Metabolic Bone Disease Unit at Columbia University were invited to participate. Hypoparathyroidism was defined as hypocalcemia with

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low or inappropriately normal parathyroid hormone (PTH) levels. Exclusion criteria included diseases or medications known to influence calcium metabolism as well as current or ever use of PTH treatment, including teriparatide or recombinant human PTH(1-84). The study was approved by the Columbia University Irving Medical Center Institutional Review Board and informed written consent was obtained from all.

Study Protocol

Background and physical information were collected, including age, sex, menopausal status (menopause was defined as at least 12 months of amenorrhea), race, ethnicity, body mass index, highest level of education achieved, years of education, and current occupation. Hypoparathyroidism-associated variables, including etiology, duration, history of kidney stones or fractures, and medication regimen within the past month were collected. Subjects underwent measurement of serum calcium, PTH, phosphate, 24-hour urinary calcium excretion, estimated glomerular filtration rate, 25-hydroxyvitamin D, and thyroid-stimulating hormone levels. The NIHTB-CB, NIHTB-EB, and SF-36 were completed by all. Serum calcium levels were measured within 1 hour of the cognitive testing.

NIHTB-CB

The NIHTB-CB Adult 2015 iPad version was administered [22-24]. It uses 7 tests to assess the core cognitive domains of processing speed (how quickly one can take in and use information), episodic memory (the ability to remember objects, people, or events experienced at particular times and places), working memory (the ability to remember and see connections between items or ideas), executive function (cognitive flexibility), and attention (the ability to focus on relevant stimuli in the presence of irrelevant stimuli) as well as vocabulary and reading [13]. The first 5 domains generate a fluid cognition score, reflecting areas of cognition that may be vulnerable to age and diseases that affect the brain [25]. The sixth domain of language generates a crystallized cognition score, reflecting knowledge gained through past learning that is highly experience dependent [25]. The fluid and crystallized together give a total cognition score. NIHTB-CB derives T-scores, adjusted for age, sex, race/ethnicity, and education, which are based on comparison to a representative normative sample [15,26]. Higher scores indicate better cognitive functioning. One of us (M.R.R.) received training to conduct the NIHTB-CB and administered the test to all participants.

NIHTB-EB

The NIHTB-EB Adult 2015 iPad version was administered [27,28]. Five measures (anger-affect, anger-hostility, sadness, fear-affect, and perceived stress) generate a negative affect score [29,30]; 5 measures (friendship, loneliness, emotional support, instrumental support, and perceived rejection) generate a social satisfaction score [31]; and 3 measures (positive affect, general life satisfaction, and meaning and purpose) generate a psychological well-being score [32]. NIHTB-EB reports these scores as age- and sex-corrected T-scores. Higher scores indicate more of the construct being measured (ie, higher negative affect scores indicate more negative affect; higher social satisfaction scores indicate more social satisfaction; higher psychological well-being scores indicate more psychological well-being).

SF-36

The SF-36 (version 1.0), developed as part of the Medical Outcomes Study, was administered for self-reported QoL [33]. It consists of 36 items covering 8 domains of physical and mental health: physical functioning, role limitations caused by physical health problems, bodily pain, perception of general health, vitality, social functioning, role limitations caused by emotional health problems, and mental health. Scores are normalized to a scale of 0 to 100. Higher scores indicate more favorable QoL [33].

Statistical Analysis

The sample size was feasibility driven. NIHTB-CB scores was the main outcome. Secondary outcomes were NIHTB-EB and SF-36 scores. Descriptive statistics were used to describe the variables and the NIHTB-CB, NIHTB-EB, and SF-36 scores.

Three composite scores were derived by averaging the standard scores of each measure: a fluid cognition composite score by averaging the standard scores of each of the fluid measures; a crystallized cognition composite score by averaging the standard scores of the crystallized measures; and a total cognitive function composite score by averaging the fluid and crystallized standard scores. For each composite score, standard scores were derived based on the new distribution.

Cognitive impairment was defined with 2 methods. The first method included a modified psychometric criterion for cognitive impairment based on the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition) [12,34]. Under this criterion, referred to as global cognition (distinct from the previously described total cognitive function composite score), impairment was present if the demographically adjusted T-score for at least 1 individual cognitive domain was 1.5 SD below the normative mean or ≥2 individual domains had T-scores 1.0 SD below the mean [12,34]. The second method explored cognitive impairment in which the crystallized score serves as an estimate of prior education and premorbid ability [12,34]. This method, referred to as premorbid-stratified fluid cognition, measures performance relative to premorbid abilities that are generally invariant to disease and predict where an individual "should" be in terms of cognitive functioning. For this method, for individuals with crystallized T-scores ≥ 58, the cutoff for clinical impairment for individual fluid tests was a T-score < 44; for crystallized T scores 50 to 57, the cutoff was a T-score < 41; for crystallized T scores 43 to 49, the cutoff was a T-score < 38; and for crystallized T-scores < 43, the cutoff was a T-score < 35 [12,34].

For NIHTB-EB, low (ie, poor) emotions were defined as >1 SD below the mean for positive emotion scales (social satisfaction and psychological well-being) and >1 SD above the mean for negative emotion scales (negative affect) [27].

Group differences were compared by either independent *t* tests or the Mann-Whitney U test as appropriate. SF-36 measures of QoL were compared with normative US reference data [35] using independent *t* tests. Correlations were performed for NIHTB-CB, NIHTB-EB, and SF-36 domains and for NIHTB-CB domains and hypoparathyroidism-related variables. Significance was defined as P-value < 0.05. All statistical tests were 2-sided. Statistical analysis was performed with SPSS (IBM SPSS Statistics, release 26.0)

Results

Patient Characteristics

The cohort characteristics (n = 19) are in Table 1. The majority were White women with postsurgical hypoparathyroidism. All had attained at least a high school degree, and most worked in professional settings. Of note, the study was conducted before the Covid-19 pandemic. Corrected serum calcium levels were slightly below the lower limit of normal, with a mean of 2.10 [interquartile range (IQR) 1.95-2.27] mmol/L (normal range: 2.15-2.6 mmol/L). Regimens were stable within the past month and were typical of hypoparathyroidism, with doses of calcium supplements of 2.0 (IQR 1.2-3.0) g/day and of calcitriol of 0.25 (IQR 0.25-0.75) mcg/day. Three patients were on medications known to affect cognitive function or emotion: 1 patient was on lamotrigine and clonazepam, 1 was on duloxetine and temazepam, and 1 was on fluoxetine. None of the subjects were on hormone replacement therapy.

NIHTB-CB Scores

The demographically adjusted T-scores for the fluid cognition composite, crystallized cognition composite, and total cognitive function composite were close to average (Table 2). However, impaired demographically adjusted NIHTB-CB scores were observed in 13 out of the 19 subjects (68%) using the global cognition method (a T-score in ≥1 individual domains of 1.5 SD below the mean or in ≥2 individual domains of 1.0 SD below the mean) and in 6 out of the 19 subjects (32%) using the premorbid-stratified fluid cognition method (a T-score in an individual fluid test below a variable cutoff based on the crystallized T score). The distribution of the individual core domains is shown in Figure 1. Subtle impairment was noted in the domains of episodic and working memory, with 37% and 32% of participants, respectively, having scores that were at least 1.0 SD below the mean. Impairment was most notable in the domain of processing speed, with 6 subjects (32%) having demographically adjusted T-scores that were at least 2 SD below the mean.

Notably, of the 3 patients on medications that affect cognitive or emotional function, 1 had unimpaired scores by the global cognition method, and none had impaired scores by the premorbid-stratified fluid method. All 3 patients had unimpaired processing speed.

In addition, of the 2 patients who were hypothyroid, 1 had unimpaired scores by both the global cognition and the premorbid-stratified fluid methods, and the other had impaired scores by the global cognition but not by the premorbid-stratified fluid method. Both hypothyroid patients had unimpaired processing speed. Of the 3 patients with unknown thyroid function, impaired processing speed was noted in 1 but was unimpaired in the other 2.

Of note, the prevalence of cognitive impairment was similar between decades of age of the female participants. Global cognition was impaired in 3 of the 4 women aged 20 to 30; in the single woman aged 31 to 40; in 4 of the 5 women aged 41 to 50; and in 5 of the 7 women aged 51 to 60.

NIHTB-EB Scores

Low (ie, poor) age- and sex-corrected NIHTB-EB scores were observed in 9 subjects (47%), most commonly in the measure of decreased social satisfaction (n = 8; 42%), followed by increased negative affect [6 (32%)] and decreased psychological well-being (n = 4; 21%). The distribution of NIHTB-EB T-scores by SD intervals is in Table 2.

SF-36 Scores

SF-36 scores were lower as compared to US normative reference data [35] in the domains of role limitations caused by physical health problems, vitality, social functioning, and perception of general health (Fig. 2).

Relationship Between NIHTB-CB, NIHTB-EB, and SF-36

Positive correlations were observed between perception of general health by the SF-36 with attention, executive function, and processing speed by the fully demographically adjusted NIHTB-CB scores (Table 3). No other correlations were observed between the NIHTB-CB and the NIHTB-EB or SF-36 scores. Medium to large effect size for correlation was observed between the age- and sex-corrected NIHTB-EB and the SF-36 scores (Table 3).

Correlation of NIHTB-CB and Hypoparathyroidism Variables

There was no correlation between duration of hypoparathyroidism and any of the fully demographically adjusted NIHTB-CB scores. Slower processing speed (ie, worse performance) correlated with lower corrected serum calcium ($r = 0.53$, $P = 0.023$) (Fig. 3) and lower 24 hour urinary calcium excretion ($r = 0.58$, $P = 0.029$) and higher serum phosphate ($r = -0.48$, $P = 0.042$) levels. When grouped into impaired (n = 6) vs unimpaired (n = 13) processing speed, serum calcium was lower (1.95 ± 0.3 vs 2.17 ± 0.3 mmol/L; $P = 0.009$), and serum phosphate was higher (1.52 ± 0.32 vs 1.39 ± 0.32 mmol/L; $P = 0.049$) with impaired processing speed. However, the difference in 24-hour urinary calcium excretion (impaired processing speed: 52.3 ± 15 vs unimpaired processing speed: 71 ± 37 mmol/24 hours; $P = 0.36$) did not reach significance.

We repeated the analysis excluding the 3 patients on medications that affect cognitive or emotional function. Slower processing speed remained correlated with low serum calcium ($r = 0.50$, $P = 0.049$) and high serum phosphate ($r = -0.67$, $P = 0.005$). The correlation with lower 24-hour urinary calcium tended toward significance ($r = 0.57$, $P = 0.05$).

Discussion

In this small pilot study, we found that 68% of hypoparathyroid patients using global cognition scores and 32% using premorbid-stratified fluid scores had possible cognitive impairment. Lower cognitive scores were associated with a self-reported worse perception of general health. The most common cognitive impairment, processing speed, was associated with lower serum calcium and higher serum phosphate levels.

Psychiatric issues are common in hypoparathyroidism. In national registry studies, surgical [17] and nonsurgical [18], hypoparathyroid patients had higher risks of psychiatric complications vs controls. Other studies used patient self-report to document poor QoL. A Web-based survey found that the majority of the 374 hypoparathyroid respondents reported fatigue and emotional and cognitive problems [2]. Although that study may have been biased as patients with worse

Table 1. Characteristics of the study cohort (n = 19)

Variable	Results
Age, years[a]	49 (30-56) [22-60]
Sex	
Male	2 (11)
Female	17 (89)
Premenopausal	9 (47)
Postmenopausal	8 (42)
Race	
White	16 (84)
Black	1 (5)
Asian	2 (11)
Ethnicity	
Not Hispanic or Latino	16 (84)
Body mass index	26.5 (24.8-28.2) [20.9-40.9]
Education	
High school graduate	3 (16)
Some college/associate's degree	6 (31)
Bachelor's degree	7 (37)
Postgraduate	3 (16)
Education, years	20 (18-20) [16-22]
Occupation[b]	
Partly skilled/unskilled	2 (11)
Skilled occupation-manual and nonmanual	5 (26)
Professional, managerial and technical	12 (63)
Etiology of hypoparathyroidism	
Postsurgical	18 (95)
Idiopathic	1 (5)
Duration of hypoparathyroidism, years	5 (2-10) [1-39]
History of kidney stones	0
History of fractures	
Yes	1 (5)[c]
No	18 (95)
Calcium dose, g/day	2.0 (1.2-3.0) [0-6.3]
Calcitriol dose, µg/day	0.25 (0.25-0.75) [0-5.0]
Vitamin D dose, IU/day	1500 (0-5000) [0-7142]
HCTZ dose, mg/day	0 (0-12.5) [0-25]
Corrected serum calcium, mmol/L	2.10 (1.95-2.27) [1.38-2.42][d]
PTH, ng/L	6.0 (1.0-10.0) [1.0-23.5][e]
Serum phosphate, mmol/L	1.45 (1.26-1.58) [1.10-1.84][f]
24-hour urinary calcium excretion, mmol/24 hours	67.25 (41.75-84) [9.25-144.50][g]
Chronic kidney disease stage by GFR, mL/min/1.73m^2	
Normal (G1: ≥90)	6 (32)
Mildly decreased (G: 60-89)	7 (37)
Mildly to moderately decreased (G3a: 45-59)	5 (26)
Moderately to severely decreased (G3b: 30-44)	0
Severely decreased (G4: 15-29)	1 (5)
Kidney failure (G5: <15)	0
25-hydroxyvitamin D, nmol/L	114.82 (92.35-129.79) [82.37-254.59]
TSH level, mU/L	
Low (<0.4)	5 (26)
Normal (0.4-4.0)	9 (47)
High (>4.0)	2 (11)
Not available	3 (16)

Data are given as median (interquartile range) [range] or n (%).
Abbreviations: GFR, glomerular filtration rate; HCTZ, hydrochlorothiazide; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.
[a]Medical history: depression (n = 2), bipolar disorder (n = 1), hypertension (n = 3), acne (n = 1), hyperlipidemia (n = 1), renal transplant (n = 2), gout (n = 1), type 2 diabetes (n = 2). Medications: fluoxetine (n = 1), duloxetine and temazepam (n = 1), lamotrigine and clonazepam (n = 1), metoprolol (n = 1), labetalol (n = 1), losartan (n = 2), spironolactone (n = 1), simvastatin and fenofibrate (n = 1), prednisone (n = 2), allopurinol (n = 1), and metformin (n = 1).
[b]Characterized by National Statistics Socioeconomic Classification [36].
[c]Metacarpal.
[d]Normal range: 2.15-2.6 mmol/L.
[e]Normal range: 10-65 ng/L.
[f]Normal range: 0.81-1.45 mmol/L.
[g]Normal range: female < 6.3 mmol/d; male < 7.5 mmol/d.

symptoms may have been more likely to respond, impaired QoL has been documented in other cohorts. We and others reported low scores using the SF-36 [3-10], and a recent report found low scores in postsurgical patients using a thyroid cancer-specific QoL instrument [37]. However, while these reports captured the patient's self-assessment of well-being [33], they did not objectively assess cognitive function.

Cognitive complaints, or "brain fog," are common and distressing for hypoparathyroid patients [2]. The largest study examining cognitive impairment in hypoparathyroidism was conducted by Aggarwal et al in 62 subjects with idiopathic hypoparathyroidism and in 70 controls who underwent a battery of neuropsychological tests [38]. The authors found neuropsychological dysfunction in 32% of the hypoparathyroid patients (95% CI 20.9-45.3) as compared to 5.7% of controls (95% CI 1.6-14.0, $P < 0.001$), including unusual cognitive deficits such as reduced inhibitory control, impairment in visuospatial functioning, and psychomotor retardation. They also found that worse cognitive function was associated with longer duration of illness, increased serum calcium-phosphorus product, and lower serum total calcium levels [38]. One limitation of that study was that it did not include postsurgical hypoparathyroid patients or adjust for demographic variables, including level of education. Nevertheless, that report and 16 case reports of cognitive impairment in hypoparathyroid patients were included in a recent systematic review [39], highlighting the need for clinical research in this area. Recently, disease-specific tools for hypoparathyroidism have been developed to assess symptoms of hypoparathyroidism from the patient perspective. An example is the Hypoparathyroidism Patient Experience Scale–Symptom, which assesses patient-reported physical and cognitive signs and symptoms, with cognitive symptoms including difficulty remembering, finding the right words, concentrating, understanding information, and thinking clearly [39]. This tool and others [40,41] will hopefully provide validated measures for assessing symptoms of hypoparathyroidism from the patient perspective.

Table 2. Distribution of overall and domain-specific NIHTB-CB (fully adjusted) and NIHTB-EB (age- and sex-adjusted) T-scores

Test	Score, mean (SD) [range]	Patients with T-scores within each interval, n (%)[a]			
		0.5 to < 1.0 SD	1.0 to < 1.5 SD	1.5 to < 2.0 SD	>2.0 SD
NIHTB-CB					
Fluid cognition composite	44.7 (13.1) [15.1-75]	1 (5)	4 (21)	2 (11)	2 (11)
Flanker inhibitory control and attention	49.3 (12.4) [24.6-71.5]	2 (11)	2 (11)	0	2 (11)
Dimensional change card sort (executive function)	55.2 (15.0) [24.3-76.3]	1 (5)	0	3 (16)	1 (5)
List sorting working memory	45.9 (9.9) [28.8-65.9]	2 (11)	3 (16)	2 (11)	1 (5)
Pattern comparison processing speed	40.0 (12.0) [8.0-56.9]	4 (21)	3 (16)	2 (11)	6 (32)
Picture sequence episodic memory	45.9 (12.1) [26.3-67.2]	1 (5)	2 (11)	3 (16)	2 (11)
Crystallized cognition composite	52.7 (9.6) [38.4-69]	2 (11)	2 (11)	0	0
Picture vocabulary	51.8 (11.6) [27.9-70.9]	2 (11)	1 (5)	1 (5)	1 (5)
Oral reading recognition	53.3 (8.1) [39.4-69.4]	1 (5)	1 (5)	0	0
Cognition total composite: composite FCC and CCC	48.2 (11.1) [24.7-75.3]	2 (11)	1 (5)	0	2 (11)
NIHTB-EB					
Negative affect (anger-affect, anger-hostility, sadness, fear-affect, perceived stress)	57.2 (10.5) [36.1-83]	6 (32)	3 (16)	1 (5)	2 (11)
Social satisfaction (friendship, loneliness, emotional support, instrumental support, perceived rejection)	43.2 (12.1) [12.6-62.9]	3 (16)	3 (16)	3 (16)	2 (11)
Psychological well-being (positive affect, general life satisfaction, meaning and purpose)	45.6 (9.4) [20.3-59.2]	3 (16)	2 (11)	2 (11)	1 (5)

Abbreviations: NIHTB-CB, NIH Toolbox® Adult Cognitive Battery; NIHTB-EB, NIH Toolbox® Emotion Battery.
[a]Each category represents the number of participants within a predefined interval measured by SD units below the mean (NIHTB-CB, NIHTB-EB for social satisfaction score, psychological well-being score) and above the mean (NIHTB-EB for negative affect score). The rates are calculated as the number of participants within each category divided by the total number of study participants (n = 19).

Table 3. Correlations between NIHTB-CB, NIHTB-EB, and SF-36 scores

Fully corrected NIHTB-CB and age- and sex-corrected NIHTB-EB and SF-36 scores							
	NIHTB-CB						
	Flanker inhibitory control and attention	Dimensional change card sort (executive function)	List sorting working memory	Pattern comparison processing speed	Picture sequence episodic memory	Picture vocabulary	Oral reading recognition
NIHTB-EB							
Negative affect	−0.01	0.08	−0.13	−0.03	−0.10	0.23	0.12
Social satisfaction	0.04	0.02	−0.21	0.13	−0.14	−0.21	−0.15
Psychological well-being	0.16	0.12	−0.16	0.28	−0.03	−0.23	−0.03
SF-36							
PF	−0.06	−0.03	0.15	−0.14	0.03	−0.23	−0.26
RF	−0.06	0.03	0.21	−0.11	0.18	−0.10	0.05
BP	−0.13	−0.10	0.11	0.24	−0.11	0.01	−0.03
GH	**0.53***	**0.58***	0.40	**0.68****	0.16	−0.02	0.38
VT	0.17	−0.07	0.19	0.07	0.32	−0.01	0.23
SF	0.23	0.14	0.08	0.13	0.24	−0.18	−0.04
RE	0.24	0.26	0.29	0.07	0.20	−0.33	−0.19
MH	0.08	−0.01	0.20	0.10	0.22	−0.29	−0.23

SF-36 and age- and sex-corrected NIHTB-EB scores								
	SF-36							
	PF	RF	BP	GH	VT	SF	RE	MH
NIHTB-EB								
Negative affect	−0.43	**−0.48***	−0.47	−0.11	**−0.58***	−0.19	**−0.71****	**−0.80****
Social satisfaction	0.44	0.27	**0.62****	0.39	0.44	0.16	0.46	0.41
Psychological well-being	0.20	**0.57***	**0.62****	0.18	0.31	0.24	0.36	**0.66****

*$P < 0.05$, **$P < 0.01$. Bolded values indicate statistical significance.
Abbreviations: BP, bodily pain; GH, perception of general health; MH, mental health; NIHTB-CB, NIH Toolbox® Adult Cognitive Battery; NIHTB-EB, NIH Toolbox® Emotion Battery; PF, physical functioning; RE, role limitations caused by emotional health problems; RF, role limitations caused by physical health problems; SF, social functioning; SF-36, Short Form Health Survey; VT, vitality.

We chose the NIHTB-CB to evaluate cognition in this pilot study because it has been validated with reliable measurement techniques and has normative comparisons. It utilizes the item response theory, which allows tests to be brief yet precise and valid [42]; sets of items are calibrated along a continuum that covers the full range of the cognitive construct that is measured. The normative comparisons in the NIHTB are based on a sample of 4859 participants representative of the US population based on sex, race/ ethnicity, and socioeconomic status, allowing for cognitive impairment to be defined relative to normative populations [21].

We found that the most commonly impaired cognitive domain in our pilot cohort was processing speed, or the amount of time it takes to process a set amount of information, with one third of subjects having demographically adjusted T-scores that were at least 2 SD below the mean. A lower score in the NIHTB-CB indicates slower speed of processing [43]. Notably, slowed processing speed can have adverse clinical effects. Increased time is required to perform everyday activities, leading to reduced QoL [44] and potentially affecting safety [45].

Self-report of emotional function by the NIHTB-EB and QoL by the SF-36 both showed impairment. Nearly half of our sample had low age- and sex-corrected emotional scores, with decreased social satisfaction being most common; these results are consistent with prior reports [17-19]. The deficits in SF-36 domains are also consistent with prior reports from us and others in which those domains, as well as others, have been reduced [3-10]. Emotional function and QoL were strongly correlated, as would be expected.

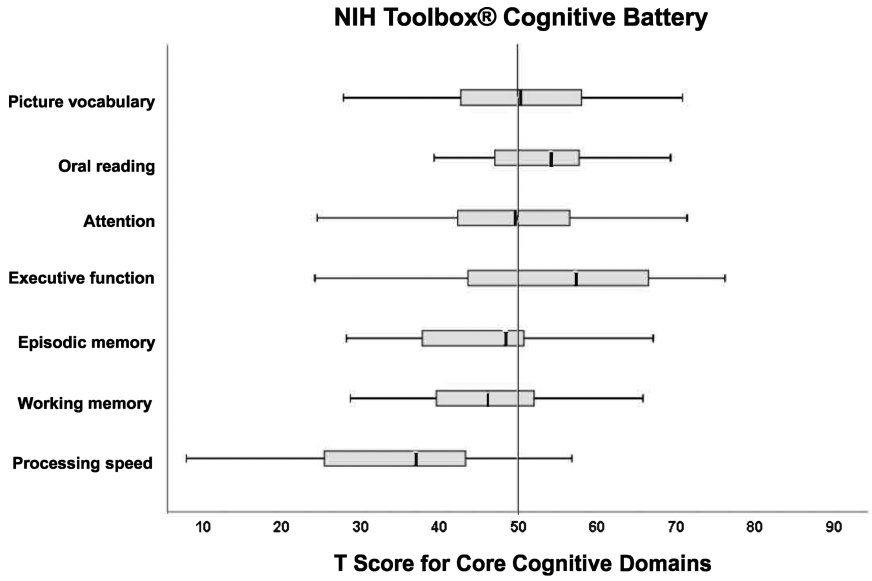

Figure 1. Distribution of NIH Toolbox® Adult Cognitive Battery scores in hypoparathyroid subjects. Box and whisker plots showing the distribution of the demographically adjusted T-scores of the core domains. A T-score of 50 represents the mean. Of all the domains, the mean T-score was lowest for processing speed.

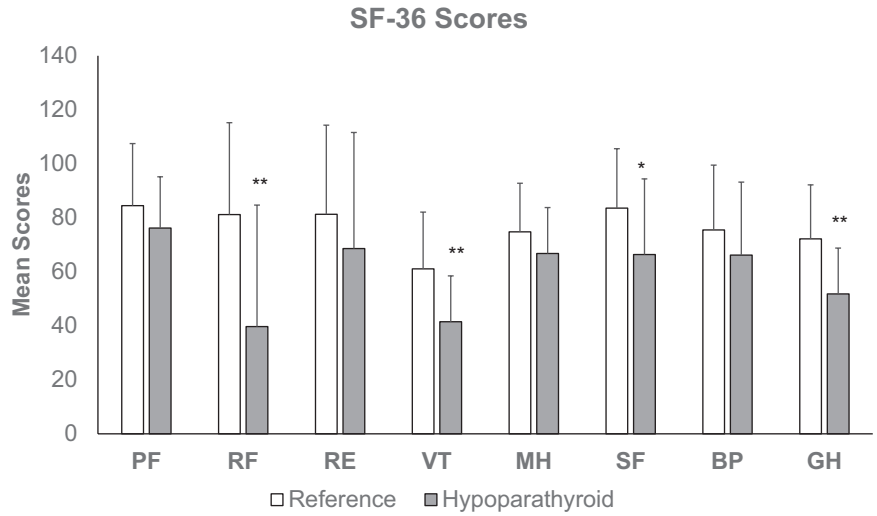

Figure 2. Short Form Health Survey scores in hypoparathyroid subjects vs normative reference data. Role limitations caused by physical health problems, vitality, social functioning, and perception of general health were lower in hypoparathyroid subjects. $*P < 0.05$; $**P < 0.01$. Abbreviations: BP, bodily pain; GH, perception of general health; MH, mental health; PF, physical functioning; RE, role limitations caused by emotional health problems; RF, role limitations caused by physical health problems; SF, social functioning; VT, vitality.

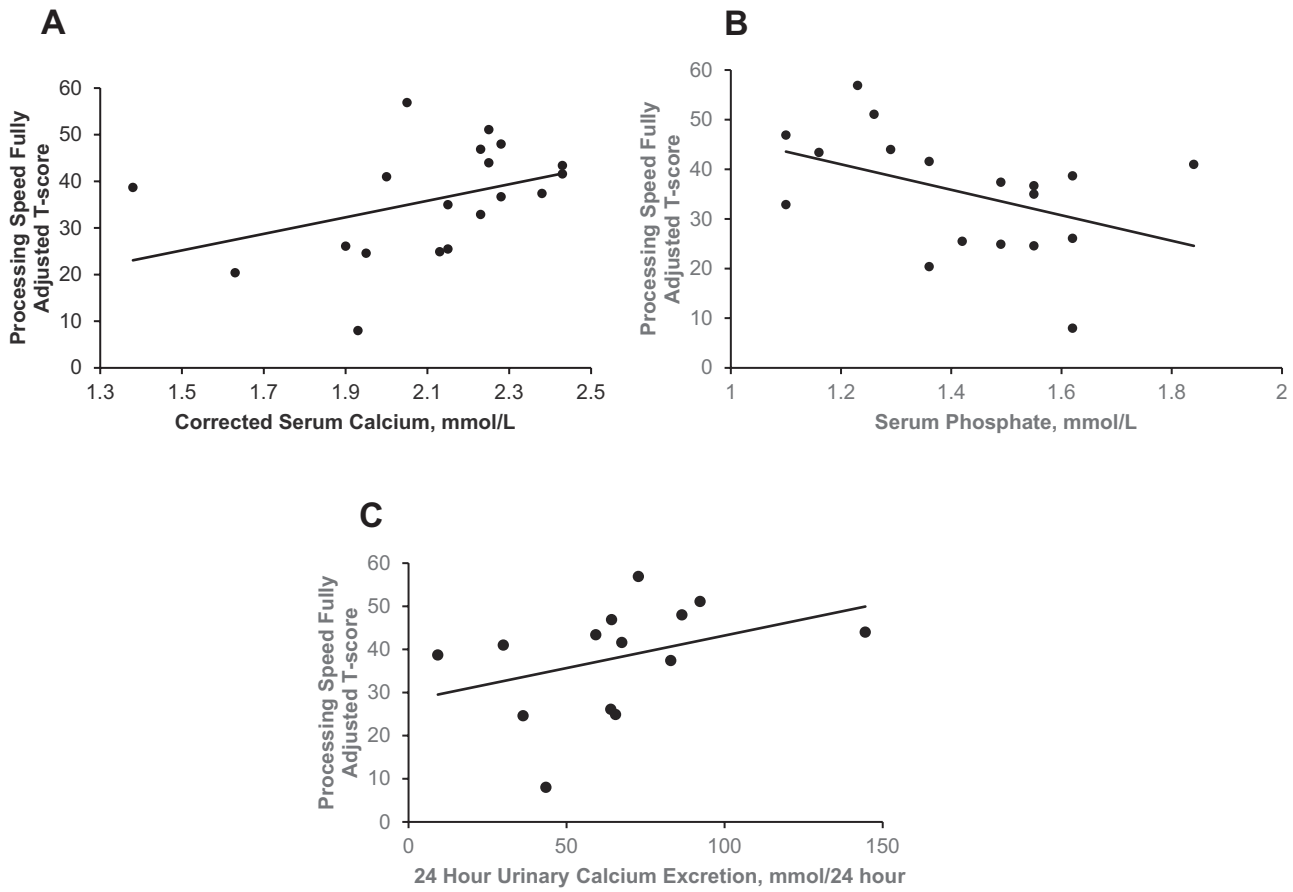

Figure 3. Processing speed and calciotropic levels. Processing speed, the most common cognitive impairment, correlated directly with corrected serum calcium levels (r = 0.53, $P = 0.023$) (A), inversely with serum phosphate levels (r = –0.48, $P = 0.042$) (B), and directly with 24-hour urinary calcium levels (r = 0.58, $P = 0.029$) (C).

We considered whether slowed processing speed could be related to impaired emotional function, with impaired emotional function either mediating the cognitive changes or impaired emotional function being caused by the cognitive impairment. Although we did not use a standard test for depression, we did not see a correlation with processing speed and any of the NIHTB-EB variables, including sadness. It may be that impaired emotional function and processing speed are epiphenomena that are related by a common driver. In other words, "brain fog" could manifest as both impaired emotional function and slowing, without one necessarily causing the other.

Interestingly, worse cognitive function in the domains of attention, executive function and processing speed was associated with a decreased perception of general health. Although this result could simply be a function of multiple comparisons, it suggests that cognitive impairments in hypoparathyroidism relate to reduced QoL.

The mechanisms for impaired cognition in hypoparathyroidism are uncertain. Hypocalcemia alters neuromuscular parameters and could theoretically be detrimental for cognitive function. Processing speed in particular, a domain that relates to nerve conduction velocity [46], might be transiently impaired during hypocalcemia, which would be consistent with the correlation we observed between slower processing speed and lower serum calcium levels. The correlation between slower processing speed and lower urinary calcium levels might further support the idea that lower body calcium stores predict worse cognitive function. Although the difference in urinary calcium levels between subjects with and without impaired processing speed did not reach significance, the correlation among all subjects between urinary calcium and processing speed likely reflects the correlation between serum calcium and processing speed, since urinary calcium levels reflect serum calcium levels in hypoparathyroidism [47].

Hyperphosphatemia is an alternative potential explanation for cognitive impairment. We found that slower processing speed was associated with higher serum phosphate levels. Hyperphosphatemia in hypoparathyroidism is associated with ectopic calcification, including progression of calcification in the basal ganglia [48]. It is theoretically possible that this might impede cognitive function, although this is unknown. It is also conceivable that PTH deficiency impacts cognitive function. PTH can cross the blood-brain barrier [49] and stimulate brain PTH2 receptors [50]. We did not find a relationship between PTH and cognitive function, although most of the PTH levels were low, potentially obscuring any correlation. Finally, hypothyroidism could be an important confounder for cognitive function. However, there was no consistent evidence of impaired cognition among the patients with hypothyroidism or with unknown thyroid levels.

A strength of our pilot study is the well-characterized cohort in which the clinical profile, treatment regimens, and biochemistries of the participants were typical of the disease.

An additional strength is that we adjusted the cognitive scores for all demographic values and for premorbid ability (ie, education). Limitations of our study include the small sample size and the homogeneous nature of our cohort, with participants being mostly White women with postsurgical hypoparathyroidism. Cognitive testing in a larger group, including more men, other ages and races, and with other etiologies of hypoparathyroidism is necessary. Our study was also limited by lack of a euparathyroid control group matched for age, sex, race/ethnicity, and education, although NIHTB-CB provided scores that were fully adjusted for these variables. An additional limitation is that we did not use a standardized neuropsychological battery. However, performance on the NIHTB-CB has agreement with performance on gold-standard neuropsychological test batteries, with $r = 0.85$, $P < 0.001$, for crystalized measures and $r = 0.58$, $P < 0.001$, for fluid measures [51]. Our objective was to capture pilot data on a range of cognitive abilities in a valid and reliable way, which the NIHTB-CB accomplished. A further limitation is that we included women in the perimenopausal range, a group at risk for cognitive symptoms, although the prevalence of cognitive impairment was similar between decades of age of the female participants, suggesting that the impaired cognition was likely independent of perimenopause. Finally, we included patients on medications known to affect cognitive and emotional function, which could have overestimated our findings of impaired cognition. However, our results remained similar when those patients were excluded.

In conclusion, this small pilot study suggests that impaired cognition might be present in hypoparathyroid subjects and may be associated with lower serum calcium and higher serum phosphate levels. These preliminary data are hypothesis-generating and lay the groundwork for further investigation in a larger sample size involving comprehensive neuropsychological evaluation in hypoparathyroid patients and matched controls. An additional future direction is to assess whether duration of hypocalcemia and/or hyperphosphatemia correlates with more impaired cognitive function. Identification of possible impairment could help with institution of targeted cognitive interventions to reduce symptom burden in this rare but debilitating disease.

Author Contributions

M.R.R: conceptualization, formal analysis, investigation, methodology, supervision, and roles/writing—original draft; G.T.: data curation, formal analysis, and writing—review and editing; B.O.: data curation, investigation, and project administration; R.M.: data curation, investigation, and project administration; C.H.: methodology and writing—review and editing; and A.M.B.: conceptualization, formal analysis, methodology, and writing—review and editing.

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Disclosures

G.T., B.O., R.M., C.H., and A.M.B. have nothing to declare. M.R.R. receives grant support from Ascendis Pharmaceuticals.

Data Availability

Some or all data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Shoback D. Clinical practice. Hypoparathyroidism. *N Engl J Med*. 2008;359(4):391-403.
2. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocr Pract*. 2014;20(7):671-679.
3. Sikjaer T, Moser E, Rolighed L, *et al*. Concurrent hypoparathyroidism is associated with impaired physical function and quality of life in hypothyroidism. *J Bone Miner Res*. 2016;31(7):1440-1448.
4. Tabacco G, Tay YD, Cusano NE, *et al*. Quality of life in hypoparathyroidism improves with rhPTH(1-84) throughout 8 years of therapy. *J Clin Endocrinol Metab*. 2019;104(7):2748-2756.
5. Vokes TJ, Mannstadt M, Levine MA, *et al*. Recombinant human parathyroid hormone effect on health-related quality of life in adults with chronic hypoparathyroidism. *J Clin Endocrinol Metab*. 2018;103(2):722-731.
6. Palermo A, Santonati A, Tabacco G, *et al*. PTH(1-34) for surgical hypoparathyroidism: a 2-year prospective, open-label investigation of efficacy and quality of life. *J Clin Endocrinol Metab*. 2018;103(1):271-280.
7. Cusano NE, Rubin MR, McMahon DJ, *et al*. The effect of PTH(1-84) on quality of life in hypoparathyroidism. *J Clin Endocrinol Metab*. 2013;98(6):2356-2361.
8. Sikjaer T, Rolighed L, Hess A, Fuglsang-Frederiksen A, Mosekilde L, Rejnmark L. Effects of PTH(1-84) therapy on muscle function and quality of life in hypoparathyroidism: results from a randomized controlled trial. *Osteoporos Int*. 2014;25(6):1717-1726.
9. Santonati A, Palermo A, Maddaloni E, *et al*. PTH(1-34) for surgical hypoparathyroidism: a prospective, open-label investigation of efficacy and quality of life. *J Clin Endocrinol Metab*. 2015;100(9):3590-3597.
10. Cusano NE, Rubin MR, McMahon DJ, *et al*. PTH(1-84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy. *J Clin Endocrinol Metab*. 2014;99(10):3694-3699.
11. Heaton RK, Akshoomoff N, Tulsky D, *et al*. Reliability and validity of composite scores from the NIH Toolbox Cognition Battery in Adults. *J Int Neuropsychol Soc*. 2014;20(6):588-598.
12. Carlozzi NE, Tulsky DS, Wolf TJ, *et al*. Construct validity of the NIH Toolbox Cognition Battery in individuals with stroke. *Rehabil Psychol*. 2017;62(4):443-454.
13. Gershon RC, Cook KF, Mungas D, *et al*. Language measures of the NIH Toolbox Cognition Battery. *J Int Neuropsychol Soc*. 2014;20(6):642-651.
14. Hessl D, Sansone SM, Berry-Kravis E, *et al*. The NIH Toolbox Cognitive Battery for intellectual disabilities: three preliminary studies and future directions. *J Neurodev Disord*. 2016;8(1):35.
15. NIH Toolbox. Scores for performance tests of function. Accessed July 8, 2020. https://www.healthmeasures.net/score-and-interpret/interpret-scores/nih-toolbox.
16. NIH Toolbox. Cognition measures. Accessed July 8, 2020. https://www.healthmeasures.net/explore-measurement-systems/nih-toolbox/intro-to-nih-toolbox/cognition.
17. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Postsurgical hypoparathyroidism—risk of fractures, psychiatric diseases, cancer, cataract, and infections. *J Bone Miner Res*. 2014;29(11):2504-2510.
18. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. The epidemiology of nonsurgical hypoparathyroidism in Denmark: a nationwide case finding study. *J Bone Miner Res*. 2015;30(9):1738-1744.

19. Arlt W, Fremerey C, Callies F, *et al*. Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. *Eur J Endocrinol*. 2002;146(2):215-222.
20. NIH Toolbox. Interpret scores. Accessed July 8, 2020. https://www.healthmeasures.net/score-and-interpret/interpret-scores/nih-toolbox.
21. Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinski CJ. NIH toolbox for assessment of neurological and behavioral function. *Neurology*. 2013;80(11 suppl 3):S2-S6.
22. Weintraub S, Dikmen SS, Heaton RK, *et al*. Cognition assessment using the NIH Toolbox. *Neurology*. 2013;80(11 suppl 3):S54-S64.
23. NIH Toolbox. Cognition measures: NIH Toolbox Cognition Batteries. Accessed July 8, 2020. http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox/intro-to-nih-toolbox/cognition.
24. Gershon RC, Cella D, Fox NA, Havlik RJ, Hendrie HC, Wagster MV. Assessment of neurological and behavioural function: the NIH Toolbox. *Lancet Neurol*. 2010;9(2):138-139.
25. Lindenberger U. *Lifespan Theories of Cognitive Development*. Elsevier Science Ltd; 2001:8848-8854.
26. Weintraub S, Dikmen SS, Heaton RK, *et al*. The cognition battery of the NIH Toolbox for Assessment of Neurological and Behavioral Function: validation in an adult sample. *J Int Neuropsychol Soc*. 2014;20(6):567-578.
27. Babakhanyan I, McKenna BS, Casaletto KB, Nowinski CJ, Heaton RK. National Institutes of Health Toolbox Emotion Battery for English- and Spanish-speaking adults: normative data and factor-based summary scores. *Patient Relat Outcome Meas*. 2018;9:115-127.
28. NIH Toolbox. Emotion battery. Accessed July 20, 2020. https://www.healthmeasures.net/explore-measurement-systems/nih-toolbox/intro-to-nih-toolbox/emotion.
29. Kupst MJ, Butt Z, Stoney CM, *et al*. Assessment of stress and self-efficacy for the NIH Toolbox for Neurological and Behavioral Function. *Anxiety Stress Coping*. 2015;28(5):531-544.
30. Pilkonis PA, Choi SW, Salsman JM, *et al*. Assessment of self-reported negative affect in the NIH Toolbox. *Psychiatry Res*. 2013;206(1):88-97.
31. Cyranowski JM, Zill N, Bode R, *et al*. Assessing social support, companionship, and distress: National Institute of Health (NIH) Toolbox Adult Social Relationship Scales. *Health Psychol*. 2013;32(3):293-301.
32. Salsman JM, Lai JS, Hendrie HC, *et al*. Assessing psychological well-being: self-report instruments for the NIH Toolbox. *Qual Life Res*. 2014;23(1):205-215.
33. Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.
34. Holdnack JA, Tulsky DS, Brooks BL, *et al*. Interpreting patterns of low scores on the NIH Toolbox Cognition Battery. *Arch Clin Neuropsychol*. 2017;32(5):574-584.
35. Ware J, Kosinski M, Keller S. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Health Assessment Lab; 1994.
36. Rose D, Pevalin D. *A Researcher's Guide to National Statistics Socio-economic Classification*. Sage Publishing; 2003.
37. Buttner M, Locati LD, Pinto M, *et al*. Quality of life in patients with hypoparathyroidism after treatment for thyroid cancer. *J Clin Endocrinol Metab*. 2020;105(12):dgaa597.
38. Aggarwal S, Kailash S, Sagar R, *et al*. Neuropsychological dysfunction in idiopathic hypoparathyroidism and its relationship with intracranial calcification and serum total calcium. *Eur J Endocrinol*. 2013;168(6):895-903.
39. Sardella A, Bellone F, Morabito N, *et al*. The association between hypoparathyroidism and cognitive impairment: a systematic review. *J Endocrinol Invest*. 2021;44(5):905-919.
40. Coles T, Chen K, Nelson L, *et al*. Psychometric evaluation of the hypoparathyroidism symptom diary. *Patient Relat Outcome Meas*. 2019;10:25-36.
41. Wilde D, Wilken L, Stamm B, *et al*. The HPQ-development and first administration of a questionnaire for hypoparathyroid patients. *JBMR Plus*. 2020;4(1):e10245.
42. Green DR, Yen WM, Burket GR. Experiences in the application of item response theory in test construction. *Appl Meas Educ*. 1989;2(4):297-312.
43. The NIH Toolbox Scoring and Interpretation Guide for the iPad v1.7. Accessed August 8, 2020. https://nihtoolbox.force.com/s/article/nih-toolbox-scoring-and-interpretation-guide.
44. Owsley C, Sloane M, McGwin G Jr., Ball K. Timed instrumental activities of daily living tasks: relationship to cognitive function and everyday performance assessments in older adults. *Gerontology*. 2002;48(4):254-265.
45. Hotta R, Makizako H, Doi T, *et al*. Cognitive function and unsafe driving acts during an on-road test among community-dwelling older adults with cognitive impairments. *Geriatr Gerontol Int*. 2018;18(6):847-852.
46. DeLuca J, Kalmar J. *Information Processing Speed in Clinical Populations*. Psychology Press; 2007.
47. Mitchell DM, Regan S, Cooley MR, *et al*. Long-term follow-up of patients with hypoparathyroidism. *J Clin Endocrinol Metab*. 2012;97(12):4507-4514.
48. Goswami R, Sharma R, Sreenivas V, Gupta N, Ganapathy A, Das S. Prevalence and progression of basal ganglia calcification and its pathogenic mechanism in patients with idiopathic hypoparathyroidism. *Clin Endocrinol*. 2012;77(2):200-206.
49. Balabanov S, Tollner U, Richter HP, Pohlandt F, Gaedicke G, Teller WM. Immunoreactive parathyroid hormone, calcium, and magnesium in human cerebrospinal fluid. *Acta Endocrinol*. 1984;106(2):227-233.
50. Usdin TB, Gruber C, Bonner TI. Identification and functional expression of a receptor selectively recognizing parathyroid hormone, the PTH2 receptor. *J Biol Chem*. 1995;270(26):15455-15458.
51. Scott EP, Sorrell A, Benitez A. Psychometric properties of the NIH Toolbox Cognition Battery in healthy older adults: reliability, validity, and agreement with standard neuropsychological tests. *J Int Neuropsychol Soc*. 2019;25(8):857-867.