Primary Hyperparathyroidism: Cognitive Abnormalities and their Reversibility with Parathyroidectomy

IMAGING CORE PILOT AWARD APPLICATION

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PROJECT TITLE: **Primary Hyperparathyroidism: Cognitive Abnormalities and their Reversibility with Parathyroidectomy**

SYNOPSIS OF PROPOSAL: (use only space provided below – minimum 11 point font)

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia and elevated parathyroid hormone. Many patients with PHPT report symptoms such as fatigue, cognitive impairment, intellectual weariness, depression and anxiety. Data regarding the causal association of such symptoms with PHPT and their reversibility after PHPT is cured by parathyroidectomy (PTX) are insufficient. Therefore, it is unclear whether these complaints should be an indication for PTX. The field has been mired by studies that are small, inadequately controlled, or lack validated objective measures. Currently, both PHPT patients and clinicians are frustrated by the lack of clear evidence regarding the effects of PHPT upon cognition and improvement after PTX. Obtaining data that brings clarity to this issue is thus of considerable pubic health importance. Studies are needed to evaluate new tools to determine which are efficacious in objectively and consistently detecting cognitive changes in this specific population. Multimodal functional magnetic resonance imaging (fMRI) of the brain represents a technique that holds promise to objectively measure the cognitive changes that may accompany PHPT as well as their reversibility after surgical cure. Our preliminary data suggests there are several aspects of cognition that are affected by PHPT, including verbal memory, non-verbal abstraction, response speed and visual attention. To lay the groundwork for a well-controlled R01, we need to demonstrate that multimodal fMRI can detect changes in brain regions responsible for verbal memory, non-verbal abstraction, response speed, and visual attention. In addition, demonstration that multimodal fMRI findings correlate with post-PTX improvements in cognitive testing and the cardinal biochemical abnormalities of PHPT, serum calcium and parathyroid hormone levels, would provide further support for a causal relationship. We propose to study postmenopausal women with PHPT undergoing PTX before and 6 months after surgery to 1) determine whether there are post-parathyroidectomy changes in neuroactivation on multimodal fMRI during performance of tasks corresponding to verbal memory, non-verbal abstraction, response speed and visual attention; and 2) determine if any observed neurofunctional changes are associated with post-parathyroidectomy improvement in PTH concentration or serum calcium levels. There is a clear need for further studies in this area to help guide clinicians in the management of PHPT patients who manifest cognitive and psychiatric symptoms. This study will lay the groundwork for a larger well-controlled R01 application to the NIH to further utilize multimodal fMRI to map cognitive changes in PHPT and other disorders of parathyroid gland dysfunction.

ALL CURRENT SOURCES OF RESEARCH FUNDING (include begin/end dates and total direct costs)

1K23ARO53507-01A1; Walker (PI); Aspects of Bone Quality in Chinese American Women; 6/2007-5/2013; No cost extension; Direct costs $599,584

Irving Scholars Career Award; Walker (PI); Cardiovascular Effects of Vitamin D Deficiency; 7/2011-6/2014; Total Direct Costs $180,000

R01 DK084986-03 Silverberg (PI); Vitamin D Deficiency in Primary Hyperparathyroidism; 7/2010-6/2015; Direct costs $2,090,654; Role: Co-investigator

R01 DK32333 Bilezikian (PI); Primary Hyperparathyroidism; 8/2008-7/2013; Direct costs $2,173,446; Role: Co-investigator

PENDING APPLICATIONS FOR RESEARCH FUNDING (include proposed begin/end dates and total direct costs)
None

12-MONTH BUDGET		
Requested Imaging Modality(ies):	**Multimodal Functional Magnetic Resonance Imaging**	
Quantity of Scans: 14		
Cost Per Scan: $750		
	SUB-TOTAL	**$10,500**
	Funds Requested	**$10,000**
	TOTAL PROPOSED BUDGET	**$10,000**

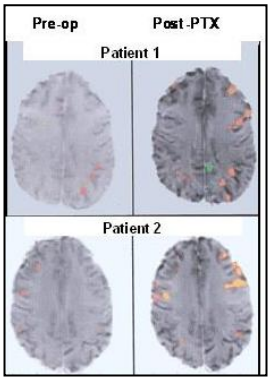
DETAILED BUDGET JUSTIFICATION: (use only space provided – minimum 11 point)

All funds from the Irving Institute Imaging Core Pilot Award will be used toward the acquisition of multimodal fMRI scans. Each of seven participants will have 2 scans – 1 BOLD fMRI scan before parathyroidectomy and 1 BOLD fMRI scan six months post-parathyroidectomy. The cost per scan is $750; this cost covers the technical fee; the fMRI cost per participant is $1,500 for a total of $10,500. $10,000 is requested from the Irving Institute Imaging Core Pilot Award to be applied toward the cost of fMRI. The additional $500 balance for imaging, cost for image analysis and processing ($1,050 total) by Dr. Iris Asllani (co-investigator) and assays for parathyroid hormone and calcium levels will be provided by Dr. Shonni Silverberg's (Mentor) NIH K24 (Midcareer Investigator Award in Patient-Oriented Research), on which Dr. Walker is a mentee.

GOALS

Background: Primary hyperparathyroidism (PHPT), characterized by hypercalcemia and elevated parathyroid hormone (PTH), is a common endocrine disorder. Classical PHPT was a symptomatic disease with obvious neurological, psychiatric, skeletal, gastrointestinal and renal effects. Today, PHPT is mild and generally diagnosed after the incidental finding of hypercalcemia on routine blood tests without end organ sequelae such as nephrolithiasis or bone disease. These patients, termed "asymptomatic," nonetheless may have non-specific neuropsychiatric symptoms that include weakness, easy fatigability, depression, intellectual weariness, cognitive impairment, loss of initiative, anxiety, irritability, sleep disturbance, and somatization (1). Data are limited on the precise nature of these symptoms, their causal association with PHPT and their reversibility after PHPT is cured of by parathyroidectomy (PTX). Additionally, most studies focused on psychiatric symptoms rather than cognition or did not control for psychiatric symptoms affecting cognitive performance. Currently, there are insufficient data to determine whether these complaints should be an indication for PTX.

Preliminary Data: We performed a case-control study comparing cognitive function in 39 postmenopausal women with PHPT to 89 normal postmenopausal controls which demonstrated that PHPT patients have more depression and anxiety than controls and worse performance on tests of verbal memory, non-verbal abstraction, response speed and visual attention (2). Post-PTX, PHPT patients' performance improved to that of controls, independent of baseline anxiety and depression (2). This study was the first to utilize well-validated measures to assess changes in cognition in PHPT, while controlling for IQ, education and psychiatric symptoms that affect cognitive performance. We subsequently performed an exploratory BOLD (blood-oxygen-level-dependent) functional magnetic resonance imaging (fMRI) study to evaluate whether the improvements in verbal and working memory after PTX were associated with BOLD fMRI changes in those areas of the brain involved in language and working memory. After PTX, 5 postmenopausal women with PHPT had increased BOLD fMRI activity as measured by BOLD voxel counts post-PTX in brain areas corresponding to the language centers during tasks known to stimulate verbal memory. Specifically (see figure), voxel counts (defined as the number of voxels surviving the preset statistical threshold) increased during synonym generation in the Wernicke's and Broca's areas (1.21±0.73 versus 3.37±1.79, p=0.02), and there was a trend towards increased voxel counts during the 2-back test in the prefrontal dorsolateral cortex, an area involved in working memory (5.27±5.09 vs. 6.71±3.17, p=0.16).



Gaps in Knowledge: Our preliminary data demonstrate reversible cognitive abnormalities in PHPT and suggest that it is feasible to utilize BOLD fMRI to further explore this finding. However, there are limitations to our BOLD fMRI preliminary data. Because BOLD is a relative measurement, we are relying on the number of voxels surviving the statistical threshold to characterize improvement. A change in the number of voxels could be due to a decrease in noise across the 2 measurements rather than a difference in signal. Another implication of the relativity of the BOLD signal is that a change in activation pattern is indistinguishable from a change in baseline function. To address these limitations, we will add arterial spin labeling (ASL) perfusion fMRI to our study. This will allow us to determine whether our prior fMRI findings, which estimated brain activity as measured by BOLD voxel counts, represent changes in neuronal activation, changes in cerebral blood flow (CBF), or both, which our prior protocol did not assess. Furthermore, in order to support a well-controlled R01, we need to demonstrate that fMRI can detect changes in brain regions responsible for response speed and visual attention (the other areas shown to be improved in our preliminary studies) in addition to those responsible for verbal memory and non-verbal abstraction. Lastly, demonstration that BOLD fMRI findings correlate with post-PTX improvements in cognitive testing and the cardinal biochemical features of PHPT, serum calcium and PTH levels, will provide further support for a causal relationship. Therefore, this proposal expands upon our preliminary data and will further delineate mechanisms of cognitive dysfunction by: 1) adding BOLD fMRI tasks that assess brain areas responsible for response speed and visual attention; 2) including ASL with BOLD to better elucidate whether the changes observed are due to changes in baseline metabolism or differences in activation patterns or both; 3) increasing statistical power by implementing the imaging protocols using a 3T rather than a 1.5T scanner. An increase in scanner strength will increase the signal to noise ratio. In this proposal, we will study 7 postmenopausal women with PHPT undergoing PTX before and 6 months after PTX with the following aims:

Specific Aim 1: Determine if there are post-PTX changes in neuroactivation on BOLD fMRI during performance of tasks of verbal memory, non-verbal abstraction, response speed and visual attention.

Specific Aim 2: Determine if any observed neurofunctional changes are associated with post-PTX improvement in PTH concentration or serum calcium levels.

This study will lay the groundwork for a larger well-controlled R01 application to the NIH to further utilize multimodal fMRI to map cognitive changes in PHPT and other disorders of parathyroid gland function.

PUBLIC HEALTH SIGNIFICANCE OF PROPOSED STUDY

PHPT is one of the most common endocrine disorders, with an incidence of approximately 1 per 1,000 people, and prevalence as high as 21 in 1000 in postmenopausal women. "Asymptomatic PHPT" has only been recognized as a phenotype since the 1980's, yet many argue that patients are hardly asymptomatic. In 2002, a NIH workshop on "asymptomatic" PHPT revised the guidelines, recommending PTX for those with end-organ effects likely to be reversed by surgery or those with a higher likelihood of disease progression. However, the three NIH and International Consensus Conferences (1989, 2002 & 2008) that reviewed available data to determine guidelines for management of PHPT did not include neurological or psychiatric symptoms as indications for PTX, because of "an inability to predict, which patients will benefit". Currently, there is insufficient data on their precise nature, association with the disorder and their reversibility after surgical correction of primary hyperparathyroidism to determine whether these complaints should be a stand-alone indication for surgical intervention. One reason for the paucity of high quality data is the variability of measures used across studies, lack of appropriate control groups, lack of validated objective measures and small sample sizes. Additionally, most studies focused on psychiatric symptoms rather than cognitive symptoms, or did not control for psychiatric symptoms affecting cognitive performance. Even 3 randomized controlled trials of surgery *vs.* observation in PHPT have not resolved the issue. Using the SF-36 to assess quality of life, each study found deficiencies and each some change after cure. However, there was no overlap in findings among the studies, making generalization impossible. Currently, both PHPT patients and clinicians are frustrated by the lack of clear evidence regarding the effects of PHPT upon cognition and improvement after PTX. Obtaining data that brings clarity to this issue is thus of considerable pubic health importance.

This proposal responds to the latest Consensus Conference summary, which identified the need for data on cognitive and psychological manifestations of PHPT as a key direction for future research. There is a clear need for further studies in this area to help guide clinicians in the management of PHPT patients who manifest cognitive and psychiatric symptoms. In addition, studies are needed to evaluate new tools to determine which are efficacious in objectively and consistently detecting cognitive and psychiatric changes in this specific population. Functional imaging studies of the brain represent a new area that has not yet fully been explored in PHPT.

Our case-control neuropsychological study cast a broad net in assessing for cognitive abnormalities in mild PHPT, and is the only study in the literature to control for education level, IQ, depression and anxiety. Although we had an age-matched control population, the study suffered from the absence of a surgical control group (see Future Plans). We demonstrated abnormalities in verbal memory, non-verbal abstraction and response speed and visual attention in mild PHPT that improved after surgery. Very preliminary BOLD fMRI data, which we will pursue in this application, found improvements during synonym generation in Wernicke's and Broca's area, where changes in verbal memory might be expected. This finding highlights the importance of designing our fMRI studies so that the tasks assessed are tightly connected to cognitive deficiencies of interest. The very limited available data in this area come from small (N=6, 18) studies from one group, utilizing BOLD fMRI to pursue the finding of hypersomnolence in PHPT with the counting Stroop task (3). This task is not clearly associated with hypersomonolence, making the positive findings in one and lack of findings in another study, difficult to interpret. They did report an association between the change in serum PTH and change in left precentral gyrus voxel activity at 6 months, underscoring the importance of assessing any functional changes with regard to changes in indices of PHPT disease activity. Indeed elevations of either PTH or calcium, the biochemical hallmarks of PHPT, could cause CNS changes that result in cognitive impairment.

Demonstration of functional changes on BOLD fMRI that map neurocognitive deficits in a metabolic disorder, particularly if they improve with an intervention (i.e. parathyroidectomy), will have significant public health importance in and of itself, with implications for the use of BOLD fMRI in the investigation of other metabolic diseases. This research is also significant because it would represent the first systematic investigation of PHPT with fMRI and will fulfill a key "blueprint" of the most recent International Workshop on Asymptomatic Primary Hyperparathyroidism research agenda. Ultimately these data will help shape evidence-based guidelines for surgery for patients with PHPT. Moreover, this interdisciplinary pilot study will take advantage of expertise at Columbia in Endocrinology, Neurology/Psychological testing and Neuroradiology to further the investigation of modern day PHPT, continuing our record as the group that has contributed more than any other in the world to the understanding of this disease. With the data collected in this grant, we will be poised to make further contributions to the understanding of the cognitive manifestations of PHPT, and hopefully bring clarity to what is arguably the most contested area of discussion in the literature of this disorder.

IMAGING MODALITY

Multimodal fMRI: Since cognitive abnormalities arise from underlying brain function or dysfunction, measurement of cortical activity permits precise identification of the sites and cerebral characteristics that underlie testing abnormalities. Multimodal fMRI offers advantages over other methods because it offers non-invasive dynamic testing of functional brain changes during cognitive tasks without involving contrast enhancing or radioactive agents. A variant of fMRI, BOLD, is based on the discovering that deoxyhemoglobin acts as an endogenous paramagnetic contrast agent that alters the magnetic susceptibility adjacent to blood vessels which causes signal loss on T2 and T2* weighted images. Neural activation within the cerebral cortex is associated with a relative greater increase in cerebral blood flow versus the degree of oxygen extraction. This causes a relative decrease in the capillary and venous deoxyhemoglobin concentration, and thus an increase in the T2* weight magnetic resonance signal (4).

We will employ the 3T Philips (Achieva) scanner located in the basement of the Neurological Institute Building at Columbia Presbyterian Medical Center. One of the major drawbacks of BOLD fMRI is that its signal represents a concerted and complex interplay among changes in flow, volume and metabolism associated with neural activation. In contrast, ASL perfusion fMRI measures a single physiological parameter, namely CBF, which can change at baseline (e.g. in the presence of disease) and during activation. Importantly, the ASL signal provides CBF values in absolute and meaningful units of flow, whereas BOLD is a relative measurement. This is especially relevant to our study because we will scan at two time points – ASL measurement will be used to investigate changes in baseline across time. Any observed difference in the BOLD activation pattern between the two time points will be correlated to baseline changes in flow.
Image acquisition: (1) Reference scan; (2) MPRAGE structural 3D scan that will be used for tissue information processing of both BOLD and ASL images; (3) BOLD gradient-echo whole brain (2x2x5) as previously described and in concordance without our previous acquisition; 5 minute baseline ASL CBF images will be acquired as described in Borogavac et. al (5).

Neurocognitive Battery: We will repeat the validated neurocognitive battery as developed by Walker et al. (2) to confirm that any changes in fMRI correlate to findings on neurocognitive testing. This battery includes the Beck Depression Inventory (BDI); State-Trait Anxiety Inventory, Form Y (STAI-Y); North American Adult Reading Test; Wechsler Memory Scale Logical Memory Test, Russell revision (LM); Buschke Selective Reminding Test; Rey Visual Design Learning Test; Booklet Category Test; Victoria Revision (BCT); Rosen Target Detection Test; Wechsler Adult Intelligence Scale-Revised Digit Symbol Subtest; Wechsler Adult Intelligent Scale Digit Span Subtest (DSpan).

Multimodal Functional MRI Tasks: The cognitive tasks to be performed during BOLD fMRI were chosen to assess areas of neurologic function identified by Walker et al. (2) to be affected by PHPT and ameliorated by parathyroidectomy on repeat cognitive testing. Specifically, these affected areas were in verbal memory (LM), response speed and visual attention (DSpan), nonverbal abstraction (BCT), and depression (BDI) and trait anxiety (STAI-Y).

The BOLD fMRI cognitive tasks will consist of well established paradigms as follows:

1. **Synonym generation**: a test that evaluates language.
2. **N-back test**: a test assessing working memory and non-verbal abstraction. Subjects monitor a series of visual stimuli and are asked to respond whenever a stimulus is presented that is the same as the one presented “n” trials previously, where “n” is a prespecified integer, usually 1, 2, or 3.
3. **Emotional Stroop test:** a test assessing cognitive control of emotion processing systems and visual attention.
4. **Colored faces**: a test measuring anxiety and response speed. Subjects are asked to identify the color of either fearful or neutral faces presented consciously or unconsciously by pressing a button

Statistics: An analysis of covariance will be employed for the planned R01 application to assess between-group differences in the within-person changes in fMRI measures following either parathyroidectomy or medical follow-up. Our pilot data provides the basis for a power and sample size determination assuming an independent T-test, 80% power, 5% alpha and equal sample size and unequal variance (2:1 ratio) that calculates the requirement for 7 subjects per group to detect an approximate 1.6-SD difference between groups. This application seeks funding to replicate and extend the pilot experiment to 7 subjects in the parathyroidectomy arm to serve as preliminary data for the future funding application. Neuroimaging findings and changes in them will be correlated to our cognitive battery and changes in the biochemical hallmarks of PHPT, namely calcium and PTH levels

LONG TERM AIMS & FUTURE PLANS

The data to be collected will form the basis for an R01 application, planned for 2014, to investigate the effect of PTH on cognitive function and functional brain changes. The ultimate plan would be to perform the battery of cognitive tests described above along with fMRI not only in a larger group of subjects before and after parathyroidectomy, but in several other cohorts as well. Investigation of these additional cohorts will both assure that our data are not confounded, and broaden our understanding of the association of our findings to different aspects of the hyperparathyroid process. In addition to the fMRI tasks described in the current study, additional tasks would be added if suggested by findings from the current proposal.

The cohorts we will propose to study in the R01 include:

1. **Larger group of PHPT subjects undergoing parathyroidectomy**
2. **Surgical control group**: There are several different ways in which surgery itself could contribute to the changes in neurocognitive testing and/or changes in BOLD fMRI. These include the well-known effects of improved sense of well-being that accompanies surgical cure of a disorder, with a decrease in indices of anxiety and depression. These changes have been documented in patients with PHPT by our group and others. In addition, the inclusion of this group will control for any effects of anesthesia on some of the neurocognitive testing and BOLD fMRI. For this purpose we will propose a cohort of patients undergoing another surgical procedure on the neck - thyroid surgery patients. All will be euthyroid individuals who are having surgery for non-cancer diagnoses, as abnormal thyroid function can affect testing of interest, and a cancer diagnosis often leads to psychological effects that could confound the study.
3. **Non-surgical PHPT control group**: Study of age- and gender-matched participants with PHPT will allow us to determine if there is a decline in cognition in PHPT patients who are untreated and will also allow us to control for learning effects with repeated neuropsychological and BOLD fMRI studies.
4. **Hypoparathyroid patients beginning treatment with PTH**: Hypoparathyroidism (a disorder characterized by inadequate PTH levels and low blood calcium) is the sole hormone deficiency syndrome for which replacement therapy is not yet FDA-approved. Our group has been working on the clinical efficacy, skeletal and quality of life response of hypoparathyroid patients to administration of PTH, which is now available for subcutaneous administration in two different forms, PTH(1-34) and the native hormone PTH(1-84). General quality of life measures have been assessed in this group, using the SF-36 vehicle. However, there are no data on neurocognitive and BOLD fMRI effects of beginning PTH treatment in this deficiency state. The data from this cohort will have interest and importance in its own right, but in the context of this RO1, this group will provide a key counterpoint to the data collected in our patients with PHPT. In the latter group, both PTH and serum calcium is expected to normalize, while in the hypoparathyroid patients, PTH will increase while serum calcium is generally low normal and is not expected to change markedly. The availability of similar data in these two groups will allow us to tease out the differential effects of calcium and PTH on the indices in question.
5. **PHPT group treated with medical management**: Currently cinacalcet, a medication which lowers serum calcium into the normal range but does not normalize PTH, is approved for PHPT patients with severe hypercalcemia who are not candidates for surgery. Study of a group of PHPT patients before and after treatment with cinacalcet and comparison to the above cohorts will allow further delineation of whether changes in cognition in PHPT are due to elevations in serum calcium or PTH.

In aggregate, these studies would elucidate the mechanism by which deviations in PTH level from normal affects neurocognitive functioning and BOLD fMRI findings, while assessing for the differential changes contributed by calcium, surgical procedure, and repeat testing. On a broader scale, these studies would also advance multimodal fMRI as a clinically useful tool. While providing a better understanding of the functional brain changes underlying the cognitive abnormalities in patients with PTH dysfunction, this project would also highlight the potential of multimodal fMRI in the investigation of metabolic abnormalities.

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