Response to Previous Critique

Introduction to revised proposal

We have carefully read and considered the summary/resume of discussion and the specific comments of the reviewers generated from our initial R01 submission and find them direct and helpful. We are delighted that the importance of the problem addressed and the various strengths of our submission were recognized. Below, we have responded in detail to the specific comments in the Resume and of each reviewer (with reference to changes in the proposal). Within the body of the proposal, specific areas have been re-written and we have used the Arial font to highlight those revisions.

There have been personnel changes related to this re-submission: Dr. Maureen Lacy (30% effort) will oversee the bulk of the neuropsychology testing and will continue to work with Dr. Scott Hunter in the specific evaluation of pediatric examinations. Dr. Neil Pliskin, despite moving to the University of Illinois at Chicago several miles from our main campus, will continue in his role as advisor and overall supervisor of the neuropsychology portion of the project as an affiliated collaborator. Dr. Richard Penn (5% effort), in parallel with clinical and laboratory collaborations with Dr. Frim in the area of hydrocephalus, will provide additional support in the neurosurgical aspects of this study, particularly with the adult study populations. Christina Amidei, R.N., (50% effort) will serve as nurse coordinator at an increased effort reflecting our recent experiences with coordination of subjects in other hydrocephalus-related clinical studies. Dr. Theodore Karrison, Ph.D., (10%, 5%, 5%, 10% effort) and Kristen Kasza (15%, 5%, 5%, 15% effort) will function as our biostatisticians due to their familiarity with other neuropsychologically related clinical studies. The increased statistical effort reflects our response to statistically related critiques as well our analyses of additional preliminary data.

Since the initial submission, we have accrued additional preliminary data related to cognitive function after acute changes in ICP. With these data to guide us, we have determined that we will require a greater number of subjects and controls in order to obtain the appropriate power for our studies. Because of these additional required subjects, we are now proposing a *four*-year study enrolling 81 subjects per year for a total of 324 subjects spread amongst the four aims of the project. We have chosen to lengthen the study rather then enroll more patients for each year because of the practical limitation of the number of neuropsychological tests that can be performed each year (81 subjects spread amongst the four aims of the study will result in nearly 200 testing sessions per year) as well as the number of eligible subjects that would undergo shunt surgery per year. Our funding request has increased accordingly. Though requested in the committee's budget recommendations, we have not included any specific patient-related costs in our budget justification. This is due to a strategy to reduce costs as much as possible by proposing funding for a testing technician/data manager as opposed to funding for reimbursement per testing session, which would be far most costly. Thus, nearly all the costs of this study are personnel related with a small amount required for the actual "pencils and paper" of the neuropsychological testing materials. All clinical care related to hydrocephalus treatment of subjects enrolled in this study is outside the study protocol and is reimbursable by third party payors.

There are additional innovations in the technology that have become available for this study since our initial submission that we have included in this re-submission. There are now two FDA-approved programmable shunt valves and we propose using both types of programmable valves for Aim #1 of this proposal. Also, as a site for the feasibility trial of the Medtronic InSite telemetric ICP monitor, we have populations of patients implanted with the Radionics Telesensor or the Medtronic InSite monitor and will propose to include both ICP monitors in order to enlarge our patient population.

Specific responses to Criticisms

A. Resume and Summary of Discussion

1. *"scant preliminary data"*: We have been able to perform cognitive testing on 14 patients with hydrocephalus before and after acute ICP reduction in a fashion similar to Aims #1 and #2. This data is presented in the Preliminary Data section and replaces the data from an individual patient who underwent acute ICP reduction and testing. We chose to obtain data from hydrocephalic patients before and soon after lowering

of ICP to show the presence of a pattern of changes in cognition. These changes should represent the minimum of changes that occur, as waiting longer after the ICP change allows more brain recovery and more improved cognition. In this fashion, the cognitive improvement that we observed (and present in the Preliminary Data section) should also predict a pattern of improvement 2 weeks and 1 year after the lowering of ICP as proposed in Aims #2 and #3. We have retained previously presented preliminary data from the single child who underwent shunt revision and cognitive testing similar to that proposed in Aim #2 and we have added data from another individual patient who underwent third ventriculocisternostomy and cognitive testing analogous to that proposed in Aim #3. These data are provided as examples of the safety and feasibility of our protocols. The preliminary data from these 16 patients who have undergone cognitive testing protocols represent approximately 15% of the total experimental subject data (108 subjects) proposed for Aims #1, #2, and #3 in this grant application.

2. *"possible contribution of varying etiology within the patient population is not considered"*: in response to this criticism, we have limited the etiology of hydrocephalus in Aim #1 to subjects with normal cognition and non-congenital communicating (absorptive) hydrocephalus in order to reduce any confounding neurodevelopmental factors in assessing effects of acute ICP changes; Aim #2 is limited to subjects with perinatal hydrocephalus and development within one school year of normal to limit the possible confounding issues of other etiologies such as brain tumor, hemorrhage, etc.; Aim #3, by design, is limited to patients with benign aqueductal stenosis; and Aim #4 is also limited to subjects with congenital hydrocephalus as in Aim #2. These limitations should minimize etiological differences within each Aim. The varying etiologies will interfere with inter-Aim comparisons; however, since the questions asked by each separate Aim protocol are different in both time course of ICP change and CSF dynamics, inter-Aim comparison will be confounded within this study. Follow-up studies to the significant findings determined from this proposal (which will be proposed in renewal applications) will address the inter-Aim issues.

3. *"constant level of pressure for one year period….varying pressure…will confound the interpretation"*: With the telemonitors available to us, we will plan to exclude patients who have observed increases in pressure or additional shunt malfunctions within the one year follow-up period for Aims #1 - 3.

4. "*more experimental tools are required for meaningful assessment of attention, memory and speed of processing.…research design lacks attention on structural variation of brain, specifically measurements of ventricular size"*: The focus of this initial study is to gain a greater understanding of the cognitive impact of ICP. Currently, one of our goals is to assess whether changes in ICP will result in a specific pattern of improvement in cognition: determining which clinical measures are sensitive to changes in ICP. Further studies will focus on the neural substrates of these impairments. We have considered adding additional experimental measures to our design; however, our initial experience indicates that patients fatigue quickly during the testing phase. In order to obtain valid data we have in fact needed to streamline our battery, with a focus on clinical function. As we develop a sensitive clinical battery, more experimental measures can be added to future studies. Outside of the cognitive testing, we have responded to the issue of structural variation in the brain by proposing the measurement of ventricular size for each patient by utilization of a V-C ratio (frontal horn to frontal horn:cortex to cortex distances measured bitemporally at the level of the foramena of Monro on axial CT scanning).

B. Reviewer#1

1. *"it will prove difficult to isolate more specific deficits…more experimental tools (in addition, of course, to the clinical ones) would be desirable, insofar as being able to isolate specific structure-function relations..."* See **A.4** above. We propose in this revised study using measures of ventricular size as an initial assessment of structural changes. We cannot add additional experimental tools at this time due to the issue of patient fatigue. Once we have identified significant cognitive changes, we will propose subsequent studies directly examining the specific deficits and improvements.

2. ***"****Although, the PI is proposing to use a brief neuropsychological battery, it may prove desirable to factor analyze the full battery in order to isolate which specific tasks are most sensitive to effects of CH."* This type of analysis will be available *post hoc* from the proposed study and will be used to design testing batteries in

our future proposals. At this point, however, we feel that the group sizes and the need to collect data from test batteries of fairly short duration will not allow this type of approach *a priori*.

3. *"it maybe beneficial to subdivide patients into smaller groups and examine outcomes of these subgroups."* The power considerations predict against any significant data being generated from smaller groups. *Post hoc* analysis may provide predictions for outcome analyses in potential follow-up studies.

4. "*it would seem important to consider the possibility that structural changes in the brain may account for some of the observed effects rather than ICP exclusively."* MRI based studies have examined the presence of periventricular and white matter lesions on outcome after shunting and shown that the degree of improvement depends on the severity of damage to these areas (31). However, the type of shunt malfunction or pressure variation proposed for this study should not induce or affect baseline parenchymal injury, rather ventricular size changes should be the only structural change evident. We now propose to include a ventricle to parenchyma ratio in our data collection, see **A.4** above.

5. ***"****more preliminary data than the two patients currently reported."* See **A.1** above.

C. Reviewer #2

1.a. "*Aim 1 tests the hypothesis in…subjects said to be age 17 years or older on page 31, but adults on page 32*)…" We have changed the wording to reflect that all subjects will be 17 years of age or older**. b.** ***"testing will be done several hours later although the exact length of time is not clearly stated"***. We have now explicitly stated 2 - 4 hours later.

2. (Aim #3) "*the use of normal controls appears to bias the study against the stated hypothesis".* This point is well-taken and we have modified the control group to consist of patients who have undergone third ventriculocisternostomy for aqueductal stenosis more than one year prior to enrolling as controls. These subjects should control for the etiology of the problem as well as effects of the procedure.

4. *"Shunt type was said to have been random up to five years ago. What is not clear is whether age cohort effects could influence outcome: would older subjects have received less effective diagnosis and treatment? If so, matching groups on age would be important."* Subjects will be age matched across both experimental groups and the control group.

D. Reviewer #3

1. "*there is a concern that the result of cognitive testing will be dependent upon etiology as well as ICP…*" We agree that this is a valid concern and have further limited our inclusion criteria in each various Aim as discussed in **A.2**, above: Aim #1 to include only patients with normal cognition and non-congenital communicating hydrocephalus from malabsorption without any other brain anomalies or injuries; Aim #2 to include congenital communicating hydrocephalus shunted before age 1; Aim #3 to include patients with aqueductal stenosis without any other brain anomalies; Aim #4 to include patients with the identical criteria as Aim #2.

2. (Aim #1)…"*effects of ICP on subjects of mixed…or unspecified etiology will < not > provide sound data to establish ..ICP sensitive …cognitive function".* Etiology of the hydrocephalus will be limited to hydrocephalus caused by CSF malabsorption without any associated brain congenital anomalies or brain injury (such as stroke or trauma), as now stated.

3. *(Aim #2) lack of preliminary data…"* See **A.1** above.

4. "***there is less attention paid to the structural changes…reduction in ventricular size, the applicants do not consider the effect of these changes…."*** We have added a measure of ventricular size before and after shunt malfunction (Aim #2) or ventriculocisternostomy (Aim #3) to address this concern.

5. This reviewer offered concern centering on the proposed one-year testing period and interpretation of long-term cognitive measures given the uncertainty that *"these patients will remain at the same level of pressure for the one-year period.*" This is a valid concern to which we have responded by limiting our study to individuals without shunt revisions and who demonstrate stable ICP over the proposed one-year intervals in Aims #1, #2, and #3.

A. Specific Aims

Hydrocephalus, a build-up of cerebrospinal fluid (CSF) in the intracranial space, is a disease that can cause significant neurological injury. Though the associated life-threatening intracranial hypertension can be well treated by diversion of cerebrospinal fluid to an absorptive surface outside of the brain, the short- and long-term cognitive effects of elevated intracranial pressure (ICP) and altered cerebrospinal fluid pressure dynamics are incompletely understood. The overall objective of this proposal is to determine the acute, short-term, and long-term cognitive effects of changes in supine intracranial pressure and altered CSF pressure dynamics in a population of hydrocephalics. In addition, these studies may help to determine the pressures needed to optimize cognitive outcome in the treatment of hydrocephalus. Many shunting devices are available which contain valves that generate a specific pressure dynamic or valves that can manipulate ICP values. In addition, ICP monitoring capabilities can also be incorporated. Therefore, treatment of hydrocephalus now allows unprecedented access to the monitoring and manipulation of ICP in the awake human. We propose using novel technology for the non-invasive measurement and manipulation of CSF pressure to determine the impact of changes in ICP on neuropsychological tests of higher cortical function. Specifically:

Aim #1: We will determine the acute neurocognitive effects of small, defined increases in intracranial pressure (Hypothesis: some areas of cognitive function, e.g., attention, memory, and mental speed, will be ICP sensitive while others will be relatively ICP independent after an acute ICP change, e.g. language).

Aim #2: We will determine the changes in cognitive function seen 10 – 14 days and 1 year after the lowering of chronically elevated intracranial pressure at the time of treatment of extracranial CSF shunt malfunction (Hypothesis: treatment of hydrocephalus and its associated intracranial hypertension will improve specific pressure dependent cognitive functions, e.g., attention, memory function and mental speed, as hypothesized in Aim #1).

Aim#3: We will determine the pre-treatment cognitive deficits and short- and long-term post-treatment improvement in the sub-population of hydrocephalics with aqueductal stenosis who are treated by restoration of ICP dynamics identical to those seen in non-hydrocephalic controls (Hypothesis: endoscopic third ventriculocisternostomy, a non-shunting bypass of aqueductal obstruction, restores normal pressure dynamics and normal cognitive functioning).

Aim #4: We will determine the differences in cognitive performance between normal controls and hydrocephalics who have been treated with extracranial shunting systems that utilize siphoning or non-siphoning valve types--both of which produce non-normal ICP dynamics (Hypothesis: different shunting dynamics will differentially affect neuropsychological performance and further define ICP-sensitive and ICP-insensitive cognitive functions).

B. Background and Significance

Cognitive function and intracranial pressure

Higher cortical function in the human as measured by neurocognitive testing is sensitive to a variety of neurophysiological parameters. One such parameter that has not been fully investigated with regard to its effects on cognitive function is that of global changes in intracranial pressure (ICP). ICP measurement is important in the monitoring of brain function in severely injured adults and children after head injury (53). However, measures of brain function in that situation are necessarily quite crude. These measures have included only such functions as spontaneous and elicited motor function, eye movement responses, and the ability to respond to verbal stimuli. Moderately elevated ICP that does not cause gross impairment may affect neurocognitive development and function in as yet undetermined ways.

Many common disease states, including craniocephalic disproportion syndromes such as the craniosynostoses (55), expanding intracranial masses such as brain tumors, and hydrocephalus, where a cerebral spinal fluid (CSF) volume increase causes a rise in global ICP (41), can cause long-term moderate elevations in ICP. The neurocognitive effects of these changes in ICP, before they become acute and life-threatening, are undefined. The ICP effects on the brain are presumably reversed by definitive treatment of the underlying problem, such as placement of an extracranial CSF shunting system in a hydrocephalic. However, there is a paucity of neurocognitive data to confirm this assumption for higher cortical function in the human (9). For hydrocephalus, neuropsychological examination before and after shunting has been clouded by confusion in the etiology of the hydrocephalus as well as the post-shunting ICP (59). In addition, the differential susceptibility of specific cognitive functions to ICP changes is unknown.

The clinical problem of human hydrocephalus

The incidence of congenital hydrocephalus has been estimated to be between 1.5 to 15 per 10,000 live births with a prevalence in the United States that exceeds 125,000 (7). There is an unknown number of additional children and adults who present later in life with acquired hydrocephalus. The number of hydrocephalus-related surgical procedures in the United States annually exceeds 30,000 (7) at a cost of over $10,000,000 with a post-surgical mortality of 1% per year after implantation of an extracranial shunting system (personal communication, D.McLone). The magnitude of the clinical problem of hydrocephalus is under appreciated because of the often dramatic disappearance of overt symptoms of increased ICP in response to extracranial cerebrospinal fluid (CSF) shunting. However, basic questions currently remain unanswered in the surgical treatment of hydrocephalus: what is the appropriate goal of ICP management in a hydrocephalic--is it pressure that is higher or lower? What is the appropriate choice of shunting system for a specific etiology of hydrocephalus--is it a differential pressure system or a non-siphoning system, and at what supine pressure? What type of shunting system will maximize the cognitive function of a child who may already be impaired by a disease process underlying the hydrocephalus?

The clinical impact of answering these questions will be enormous. The thousands of hydrocephalus surgeries performed each year will be affected by defined guidelines designed to maximize cognitive outcome. In addition, the unknown number of hydrocephalics, both children and adults, whose intracranial pressure is undertreated (or overtreated) in the management of their hydrocephalus will benefit from these answers.

Management of human hydrocephalus and measurement of global changes in ICP

Human hydrocephalus is multi-factorial in etiology. However, universal to the presentation of hydrocephalus is a global increase in ICP caused by an increase in intracranial CSF volume (41). Treatment of hydrocephalus is also varied, depending upon the underlying cause of the obstruction to CSF flow or re-absorption. CSF is produced and secreted by the choroid plexus of the lateral, third, and fourth ventricles of the brain. It circulates from the lateral ventricles through the paired foramena of Monro to the third ventricle. From the third ventricle, CSF flows along the cerebral aqueduct of Sylvius to the fourth ventricle, leaves the ventricular system through the foramena of Lauschka and Magendie, and is circulated to the convexities of the hemispheres where the CSF is reabsorbed into the venous system via arachnoidal granulations. Hydrocephalus can occur when there is a physical blockage to the flow of CSF from a mass lesion, such as a brain tumor ("obstructive hydrocephalus"), or when the absorptive surface is incapable of adequate CSF re-absorption after a chemical or inflammatory insult, such as intraventricular hemorrhage ("absorptive hydrocephalus"). Obstructive hydrocephalus can sometimes be treated by bypassing the internal obstruction of CSF flow that will restore near normal ICP dynamics (24, 60). Other forms of hydrocephalus must be treated by insertion of an extracranial shunting system.

The history of the treatment of hydrocephalus to this day is centered on the technology of shunt tubing and CSF valves. Despite the resources that have been expended to develop improved shunting materials, shunt failure is common and generally unavoidable. The need to diagnose shunt failure and its attendant rise in ICP led to the development of a non-invasive telemetric monitor of ICP implanted "in-line" with the shunting

products (Telesensor, Radionics, Inc., Burlington, MA) (11). The in-line telemonitoring device allows the measurement of global intracranial pressure in a noninvasive fashion in the awake and responsive treated hydrocephalic (10, 24, 42). Only recently has the telesensoring device been used to investigate the pressure dynamics of specific shunting systems in hydrocephalics (25, 42), or of the brain of an unshunted patient if implanted for clinical reasons other than overt hydrocephalus (25). The dynamic ICP measurements obtained in this fashion have not yet been correlated with changes in cognitive function seen after treatment.

The accepted treatment for absorptive hydrocephalus and most forms of obstructive hydrocephalus is insertion of an extracranial CSF shunting system designed to transport CSF to another absorptive surface in the body, such as the peritoneum, pleura, or intravascular space. The shunting system can consist of a differential pressure valve (20), a valve with flow-regulating properties (13, 20), or a differential pressure valve coupled to a non-siphoning component to reduce negative pressure in the upright position (61). Though all of these technical approaches alleviate the elevated ICP associated with untreated hydrocephalus, the resulting pressure dynamics are hardly "normal" when compared to the non-hydrocephalic (25). In fact, each of the shunting systems produces distinct and measurably different *in vivo* ICP dynamics (25). This may cause a series of symptoms related to subtle mismatches between individual pressure needs and the shunting system used. The effects of these variations in ICP dynamics presumably must affect cerebral blood flow and neurocognition. Recent advances in shunt valve technology have produced variable pressure programmable valves that can be manipulated to produce ICP within a set range (47). These valve systems provide an opportunity to alleviate chronic over- and under-shunting by "fine-tuning" ICP in an individual patient, though the resultant predicted ICP dynamics are those of a standard differential pressure valve (13). This type of valve can provide an opportunity to evaluate the effects of small, defined variations in ICP on measures of neurocognitive function.

Obstructive hydrocephalus caused by stenosis at the level of the aqueduct of Sylvius may often be treated with an endoscopic procedure to bypass the obstruction by fenestrating the third ventricle into the prepontine cistern (29, 60). This allows CSF flow to proceed into the convexity reabsorptive surface by bypassing the fourth ventricle. The ICP dynamics after this treatment are believed to be nearly normal, as has been observed by telemetric monitoring in a published case report (24) and a larger preliminary series (27). However, during the first several weeks after this treatment, the ICP is quite variable before returning to a baseline by 3 months after treatment. This mode of treatment is fundamentally different than implantation of an extracranial shunting system presumably resulting in the different time course of recovery and other as yet undefined long-term consequences. The population of hydrocephalics successfully treated by ventriculocisterostomy offers a unique opportunity to study the short- and long-term cognitive effects of hydrocephalus/increased ICP after restoration of normal CSF dynamics. This contrasts with the abnormal ICP dynamics established by the currently available CSF shunting systems.

Cognitive changes observed in hydrocephalics

Studies investigating the relationship between hydrocephalus and cognitive development have shown that children with hydrocephalus typically demonstrate a reduction in their overall level of cognitive functioning (17, 19). Studies that included both shunted and unshunted patients with hydrocephalus have consistently found a lower performance level on measures of global intelligence as well as more specific measures of cognitive functioning for shunted children (67, 22). This discrepancy is likely due to the greater severity of hydrocephalus in children requiring shunt placement versus in those who do not (who may have compensated ventriculomegaly rather than true hydrocephalus). It has been reported that 75 percent of individuals with hydrocephalus have a Full Scale IQ score greater than 70 (6). Many studies have shown that children with hydrocephalus have poorer nonverbal, visual-spatial skills as compared to verbal or more language based skills (16, 51). To date, most neuropsychological studies of children with hydrocephalus have focused on a limited number of cognitive variables. Specifically, many studies have been limited to evaluating overall level of intellectual functioning and focused on one area of cognitive development, such as perceptual and motor function (1, 51), memory (12, 50) or language functions (16). Few comprehensive neuropsychological examinations of children with hydrocephalus have been conducted and no studies, to our knowledge, have

examined the relationship between ICP and the patterns of decrease in higher cognitive functioning in this population.

Studies examining the neurocognitive profile of children with hydrocephalus have identified relative deficits in the area of nonverbal, visual-spatial deficits. Children with hydrocephalus experience particular deficits in the area of visual-motor integration (23, 57, 67), while their visual perceptual skills appear to be intact (56). Discrepancies between verbal and nonverbal skills appear to be stable over time (8). The finding of lower nonverbal, visual-motor skills as compared to language based skills is widely accepted in children with hydrocephalus. However, the underlying processes that account for these deficits are less clear.

Verbal and nonverbal memory skills have been examined in a limited fashion. In some studies, children with hydrocephalus have been found to perform significantly lower in comparison to control children on verbal recall tasks. Hydrocephalic children recalled fewer items on an initial recall trial and demonstrated poorer consistency of recall over five trials as part of a selective reminding paradigm. Nonverbal memory has been found to be significantly impaired on a graphomotor task, involving the reproduction of line drawings from memory, while recognition memory was intact (45). In a recent study examining memory functioning in children with hydrocephalus (50), shunted children displayed a pervasive pattern of memory deficits. They experienced memory problems on both verbal and nonverbal measures. Memory problems were suggestive of both encoding and retrieval difficulties.

Preliminary evaluation of attention and concentration in children with hydrocephalus revealed variable results. Billard (6) reported that 42% of subjects with hydrocephalus had attention and concentration disorders. In a study by Lollar (39), children with hydrocephalus performed within normal limits on the Gordon Diagnostic System, a computerized measure of sustained attention, concentration, and impulsivity. Prigitano (45) investigated the "speed of information processing" in a sample of 5 to 9 year old children with hydrocephalus through use of the Trail Making Test. This test consisting of first, a rapid connection of consecutive numbers, and second, a more challenging task, the speeded connection of alternating letter/number sequences, assesses speed of visual search, immediate visual attention, and visual-motor processing. No significant differences were obtained on the first part, while children with hydrocephalus performed significantly slower as compared to control children on the second. It was suggested that children with hydrocephalus might be able to focus and sustain attention during a simple reaction task, while they experience more difficulty on more active tasks involving sequencing, planning, and cognitive flexibility.

Academic achievement skills have also been examined. Some studies found that children with hydrocephalus progress at the same rate as their peers in the area of reading achievement (45) and writing (23). A more detailed study of specific reading skills (2) found that children with hydrocephalus do not differ from controls on their phonics and word recognition skills, but perform less well in the area of reading comprehension. Lower performance of hydrocephalic children has also been described on standardized measures of arithmetic (23).

In summary, studies examining the neuropsychological functioning of children with hydrocephalus have identified several areas of deficit, typically involving right hemisphere dysfunction. Specifically, children with hydrocephalus tend to have lower Performance IQ scores as compared to Verbal IQ scores. Deficits on tasks of visual-motor integration, fine motor coordination, and attention have been described quite consistently. At this time, it is unclear if children with hydrocephalus also experience difficulty with visual perception. Studies examining memory function have found both verbal and nonverbal memory deficits, with nonverbal memory skills often being lower. Finally, in the area of academic achievement, children with hydrocephalus have particular difficulties with math calculation**.** Difficulties with reading comprehension have also been described, while their reading decoding and writing skills tend to be intact.

Whereas the preceding findings provide some indication of the putative long-term neuropsychological deficits associated with hydrocephalus in children, far less is known about the acute or short-term cognitive changes that result from treatments such as shunt placement. Moreover, the aforementioned studies fail to provide answers regarding the direct effects of treatments (e.g. shunts) on functioning, as the described cognitive deficits could arise from underlying neurological dysfunction related to the etiology of hydrocephalus

in addition to the hydrocephalus and its treatment specifically. The only direct way to assess the effects of treatments on functioning is through pre- and post-treatment assessments. Unfortunately, the bulk of the few studies that have investigated cognitive changes associated with shunts have been conducted in patients with suspected normal pressure hydrocephalus (NPH), a condition that seems to bear little resemblance to congenital or other forms of childhood hydrocephalus. These differences are most obvious with regard to issues involving intracranial pressure.

Nevertheless, current studies investigating the effects of shunt placement on cognition in NPH indicate that improvements can be observed in the functioning of these patients (52). Additionally, one of the emerging predictors of neuropsychological outcome may be chronicity or duration of illness which favors patients with a rapid onset (37). Whereas patients with acute onset of symptoms may show early improvements in functioning (44), improvements are sometimes not noted until one year after the shunt operation (34). Improvements, however, may not be limited to acute onset patients, as these have also been noted in more chronic patients (36). The cognitive functions that appear most likely to improve include measures of attention, motor speed, and visual-spatial function, but not language or IQ (34, 58). Other studies, however, suggest that the improvements resulting from shunt procedures primarily affect gross physical and neurological parameters such as incontinence and gait, and to a lesser extent cognition (54). Despite the preliminary suggestion that at least some patients may benefit from shunting, many questions remain unanswered. Conclusions from prior studies are limited by multiple factors including small sample sizes (in many instances case studies are reported), use of inadequate neuropsychological measures, the lack of control groups to assess the influence of practice effects, and the lack of assessment of both acute and long-term outcome.

We propose utilizing human hydrocephalus as a model of reversible elevation of ICP. Novel technology in the telesensing of ICP in implanted CSF shunting systems allows us direct non-invasive access to ICP measurements (10, 24, 42). These pressure measurements can then be correlated with tests of neurocognitive function to reveal patterns of functional changes associated with ICP changes. Presumably, these observations will define ICP-sensitive and ICP insensitive cognitive functions. Based on the above discussion, we would hypothesize that nonverbal, visual-motor and attentional skills may be more affected by ICP elevation than verbal function. Data collected correlating different shunting dynamics with cognitive outcome may also help to predict the pressure dynamics that will produce the best cognitive outcome for a specific hydrocephalic patient.

C. Preliminary Studies

Measurements of dynamic ICP in vivo in humans

Preliminary data on the dynamic ICP generated by different shunting systems has been collected (25) after implantation of non-invasive telemonitors in-line with the shunting systems or in unshunted controls for measurement of ICP. Data was first obtained from 3 unshunted patients that were monitored for potential hydrocephalus that did not occur. This data is depicted below in Figure 1.

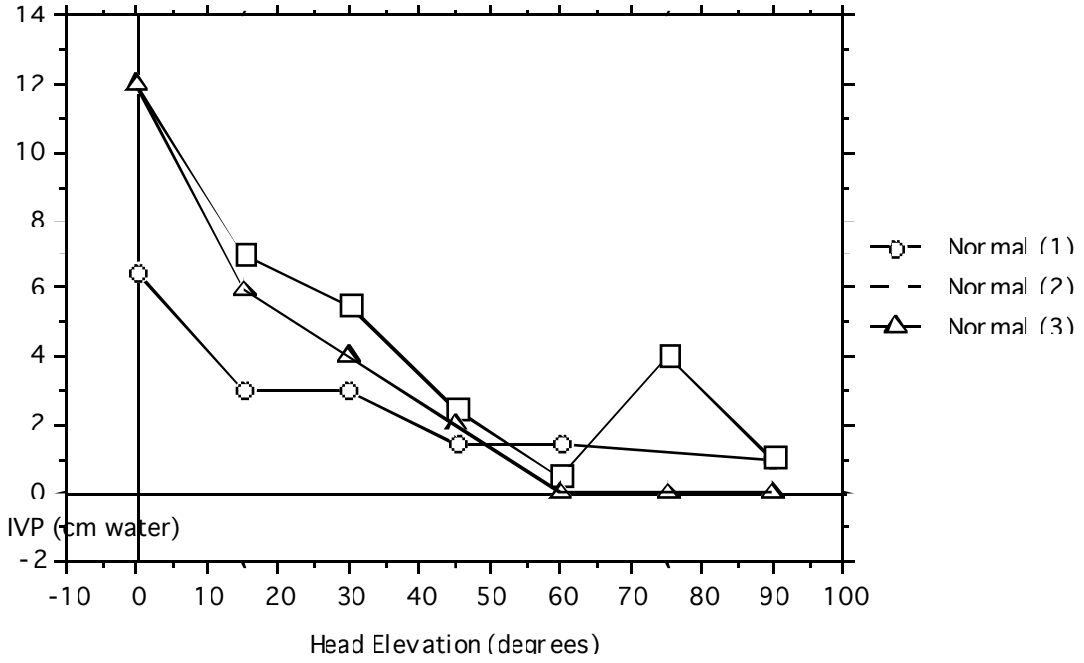

Figure 1. ICP dynamics in unshunted controls. Depicted are the postural ICP tracings of three patients with ICP telemonitors that do not have shunts or hydrocephalus.

The shape of the pressure curves for these unshunted patients is rather flat, and the pressure does not become zero in any case until 60 degrees of head elevation. The best fit regression coefficient for the curves obtained in this group (r) is -0.112 ± 0.037. After this data was obtained, twenty five shunting systems in treated hydrocephalic patients were then examined telemetrically for postural pressure dynamics. The dynamics of several of the differential pressure valve patients are shown below, graphed with the unshunted controls:

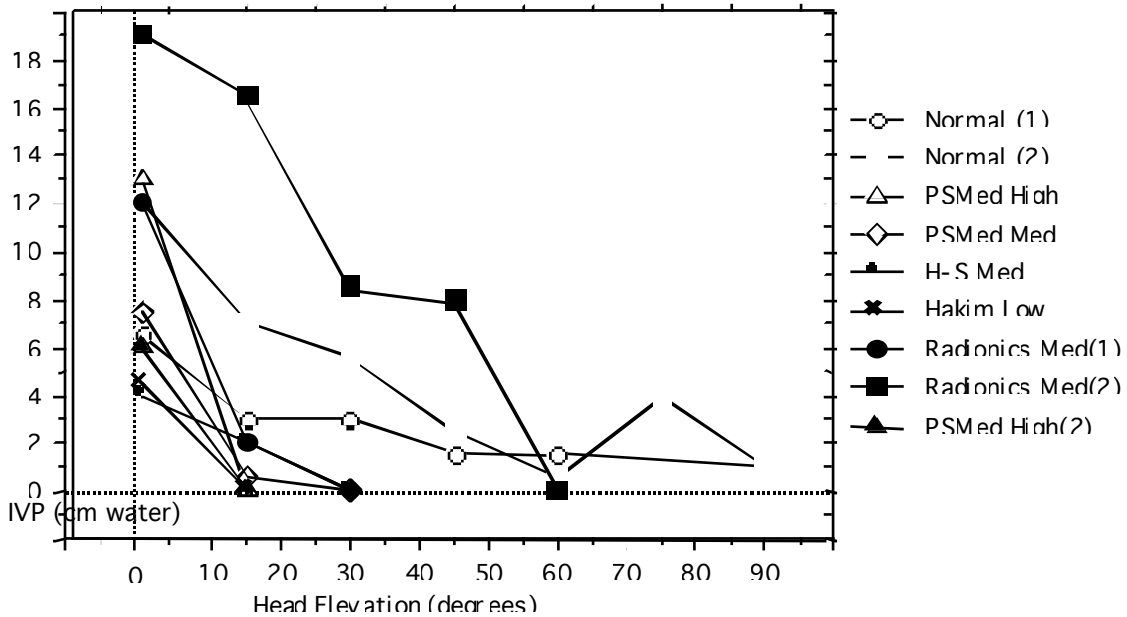

Figure 2. Pressure dynamics of differential (siphoning) shunt systems. Depicted are the pressure tracings of 2 unshunted controls shown in Figure 1 along with 7 differential pressure valve shunting systems. Note that nearly all of the shunting systems shown create a zero or negative pressure by 30 degrees of head elevation with a pressure curve unlike and much steeper than the unshunted controls.

The regression coefficient for this group (n = 12) was r = -0.321 ± 0.061 which was significantly different from controls (p = 0.049, ANOVA). This observation indicates that the dynamic pressures of patients shunted with this type of system will cause fundamentally different cerebral perfusion and CSF flow.

Non-siphoning shunting systems (valves containing anti-siphoning components) when examined produced curves that were also significantly different than the differential pressure valves (r = -0.158 ± 0.027; n = 10; p = 0.023), as shown in Figure 3.

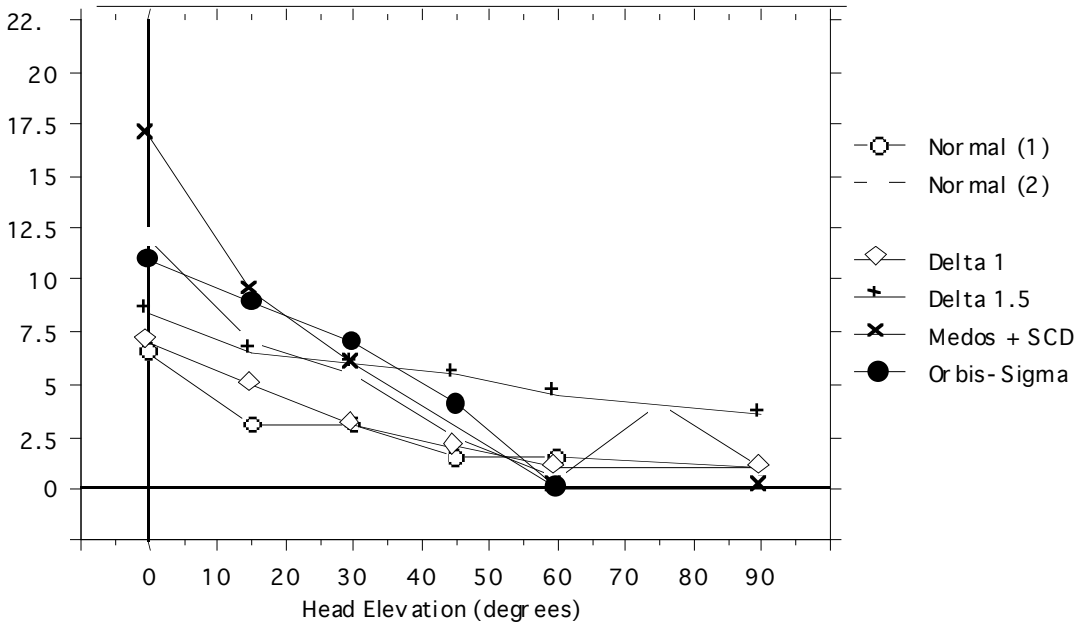

Figure 3. ICP pressure dynamics of non-siphoning shunts. Depicted are examples of non-siphoning shunt systems monitored telemetrically. Two unshunted controls are also shown. Note that the curves approximate the control curves, though the zero intercept is greater in many cases.

Though these curves approximate those of the controls, the zero intercept trends toward a higher head elevation. Presumably, this will also contribute to variation in cerebral perfusion and CSF flow when compared to normals.

Pressure data obtained with the telemonitor are constant over the period of examination and are expressed as means of 2 - 3 measurements at each degree of head inclination. We have noted day to day variation of several cm of water pressure in the supine ICP; however, there is uniformity in the curve shapes and regression coefficients.

These data show that there are observable dynamic ICP differences after implantation of commonly used shunting devices. These observations are difficult to correlate with overt symptomatology, since any shunting procedure generally relieves overt symptoms of elevated ICP (e.g., vomiting, headache). We have also had an opportunity to non-invasively monitor the ICPs generated by defined changes in a programmable CSF shunt valve (26) and found that the programmed changes are nearly identical in magnitude to what is predicted by the valve mechanism (data not shown). In addition, over several months, the telemetric measurements of ICP do not demonstrate any drift relative to the valve setting or to direct CSF measurements by shunt tap. These observations provide the basis for direct manipulation of ICP as a test for the pressure dependence of specific cognitive function.

Observation of ICP-mediated effects on neurocognition

Data for acute changes in cognitive function with manipulations of ICP has historically been difficult to derive and are generally individual case–related. We have had an opportunity to examine by neurocognitive testing 14 hydrocephalic patients both before and after an acute decrease in CSF pressures by continuous lumbar CSF drainage lasting 3 - 5 days. The range of initial ICPs was from 14 to 19 cm of water pressure and all patients underwent CSF drainage to a pressure of 0 cm of water. CSF drainage and ICP reduction was performed to evaluate shunt function or status of hydrocephalus.

	Pre-Drainage	Post-Drainage	
Repeatable Battery for the Assessment of Neuropsychological Status			
			$Z_{dif.}$ score change
Immediate Memory Index	66.0	76.56	
Stories	11.36	12.46	+.32
List	15.5	19.38	+.78
Visual Construction index	74.46	75.67	
Figure Copy	12.0	12.15	+.08
Line Orientation	13.31	14.17	+.3
Language Index	84.0	86.58	
Naming	9.46	9.50	+.08
Fluency	12.36	12.92	+.12
Attention Index	74.77	75.54	
Digit Span	9.57	9.77	+.1
Coding	21.15	22.37	+.15
Delayed memory Index	58.38	64.15	
List	.86	1.62	+.34
List-Recognition	15.9	16.46	+.46
Story	4.07	5.31	+.59
Figure	4.31	6.07	+.44
Stroop Color Word Subtest	27.42	30.71	+.30
Trail Making Test	*seconds to complete*		
Trails A	80.11	47.00	+2.78
Trails B	117.83	89.17	+.75
Grooved Pegs	*seconds to complete*		
Dominant	165.85	144.67	+1.45
NonDominant	194.14	141.33	+3.4

These data indicate relatively stable language abilities, simple attention, and visuoperceptual skills following the acute decrease in ICP, with a trend suggesting improved complex attention, cognitive flexibility, and memory functioning after the ICP decrease in this cohort of subjects. Thus, as hypothesized, these data document significant acute changes in selective neurocognitive domains after only a short interval of decreased ICP. Our power analysis suggests more pronounced neurocognitive changes will be seen as our sample size increases. Furthermore, more pronounced changes are also expected across longer periods of stable ICP, which will be seen in the 14 day and 1 year follow up included in the study design of this proposal.

Preliminary data of a child's performance on the pre- and post-surgery battery before and after shunt revision

Limited data is available regarding the changes in cognitive functioning in children after treatment of elevated ICP such as is seen with VP shunt malfunction. To evaluate the feasibility of our proposed protocol (see Aim#2 below), we evaluated a 9-year-old boy with hydrocephalus due to shunt malfunction

immediately prior to shunt revision and again two weeks later. The boy experienced behavioral changes at school that his grandmother recognized as being possibly related to his shunt malfunctioning. A sedated lumber puncture before testing showed an opening CSF pressure of 36 cm of water. At surgery, a telemonitor was inserted with the revised shunting system and ICP was measured at 12 cm of water two weeks postoperatively. The patient was cooperative during the pre- and post-testing and did not appear to suffer any obvious consequences due to his elevated intracranial pressure (pre-testing) or his recent surgery (post-testing). The pre- and post-surgery battery took approximately 90 minutes to complete. His neuropsychological test scores are summarized below in Table 2.

Table 2. Results of neuropsychological testing pre- and two weeks post-shunt revision.

Test	***Pre-op***	***Post-op***	***Status***	***Change***
Attention/Processing Speed				
Digit Span (WISC-III), ss[1]	8	13	improved	> 1sd
Receptive Attention (CAS), ss	11	13	mildly improved	2/3 sd
Planned Codes (CAS), ss	8	8	unchanged	
Vigilance Task (GCS)				
Total commissions, rs[2]	2	3	unchanged	
Commission block variability	0.57	1	unchanged	
Total correct	38	42	improved	1sd
Memory				
Verbal Learning (WRAML), ss	11	14	improved	1sd
Stories (CMS), ss				
Immediate recall	5	8	improved	1sd
Delayed recall	6	7	unchanged	
Delayed recognition	5	6	unchanged	
Dot Location (CMS), ss				
Learning	10	14	improved	> 1sd
Total score	9	14	improved	> 1sd
Long Delay	7	12	improved	> 1sd
Rey Complex Figure Test, SS[3]				
Copy	51	76	improved	> 1sd
Immediate recall	73	87	improved	>2/3sd
Delayed recall	74	74	unchanged	
Recognition	102	119	improved	> 1sd
Fine Motor Coordination				
Grooved Pegboard, SS				
Dominant hand	88	88	unchanged	
Non-dominant hand	85	88	unchanged	

[1] Scaled Score (mean = 10, standard deviation = 3), [2] Raw Score, [3] Standard Score (mean = 100, standard deviation = 15); WISC-III, Wechsler Intelligence Scale for Children-Third Edition; CAS, Cognitive Assessment System; GDS, Gordon Diagnostic System; WRAML, Wide Range Achievement Test; CMS, Children's Memory Scale

To summarize these findings, the boy made modest gains in his attention and concentration. These gains are likely not due to a practice effect since measures of attention and concentration typically do not

improve with repeated exposure. Significant improvements were observed on the verbal and nonverbal memory tests. Since there are no alternative forms available for children, it is unclear how much of the change can be attributed to the reduction in intracranial pressure and how much is due to a practice effect. This question will be addressed in the larger study (see Aim #2, below) through the use of a control group.

These observations demonstrate that specific observable changes in neurocognition that are on the order of one standard deviation in certain sub-tests, are seen with ICP changes. In addition, the testing battery performed was well tolerated under the acute testing conditions and before and after shunt revision surgery. This child was followed for a year after the initial testing without shunt malfunction or ICP changes monitored on his TeleSensor device.

We also had opportunity to evaluate the cognitive function in a 14-year-old child before and after endoscopic third ventriculo-cisternostomy as treatment for aqueductal stenosis. This evaluation was performed in a fashion similar to that proposed in Aim #3 (below). The cognitive changes observed and tolerance to the protocol prove the feasibility of examining patients undergoing this type of ICP reduction and CSF dynamics change.

Test	Pre-Surg	Post-Surg	Status	Change
Verbal IQ	120	122	Unchanged	
Performance IQ	93	103	Improved	+ 0.75
Verbal Memory Stories (CMS), ss[1]				
Immediate Recall	5	7	Improved	+0.75
Delayed Recall	6	8	Improved	+0.75
Recognition	6	8	Improved	+0.75
Visual Planning & Memory Rey Complex Figure Test, ss[2]				
Copy	69	104	Improved	> +2.0
Immediate Recall	60	84	Improved	+ 1.50
Delayed Recall	57	84	Improved	> +2.0
Recognition	99	107	Unchanged	

[1] Scaled Score (mean = 10, standard deviation = 3), [2] Standard Score (mean = 100, standard deviation = 15); Wechsler Child Intelligence Scale-3; California Verbal Learning Test; Rey Complex Figure

This child tolerated the testing sessions well and showed improvement in memory function and visual-spatial function.

Application of these tests of neurocognition to a population of hydrocephalics before and after ICP reduction should provide significant data regarding the neurocognitive effects of ICP manipulations.

D. Research Design and Methods

We propose using neuropsychological measures of higher cortical function to define the cognitive response to changes in ICP seen in a population of hydrocephalics. Acute (same-day) neurocognitive changes seen with increases and decreases in ICP and short term (10 – 14 day) cognitive changes seen with decrease in ICP will be assessed. Short and long-term (1 year) changes in neuropsychological measures will be evaluated

in patients with hydrocephalus of two etiologies (obstructive versus absorptive), and chronic cognitive function will be assessed in patients with two types of shunting systems (differential pressure versus non-siphoning). Our technique for measuring ICP will be the use of non-invasive telemonitoring devices for ICP measurements (TeleSensor, Radionics; InSite, Medtronic) in shunted patients or patients who have undergone a ventriculocisternostomy. Implantation of this type of device during all hydrocephalus related procedures preformed on older children and adults is currently the standard of clinical care at our institution. Higher cortical function will be assessed by selected standard neuropsychological test batteries. All subjects and controls must be independent (if adults) or have been delayed in school enrollment by not more than 1 year at age 6 years. This will maintain relative uniformity in baseline cognitive function and reduce the confounding effects of cognitive impairment due to underlying concurrent disease. Subjects with concurrent neurological diagnoses (e.g., stroke) will also be excluded. We anticipate enrolling 324 subjects in a four-year longitudinal study as described below.

There will be four separate protocols that will address the hypotheses presented above in Specific Aims #1 through #4.

Protocol for Specific Aim #1:

The hypothesis for this aim of the study is that specific areas of cognitive function, e.g., attention, memory, and mental speed, will be ICP sensitive while others, e.g. language, will be relatively ICP independent after an acute ICP change.

This experimental group will consist of 36 hydrocephalic subjects that have been implanted with variable pressure programmable valve shunting systems (Codman-Medos Shunt System, Codman-Johnson & Johnson or Strata Valve Shunt assembly, Medtronic, Inc.) coupled to in-line TeleSensors; 36 shunted controls will undergo similar neurocognitive testing. Subjects will be over 16 years of age and will be without any overt symptoms of hydrocephalus at the time of examination. Etiology of the hydrocephalus will be limited to communicating hydrocephalus caused by CSF malabsorption without any associated brain congenital anomalies or brain injury (such as stroke or trauma). The programmable valves can be set at pressures from approximately 3 to 20 cm of water. We will plan to manipulate the valve by up to 10 cm of water pressure, as limited by the baseline setting (e.g., patients set at 13 cm of water pressure would only be able to have a 7 cm increase in pressure to the maximum of 20 cm) and as measured on the telemonitor. Subjects will undergo two tests (exam 1 and 2) with pressure either lowered or raised. The order of the tests (raising first or lowering first) will be randomized for each patient enrolled. Neuropsychological examiners will be blinded as to the treatment (raising or lowering pressure) and to the baseline pressure values. If there is shunt malfunction or other change in baseline ICP between the two testing sessions, the subject will be excluded from the study.

Protocol. After informed consent for participation is obtained, patients will be tested for tolerance of variable ICPs in the clinic. Beginning at their current baseline, we will increase (or decrease) the pressure by up to 10 cm of water to determine if any symptoms (such as headache) occur. Subjects will be excluded if symptoms occur (such as headache) within the 10 cm variation in pressure. If tolerated, subjects' shunts will be reprogrammed to their baseline ICP and entered into the study. Short battery neuropsychological testing will then be performed, as appropriate for age (described below), to comprise a baseline. Data will be correlated with ICP, as measured immediately before testing. Two to 4 hours later, subjects will undergo a similar test battery after their ICP has been elevated (or lowered) by up to 10 cm of water (exam 1) or lowered (or elevated) by up to10 cm of water (exam 2). Exam 1 and 2 will need to be separated by at least one year's time to reduce the practice effect To control for the potential practice effect from 2 short test batteries performed on the same day, 36 age-matched shunted hydrocephalic subjects will undergo two short battery tests on the same day that will be repeated after one year without any valve changes. This will establish the magnitude of the practice effect, though, as presented below, the testing battery is designed to reduce that risk.

The ICP will remain increased for the duration of the neuropsychological testing and be measured again for confirmation before the valve is reset to baseline after the second testing session. The data obtained in this

fashion will be subjected to analysis of variance over ICP change with the cognitive testing sub-scores as the dependent variables. This analysis will determine whether the hypothesis is correct that changes in specific sub-scores will occur. Power calculations relative to group size and variables are discussed below in the Power Considerations section.

Over the last two years, beginning shortly after the programmable valve was approved by the FDA, over 20 programmable valve systems per year have been implanted at our institution. Enrolling the proposed number of patients over the first three years of the study (for data collection over all four years of the study) should pose no difficulty. Since the majority of these valves have been implanted in adult patients, only individuals older than 16 years of age will be included in this aim of the study. The control group will be selected from the large shunted population followed at our institution and will be age matched. This should not confound the analysis.

Protocol for Specific Aim #2

The hypotheses for Aim #2 states that treatment of hydrocephalus and its associated intracranial hypertension will improve specific pressure dependent cognitive functions, e.g., attention, memory function and mental speed, as hypothesized in Aim #1. We will address this hypothesis with a controlled study (at 10 – 14 days and 1 year after intervention) that will consist of two groups of 36 subjects each.

The first group (group 1) will consist of patients enrolled at the time of presentation with shunt malfunction (a period of elevated ICP) as diagnosed by standard clinical methods. Though hydrocephalus can be life threatening due to high ICP, we are often confronted with a subclincal presentation of moderate ICP elevation. These subjects may have intermittent headache, behavioral changes, changes in school performance, or incidental finding of elevated ICP on their shunt telesensor and enlarging ventricles on serial neuroimaging studies. Subjects (children age 6 to 16 years) will be eligible for this study if they have evidence of elevated ICP due to hydrocephalus (previously treated with a shunt that is malfunctioning) but excluded for any overt symptom that causes discomfort, such as continual headache, nausea/vomiting, bradycardia, or other pain. Focal neurological deficits that are longstanding (greater than 2 weeks) and do not cause discomfort (such as extraocular palsies) will not be automatic exclusion criteria, in the absence of any other overt signs of elevated ICP. Only patients that have been shunted by standard non-siphoning valve systems will be enrolled in this arm of the study, so as not to confound the analysis by any differences between cognitive outcome with siphoning versus non-siphoning pressure dynamics (see Aim #4). Similarly, patients shunted for obstructive hydrocephalus will be excluded so as not to allow varying etiologies of hydrocephalus to confound the analysis (see Aim #3). Patients enrolled in this Aim will have been shunted by one year of age with a diagnosis of perinatal hydrocephalus and will be within one school grade of their age expectation. These criteria will further restrict the analysis to a more uniform etiological group reducing confounding effects of diagnostic variability.

The second group (group 2) will be a control group for the potential "practice effect" of two closely spaced neuropsychological test batteries. This group will be chosen as age-matched controls for group 1 with the same exclusionary criteria. Group 2 will consist of shunted patients that do not have evidence of elevated ICP or of shunt malfunction and who will undergo identical testing batteries and testing intervals as group 1. We have chosen the pediatric age group for this portion of the protocol for several reasons: (1) shunt malfunction without overt signs of increased ICP is more common in children; and (2) the subject population is readily available from the very large pediatric neurosurgery practice at The University of Chicago Children's Hospital.

Protocol. After informed consent for participation is obtained from the patient (where appropriate) and/or the guardian, a short-battery neuropsychological test will be administered (appropriate for age, as described below) during the period of elevated ICP before repair of an existing shunting system for patients in group 1. Data will be correlated with supine ICP, as measured directly before or at the time of shunt revision. If the intraoperative ICP measurement is spurious, due to CSF loss or inappropriate anesthetic/medical management, the subject will be excluded from the protocol if a pre-intervention ICP was not obtained by some

other means (e.g., direct shunt tap or lumbar puncture). Short battery testing will be repeated 10 - 14 days after the procedure which lowered the ICP, and supine ICP will be measured non-invasively at that time and recorded (as is customary in clinical practice at the clinically indicated 10 - 14 day postoperative office visit). In addition to the neurocognitive data, pre- and post-operative CT scans, routinely performed in our clinical practice in the treatment of shunt malfunction, will be analyzed for ventricular size by a standard ratio of ventricle to cortex (measured as the ratio of right frontal horn tip lateral edge to left frontal horn tip lateral edge distance and bitemporal cortical surface distance at that same anterior-posterior level determined at the level of the foramena of Monro on axial scanning). The pre- and post-ICP reduction CT-derived measurements will also be recorded and analyzed as another variable to determine if there is possible structural dependence based on ventricular size changes in neurocognitive performance. Patients from group 2 will be entered into the study upon recruitment and consent and also subjected to two short battery testing sessions with ICP measurements. These data will serve as a control for practice effects possible with the closely spaced testing batteries. The data collected at each time point (supine ICP, neuropsychological testing sub-scores) will be analyzed with respect to variance with time to determine differences before and after ICP changes in group 1 (and practice effects in group 2). Our hypothesis predicts that there will be a significant improvement in attention, memory, and mental speed. That hypothesis will be upheld or disproven by this analysis. As an additional analysis that takes into account longitudinal change in cognitive function and may add to our understanding of long-term effects of ICP changes on cognition, all subjects will undergo a full testing battery 1 year after enrolling in the protocol. This will assess any additional changes between 2 weeks after ICP reduction and one year after ICP reduction with a control for practice effect. Subjects will be disqualified from the protocol if they experience recurrent shunt malfunction within the first 14 days after entering the protocol or within the first year (for the longitudinal portion of this Aim). The rate of shunt malfunction within the first year after shunt revision is 10% at our institution for children above age 2 years. In addition, if there is any significant change in ICP as monitored telemetrically over the year of the protocol, the subjects will also be excluded.

The potential confounding factor in this protocol is practice effect as there are limited alternate testing forms for children. We maintain that age matched hydrocephalic patients are the best group to control for this effect, as unshunted controls may exhibit practice effect that will be unattainable by hydrocephalics due to baseline cognitive changes or their variability. Power calculations relative to group size and variables are discussed below in the Power Considerations section.

During calendar 2001 at The University of Chicago Children's Hospital, the Section of Pediatric Neurosurgery performed nearly 170 shunt revision procedures and evaluated over 500 additional patients for follow-up of hydrocephalus treatment. No difficulty is anticipated in enrolling the proposed number of patients; however, the enrollment period will be spread over 3 years to maximize the likelihood that 36 patients with minimally symptomatic elevations in ICP will be enrolled (out of an expected 510 who present with shunt malfunction). This will spread the full data collection for Aim #2 over all 4 years of the project.

Protocol for Specific Aim #3:

The hypothesis for this aim of the study is that endoscopic third ventriculocisternostomy, a non-shunting bypass of aqueductal obstruction, restores normal pressure dynamics and normal cognitive functioning.

This experimental group will consist of 36 patients (children age 6 years to adulthood) and 36 age-matched controls (who have undergone the third ventriculocisternostomy procedure more than one year prior to enrolling in the study) to be enrolled over the first 3 years of the study period for a one year longitudinal study. As in Aim #2, patients with subclincal presentation of ICP elevation will be included. These subjects may have intermittent headache, behavioral changes, changes in school performance, or the incidental finding of enlarging ventricles on serial neuroimaging studies. Subjects will be eligible for this arm of the study if they have evidence of elevated ICP due to hydrocephalus that is diagnosed by magnetic resonance imaging criteria as due to aqueductal stenosis. Subjects will be excluded for any overt symptom that causes discomfort, such as continual headache, nausea/vomiting, bradycardia, or other pain. Focal neurological deficits that are longstanding (greater than 2 weeks) and do not cause discomfort (such as extraocular palsies)

will not be automatic exclusionary criteria, in the absence of any other overt signs of elevated ICP. Patients will also be excluded if they are found to have other brain anomalies in addition to aqueductal stenosis.

Protocol. After informed consent for participation is obtained, a short battery of neuropsychological tests will be performed before treatment, as appropriate for age (described below). Data will be correlated with supine ICP, as measured directly at the time of endoscopic ventriculocisternostomy (fenestration to bypass the hydrocephalic obstruction). If the intraoperative ICP measurement is spurious, due to CSF loss or inappropriate anesthetic/medical management, the subject will be excluded from the protocol. A Telesensor connected to a ventricular catheter will be placed at the time of surgery as is the accepted practice at our institution. In a manner similar to Aim #2 above, subjects will undergo a repeat short battery of testing at 10 - 14 days postoperatively (this timing is chosen to minimize the effects of early postoperative fluxes in ICP, as described below, as well as to correlate with the first clinically indicated postoperative visit) concurrent to non-invasive ICP monitoring. At one year following the ventriculocisternostomy, subjects will undergo a full battery of neuropsychological tests as well as dynamic non-invasive ICP monitoring. In addition to the neurocognitive data, pre- and post-operative MRI scans, routinely performed in our clinical practice in the treatment of aqueductal stenosis, will be analyzed for ventricular size by a standard ventricle to cortex ratio (measured as the ratio of right frontal horn tip lateral edge to left frontal horn tip lateral edge distance and bitemporal cortical surface distance at that same anterior-posterior level determined at the level of the foramena of Monro on axial scanning). The pre- and post-ICP reduction MR-derived measurements will also be recorded and analyzed as another variable to determine if there is possible structural dependence based on ventricular size changes in neurocognitive performance. These data will be subjected to analysis of variance to determine whether there are significant changes from before intervention to after intervention. As a control for practice effects, a group of 36 age-matched controls who have undergone third ventriculocisternostomy for hydrocephalus of aqueductal stenosis more than one year before enrollment will undergo the same protocol. The first level of analysis will determine whether the treatment improved cognitive functioning for the surgical group at 2 weeks and 1 year when controlled for by the practice effect "control" group. However, the hypothesis will be proved or disproved by analysis of the testing scores of the treated group relative to the control group and to published norms at one year after treatment. The prediction is that there will not be a significant difference between groups in one-year follow-up as this treatment should restore normal ICP dynamics and that cognitive function should be within the normal range.

One possible confounding factor is the observation that ICP dynamics are in flux during the first several weeks after ventriculocisternostomy and may affect cognitive functioning (24). We have observed that ICP tends to be low by 14 days postoperatively. Though the ICP may be significantly different by the one year follow-up examination, an early follow-up may yield additional insight into short term changes in cognition with ICP changes. Power calculations relative to group size and variables are discussed below in the Power Considerations section.

During calendar 2001 at The University of Chicago Children's Hospital, the Section of Pediatric Neurosurgery performed 18 endoscopic fenestrations of this type on children and young adults with a long-term rate of ostomy patency of approximately 80%. Over a three year period, we anticipate being able to enroll 36 subjects. Approximately 60 patients who have previously undergone this procedure are followed in the University of Chicago Neurosurgical clinic and should be available to serve as control subjects. Data collection will occur over all four years of the study.

Justification for including both children and adults in this arm of the study is that the presentation of aqueductal stenosis is most common in older children and young adults. Therefore, exclusionary age criteria would make it difficult to attain adequate sample size. The protocol design includes an age-matched control group that can be used to control for practice effect as well as provide data for a controlled longitudinal analysis. This will test the hypothesis of improvement in function effectively. This analysis will test the hypothesis of whether the treatment returns normal function as well as normal ICP dynamics.

Protocol for Specific Aim #4:

The hypothesis for this aim of the study is that different shunting dynamics will differentially affect neuropsychological performance and further define ICP-sensitive and ICP-insensitive cognitive functions. These experimental groups will consist of 3 groups of 36 subjects between the ages of 6 and 16 years. Group 1 will consist of children shunted with siphoning valves; group 2 will consist of children shunted with non-siphoning valves; group three will consist of unshunted control subjects. All hydrocephalic subjects will have a history of absorptive hydrocephalus so as not to confound the analysis with varying etiologies of disease. Subjects will also have been shunted within the first year of life, which is common for absorptive hydrocephalus due to intraventricular hemorrhage in the perinatal period. Subjects will be age matched across the three groups.

Protocol. The subjects enrolled in all groups will undergo a full neuropsychological testing battery as described below in Methods. This distribution of patients will allow analysis by a 1 x 3 matrix ANOVA using the intelligence quotient (IQ) or other testing sub-scores as the dependent variable for the shunting dynamics. Such analysis will uphold or disprove the hypothesis that different shunting dynamics will better treat hydrocephalus of absorptive etiology, based on steady state cognitive function. Subjects will be disqualified from the study if they have experienced shunt malfunction or increased intracranial pressure due to other causes within the year prior to enrolling in the study. For those with TeleSensors, any evidence that the monitored dynamic pressure does not conform to the predicted curve (see Preliminary Data) or is unreadible (potential proximal shunt malfunction) will exclude that specific subject from the study.

We are unable to predict the differences in neuropsychological sub-test scores or overall IQ scores between patients with different shunting dynamics. Power calculations relative to group size and variables are discussed below in the Power Considerations section. Randomizing valve assignment in this protocol is impractical as the majority of absorptive hydrocephalics suffer hydrocephalus of prematurity and are shunted as neonates. This approach would then entail waiting >6 years to perform meaningful testing—if subjects attained adequate function (<1 year delay by 6 years of age)—to enroll in the study. However, this aim of the study is observational to shunts already implanted and not longitudinal. Of note, there are currently no guidelines for implantation of a specific type of shunt valve and children shunted as infants 5 - 6 years or more before study initiation would occur did not have the benefit of a pediatric neurosurgery service at our institution. The logic of proposing this protocol as a retrospective study is the observation in our institution that shunt hardware choice was random to surgeon preference before the establishment of the Pediatric Neurosurgery Service 7 years ago. The age inclusion criteria and the criteria for shunting before 1 year of age requires all subjects to have been shunted under these conditions. In addition, restricting enrollment to patients that are less than one year delayed with the diagnosis of absorptive hydrocephalus should exclude much of the clinical variability that could have potentially led to a bias in shunt valve choice. We plan to approach all patients who fulfill the inclusion criteria when presenting for routine yearly "shunt check" in our clinical practice in a consecutive fashion. The random presentation in clinic over time should also remove some additional potential bias of hardware selection.

Over 500 children are seen yearly in our institution for routine follow-up of shunted hydrocephalus. The current estimated ratio of siphoning to non-siphoning valves is approximately 1:1 in the 6 to 17 year age group. By consecutive invitation to enrollment, we anticipate no difficulty in finding 36 subjects with each type of shunt over the period of the study.

Conclusion

This study addresses four specific hypotheses regarding the treatment of hydrocephalus and cognitive function associated with ICP changes or ICP dynamics. We anticipate that anomalies in measures of cognitive function previously observed in hydrocephalics will be further elucidated and defined by this study. The novel sensing ability for ICP dynamics that we will use to correlate ICP with cognitive function is unexplored for this use and will provide valuable data. The clinical impact of these data will be profound, since proof of our

hypotheses will affect the choice of shunting materials for the many thousands of shunting procedures performed each year. Hopefully, the application of these results will be a step towards providing a better environment for brain development and function in the hydrocephalic child. We anticipate that our results will stimulate significant further investigations into specific anatomical correlates of ICP and brain function, such as those based on emerging modalities of functional imaging technology and 3-dimensional EEG wave acquisition. The data collected in the present protocol is therefore critical to the construction of additional studies that will elucidate the anatomical bases for observed effects of ICP changes on cognition.

Methods

Power Considerations. For Aims #1 - 3 of this study, there will be two groups being compared per Aim. For Aim 4, there are three groups of interest. Thus, there are a total of nine groups of subjects needed for this study. For a total N=324, each group will have 36 subjects. With groups of this size, we will have power of 1-β to detect a difference of $\delta = (z_\alpha + z_\beta) * \sigma * \sqrt{(2(1-\rho))} * \sqrt{(2/n)}$ between groups. Note that σ is the standard deviation of scores (it is assumed that pre-treatment, acute and long-term post-treatment scores have similar standard deviations); ρ is the correlation between pre and post-treatment scores; n=36 subjects per group. For a two-sided significance level of 5%, z_α =1.96. Also, z_β = 0.84, 1.04, and 1.28 for 80%, 85%, and 90% power, respectively. The table below lists the relative effect size (δ/σ) detectable with n=36 subjects per group for varying amounts of power and ρ.

	Power		
Correlation (_)	**80%**	**85%**	**90%**
.25	0.81	0.86	0.93
.50	0.66	0.71	0.76
.75	0.47	0.50	0.54
.90	0.30	0.32	0.34

Relative Effect Size Detectable with n=36

Data we have collected on fourteen patients indicates that correlations of about 0.75 between pre-treatment scores and acute post-treatment scores can be expected with correlations as high as 0.9 for some measures. Correlations between pre-treatment and long-term post-treatment scores, while being less than those for the acute cases, are expected to be anywhere from 0.50 to 0.25 with correlations for most measures being closer to 0.50. Thus, effect sizes on the order of 0.5 can be detected with good power for acute changes and effect sizes of 0.7 for long-term changes. For example, using standard deviations from the data already collected (see Preliminary Data section), this indicates that we would be able to detect an acute difference in the RBANS immediate memory index of 8.5 points between the two groups, a difference in the RBANS attention index of 6.25, and a difference in the Trail Making Test B of 21 seconds.

Data Handling and Statistical Analysis For Aims #1 - 3, repeated measures analysis of variance will be performed on the cognitive measures to examine group (valve vs. control), evaluation (pre- vs. post assessment), and group by evaluation interaction effects. It is expected that for attentional, motor, and memory measures, there should be a group by evaluation interaction, whereas this will be not be present for the language measures. Analyzing the data in this way amounts to using 2-sample t-tests to compare the differences in score changes between the two groups, and this was the approach that the power calculations were based on. In addition, analysis of covariance will be done on post-treatment scores treating pre-treatment scores as a baseline. Acute and long-term changes will be

analyzed separately. For Aim #4, data will be analyzed by one-way ANOVA with Tukey post-hoc comparisons.

Due to the fact that a large number of cognitive measures are being used, multiplicity does become an issue and appropriate adjustments will be made. The Bonferroni adjustment is too conservative, so we will employ O'Brien's method, which is based on a nonparametric rank-sum test (43)

Data for each subject will be collated for ICP values, ventricular size changes (Aims #2, #3) and cognitive testing and stored in the Section of Pediatric Neurosurgery offices in a locked cabinet. Upon completion of the enrollment and data collection in each protocol aim, the data will be entered into a computer file and transmitted to the study biostatisticians from the Department of Health Studies for statistical analysis.

Telemonitoring of ICP. Intraventricular pressure measurements will be performed as described (10, 24) using the Radionics (Burlington, MA) Tele-Sensor device (11) in the supine position (Aims #1, #2, #3) or with postural changes (Aim #4). Angles of elevation of the head are estimated from a tilt table. Measurements will be performed 2-3 times over 20-30 seconds either in the supine position or at each postural elevation. Intracranial pressures will be expressed in cm of water, as calibrated on the Radionics ICP-M4 telemonitor system, measured at the site of the TeleSensor. Due to a hysteresis effect in head raising and lowering reported previously(10), ICP is expressed only for head of bed elevation. Results will be collected and graphed directly as pressure versus degree of head of bed elevation . TeleSensor devices are either implanted "in-line" integrally connected to the Radionics Teleshunt system, or can be spliced into an existing shunt system (or into a non-Radionics system, e.g., the Codman-Medos programmable valve system, Aim #1), distal to the ventricular catheter, but proximal to the valve. We have encountered no complications relative to the TeleSensor nor has a TeleSensor malfunctioned requiring replacement over the past 5 years of implantations.

Neuropsychological Testing Materials. Subjects meeting the eligibility criteria for the study will then undergo a 1 to 2-hour baseline (pre-surgery or pre-valve adjustment) neuropsychological evaluation. Since the patients will likely experience some discomfort due to their increased intracranial pressure, the pre-surgery evaluation only involves screening measures of cognitive skills that most likely will be affected. Specifically, the pre-surgery battery will provide an estimate of overall intellectual functioning and achievement and examine such skills as attention, memory, visual-spatial skills, and fine motor speed. All tests to be administered to children between 6 and 16 years of age are listed and described below, organized according to neuropsychological domains. Tests to be administered to the adult population are discussed separately in the section following the child tests. All tests will be administered by trained technical staff of the Pediatric or Adult Neuropsychology Service at The University of Chicago who will be blinded to conditions of treatment. These measures are primarily paper and pencil in nature and take approximately 1 to 2 hours. All neuropychological tests proposed for use in this study are reliable and valid measures of cognitive functioning and are commonly used in clinical practice and research. Generally, a reliability coefficient of .80 or higher is considered to be acceptable.

Child Pre-Surgery Battery (ages 6 - 16)

IQ Estimate and Assessment of Current Language Skills

Wechsler Abbreviated Scale of Intelligence (WASI). Children between the ages of 6 to 16 years will complete the four subtests of the WASI. The Vocabulary subtest involves picture naming and word definition tasks, while the Similarities subtest assesses verbal analogical reasoning skill development. Together, these tasks comprise the Verbal factor of the WASI, which provides information about current expressive and receptive language capabilities. The WASI Performance factor is comprised of two measures, Block Design, which assesses visual-perceptual skill development, and Matrix Reasoning, which measures nonverbal, abstract reasoning. This provides information concerning

current visual-perceptual and spatial processing skills. These four subtests together form a Full Scale IQ estimate. The WASI is a new, shorter measure of intellectual functioning, which provides an estimate of intellectual functioning based on the administration of two or four subtests. It is linked to the Wechsler Intelligence Scale for Children-Third Edition (WISC) and the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). Norms are available for ages 6 through 89 years (65).

Achievement

Wide Range Achievement Test, Third Edition (WRAT-3). Reading Decoding and Arithmetic subtests will be administered as an estimate of the child's academic achievement. This measure can be used with individuals between the ages of 5 and 80+ year of age.

Attention/Concentration and Executive Functioning

Wechsler Intelligence Scale for Children-Third Edition (WISC-III). Children between the ages of 6 to 16 years will complete the Digit Span subtest of the WISC-III, which is a measure of immediate auditory attention and working memory (62).

Cognitive Assessment System (CAS). The Receptive Attention subtest of the CAS will be used as a measure of visual attention. As part of this task, the child is asked to find and underline pairs of pictures (ages 5-7) or pairs of letters that are physically the same or have the same name (ages 8-17). The Planned Connections subtest will be used as a measure of planning ability/executive functioning. The child's task is to connect a series of boxes containing numbers of letters in correct sequence. The more difficult items involve the connection of alternating letter/number sequences.

Memory & Learning

California Verbal Learning Test-Children's Version (CVLT-C). The CVLT-C is a verbal list learning task consisting of 15 "shopping" items. The child is read the list five consecutive times and is asked after each trial to recall as many of the words as possible. A second word list is introduced one time before the child is asked to recall the first list after a short delay (3 minutes) and a long delay (20 minutes). Following the two delayed recall trials, a recognition trial is introduced as part of which the child has to recognize the 15 target words out of a list of 45 words. Norms are available for ages 5 through 16 (15).

Rey Complex Figure Test (RCF). The RCF is a test of visuospatial constructional ability and visuospatial memory. This test requires the copy of a highly complex shape with multiple embedded figures. After the initial copy, the figure is reproduced after a short (3-minute) and long (30-minute) delay. There is also a recognition trial. Norms are available for children from ages 6-adult (40).

Visual-Motor/Visual Perceptual Functioning

Developmental Test of Visual-Motor Integration (VMI). The VMI is a measure of visual-motor integration used with children between the ages of 2-18. The test consists of 24 designs, which are to be copied in clearly delineated squares of space equal to the original. The designs follow a developmental gradient of difficulty starting with a vertical line for younger children and progressing to three-dimensional cube and star designs for older children (5).

Rey Complex Figure Test copy component. Score from copy trial will allow for assessment of visual constructional ability.

Additionally, tasks from the Performance factor of the WASI will allow for assessment of visual-spatial planning and perceptual skill development (specifically, Block Design).

Motor Skills

Grooved Pegboard. The pegboard test is a measure of fine motor coordination and dexterity. Norms are available for children and adults (Lafayette Instrument Company).

Emotional and Behavioral Functioning

The participants' parents and teachers will be asked to complete the following behavioral measures depending upon age:

Behavioral Assessment System for Children (BASC). The BASC is a 131-item behavior rating scale completed by parents on a 4-point scale, according to how well they describe a child's behavior (N = never, S = Sometimes, O = Often, and A = Always). Items are divided into internalizing and externalizing symptoms. Examples of test items include "Complains of being teased," "Worries," "Has strange ideas" and "Is easily distracted." There are 9 scales including the following: Hyperactivity, Aggression, Conduct Problems, Anxiety, Depression, Somatization, Atypicality, Social Skills, and Leadership. There are three different forms depending on the age of the child (4-5, 6-11, and 12-18). The teacher completes the teacher version of the same forms (49).

Behavior Rating Inventory of Executive Function (parents only). This questionnaire consists of 129 items on a three point rating scale (Never, Sometimes, Often). Items assess behavior problems in such areas as attention, overactivity, planning, decision making, impulsivity, etc. Parents are asked to indicate if their child had problems with these behaviors over the past 6 months (32).

Adult Baseline Battery (ages 17 and older)

Estimate of Premorbid Intellectual Functioning

Wechsler Test of Adult Reading (WTAR). This is a brief reading test that is highly correlated with premorbid intelligence (66)

General Neuropsychological Function

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). This is a brief core battery of neuropsychological tests assessing function in the areas of immediate memory (word list, story, visual design), attention (digit span, coding), language (naming, semantic fluency), visual-construction skills (judgment of line orientation, copying ability), and delayed memory (word list, story, visual design). There are alternate forms to this battery. Form A will be administered during the pre-surgical evaluation (46)

Visual Memory

Brief Visuospatial Memory Test-Revised (***BVMT-R***; (3)): Although the RBANS contains a measure of visual memory, the BVMT-R was also included because of the importance of assessing visual memory functions. This test, which has multiple forms, involves visual learning across three trials, delayed free recall, and recognition. Form 1 will be administered during the pre-surgical evaluation.

Attention/Concentration/Executive

Stroop Test (28). This is a measure of word and color naming speed, as well as ability to inhibit a dominant reading response.

Trailmaking Test, A, B: A subtest of the Halstead-Reitan neuropsychological battery which is sensitive to general cerebral dysfunction (48). Trails A measures visual-motor tracking ability, and requires the patient to connect numbers that are scattered on a page. Trails B introduces an executive component (complex attentional shifting), requiring subjects to alternate between numbers and letters.

Delis Kaplan Card Sorting Test. This a complex task, assessing concept formation, reasoning, and problem solving abilities. It has one alternative form (14).

Psychomotor Function

Grooved Pegboard Test. The pegboard test is a measure of fine motor coordination and dexterity. Norms are available for children and adults (Lafayette Instrument Company).

Emotional

***Symptom Checklist 90-Revised (1990)(SCL/90-R)*:** A self-report questionnaire which assesses the presence of psychopathology, and the degree of psychological distress that an individual is presently experiencing (18).

Beck Depression Inventory-2 *(2000).* A widely used self report measure of depressive symptomatology.

To assess the acute effects of ICP changes on cognitive functioning, all patients who underwent shunt placement, shunt revision, or ventriculocisternostomy will be undergo a brief re-evaluation one to two weeks post-surgery. Control subjects will undergo the same test battery within the same time frame following their initial evaluation. The post-surgery battery addresses areas of cognitive functioning that are most commonly affected by pressure changes, such as memory, attention, and visual-spatial skills.

Child Short-Term Post-Surgery Battery (ages 6 - 16)

Attention/Concentration and Executive Functioning

Wechsler Intelligence Scale for Children-Third Edition (WISC-III), Digit Span subtest.

Cognitive Assessment System (CAS). Receptive Attention and Planned Connections subtests

Memory & Learning

California Verbal Learning Test-Children's Version (CVLT-C).

Rey Complex Figure Test (RCFT)

Visual-Motor/Perceptual Functioning

Developmental Test of Visual-Motor Integration (VMI).

WASI Block Design subtest.

Motor Skills

Grooved Pegboard.

Emotional/Behavioral Functioning

Behavioral Assessment System for Children (BASC). The participants' parents will be asked to complete the BASC at the post-surgery evaluation to monitor any recent behavioral changes.

Adult Post-Valve Manipulation Battery (Aim #1) and Short-Term Post-Ventriculocisternostomy Battery (Aim #3)

General Neuropsychological Function

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Form B will be administered for the post-operative evaluation.

Attention/Concentration

Stroop Test

Visual Memory

Brief Visual-Spatial Memory Test-Revised (***BVMT***; Benedict, 19): Form 2 will be administered during the post-surgical evaluation.

Executive Function

Trailmaking Test, A, B.

Psychomotor Function

Grooved Pegboard Test.

Emotional

Symptom Checklist 90-Revised.

Beck Depression Inventory-2

All patients who participated in the pre-surgery evaluation will participate in a comprehensive 1-year post surgery evaluation to assess the long-term affects of increased intracranial pressure on cognitive functioning. The evaluation will examine intellectual functioning, academic achievement, language, attention and concentration, memory, visual-motor and visual perceptual skills, motor abilities, and emotional/behavioral functioning. This evaluation will take approximately 6 to 8 hours. Adults (ages 17 and up) will be evaluated in a single session, whereas children (ages 4 to 16) will be seen on two 3 to 4 hour visits.

Child Full Battery (ages 6 - 16)

Intelligence

Wechsler Intelligence Scale for Children-Third Edition (WISC-III). Children between the ages of 6 to 16 years will complete the WISC-III, which is one of the most widely used measures of general intelligence for this age group. The verbal and performance tests can be administered separately or together to yield, respectively, a Verbal (VIQ), a Performance (PIQ), and a Full Scale IQ (FSIQ) (62).

Academic Skills

Woodcock Johnson Tests of Achievement-Third Edition (WJ-3). The WJ-3 is a measure of academic achievement.. The test is intended for both handicapped and nonhandicapped populations from age 3-90 years. Four of the nine standard subtests will be used including: Letter-Word Identification: measures the ability to identify letters and words; Passage Comprehension: measures the participant's skill in supplying the appropriate word to complete a short passage after silently reading the passage; Calculation: measures the ability to perform calculations ranging from simple addition and subtraction to those involving trigonomic, logarithmic, geometric, and calculus operations; and Dictation: tests the ability to respond in writing to a variety of questions requiring knowledge of punctuation, capitalization, spelling, and word usage.

Language Functioning

Add: Verbal Comprehension substests and factor score from the WISC-3.

Peabody Picture Vocabulary Test-Third Edition (PPVT-III). The PPVT-III is a test of single word receptive vocabulary for the spoken word in standard English. It is designed as a measure of the participant's receptive vocabulary or vocabulary acquisition, and serves as a screening test of verbal ability. Norms are available from age 2 to 90 (21).

Attention/Concentration & Executive Functioning

Add: Freedom from Distractibility subtests and factor score from the WISC-3.
Gordon Diagnostic System (GDS): Vigilance and Distractibility tasks.
CAS: Planned Connections and Expressive Attention subtests.

Memory & Learning
California Verbal Learning Test-Children's Version (CVLT-C).
Rey Complex Figure Test (RCF).

Visual-Motor/Perceptual Functioning
Developmental Test of Visual-Motor Integration (VMI).
Perceptual Organization subtests and factor score from the WISC-3

Motor Skills
Grooved Pegboard.

Emotional/Behavioral Functioning
Participants will be asked to complete the following behavioral measures depending upon age:

Self-Report version of the Behavioral Assessment System for Children (BASC-SR).
Child's Depression Inventory (CDI). A 27-item self-report measure of current depressive symptomatology which has norms for children ages 7 - 17 years. Individual item choices are scored (0-2) and summed to equal a total depression score, with higher scores suggesting a more severe level of depression (35).

The children's parents and teachers will be asked to complete the same measures as during the pre-surgery evaluation:
Behavioral Assessment System for Children (BASC).

Behavior Inventory of Executive Function (parents only).
Scales of Independent Behavior-Revised (SIB-R).

Adult 1-Year Post-Surgery Full Battery (ages 17 and up)

Intelligence
Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). Adults will complete the WAIS-III, which is the most widely used measure of general intelligence (63).

Achievement
Woodcock Johnson Tests of Achievement-Revised (WJ-R). The following subtests will be administered: Letter-Word, Passage Comprehension, Calculation, and Applied Problems.

General Neuropsychological Functioning
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Form A will be administered during this assessment.

Language Functioning
Boston Naming Test: This is a 60-item test of confrontation naming ability (33)
Controlled Oral Word Association Test (COWAT) (38) The measure assesses both phonemic and categorical verbal fluency, including the total number of items generated in one minute for the letters C, F, and L (phonemic), and the number of items generated in one minute belonging to the following categories: animals, vegetables, parts of a house.

Attention/Concentration & Executive Functioning
Conners Continuous Performance Test (CPT).
Stroop Test.

Memory & Learning
Wechsler Memory Scale - 3rd edition (WMS-3): The subtest which will be administered from this memory battery is the Logical Memory subtest which assesses ability to learn and retain prose narratives (64)
Brief Visual Memory Test (BVMT): Form 3 will be administered.
California Verbal Learning Test (CVLT) (15) The CVLT is a word list learning test assessing learning across five trials, interference from a competing word list, delayed free and cued recall, and recognition.
Rey Complex Figure Test (RCFT).

Visual-Motor/Perceptual Functioning
Judgment of Line Orientation (JLO). This is a measure of the patient's ability to judge the angular orientation of line segments (4).
Rey Complex Figure Test (RCFT). Score from the copy trial will be used to assess visual construction.

Executive Function
Trailmaking Test A, B
Wisconsin Card Sorting Test (WCST): This represents a measure of "executive" functioning requiring patients to engage in abstract reasoning, to display mental flexibility and set-shifting, and to benefit from feedback (30).

Motor Skills
Grooved Pegboard Test

Emotional/Behavioral Functioning
Symptom Checklist 90-Revised.
Beck Depression Inventory-2

In order to control for the practice effect that may occur during the 2-week post surgery evaluation, the same testing protocols at identical intervals will be administered to age- and gender-matched control subjects as described above in the protocols section.

E. Human Subjects

Participation of Women and Children: As per NIH guidelines, children under age 21 will be included in this study. The study population will be recruited from the patients currently followed by the section of Pediatric Neurosurgery at The University of Chicago Children's Hospital. This population currently consists of 74% children ages 18 or younger, and 26% over age 18. Children under age 6 will be excluded due to the nature of the neuropsychological tests and their lack of applicability to very young children. Inclusion criteria of the study propose that Aims #2 and #4 are designed specifically to include only children, as hydrocephalus and shunt malfunction is generally a problem of childhood. The expertise of the research team and the suitability of the facilities of the Children's Hospital for including children in this study is established by the heavy pediatric clinical load of the investigators (>400 pediatric operative procedures, >2000 outpatient clinical visits including pediatric neuropschological testing, in calendar 2001). As the study population will consist of patients with hydrocephalus where the incidence is equal between men and women, we anticipate approximately 50% of the study population will be female.

Minority Inclusion in the Proposed Study. The study population will reflect the demographics of the pediatric neurosurgery practice at the University of Chicago Children's Hospital. There will be no inclusion or exclusion criteria based upon racial or ethnic criteria. The shunted hydrocephalic population consists of an equal number of males and females. Reported below in the Planned Enrollment Table Format is the approximate

demographics of the pediatric neurosurgery practice super-imposed upon the expected 324 participants in the proposed study:

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Hydrocephalus, Intracranial Pressure and Neurocognition

Total Planned Enrollment: 324

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	16	16	32
Not Hispanic or Latino	146	146	292
Ethnic Category Total of All Subjects*	162	162	324
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	4	4	8
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	82	82	164
White	76	76	152
Racial Categories: Total of All Subjects *	162	162	324

*The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects."

All research will take place at the primary site.

(1) Human subjects will be enrolled in the study, as described above, if they are hydrocephalics undergoing CSF shunt revision, asymptomatic shunted controls, undergoing primary treatment of aqueductal stenosis, or if they are asymptomatic and have implanted telemonitors and programmable valve systems. These subjects will undergo neuropsychological testing and measurements of ICP in a non-invasive fashion as described above. Some subjects will have their valve pressures temporarily re-programmed after and again before neuropsychological testing. We anticipate enrolling a total of 324 subjects. All subjects will be above the age of 5 years; we anticipate at least 180 of the subjects to be under age 17, as reflected by the population of hydrocephalics at our institution and the inclusion criteria for the 4 Aims of the study. The rationale for involving children in this study is that hydrocephalus is primarily a childhood disease and data that may influence the choice of shunting products, etc., should be predominantly derived from subjects of younger ages.

(2) ICP measurements and neuropsychological testing results will be obtained wholly for research purposes. This data will initially be individually identifiable until each subject is assigned a unique study identifier. At that point, data will be stored in a locked cabinet using that identifier. The study principle investigator will retain the identifier key until such time as the study is complete or the enrolled subjects have refused offers of medical intervention should medical abnormalities be identified in the course of the study and communicated to the subject or his/her guardian.

(3) Subjects will be recruited by the P.I. or the nurse coordinator from the pediatric neurosurgery practice at our institution by direct contact (either phone or interview). If the subject or his/her family is interested in participation, the P.I. will conduct a face-to-face interview to explain all aspects of the research as documented on the consent form and to review the consent form with the patient and/or guardian where appropriate. If the subject/guardian then agrees to participate, consent will be obtained by the P.I., witnessed by a member of the neurosurgery staff, and documented on the Institutional Review Board approved consent form. A copy of this form will then be given to the participant, and the original will be kept with the patient's data file. No modification or waiver of the elements of consent has been approved by the IRB.

(4) There are no risks associated with the non-invasive measurements of ICP. There are no known risks associated with the neuropsychological testing procedures except fatigue and frustration. In order to minimize this, where age appropriate, frequent breaks in the testing or separate serial testing sessions will be planned. If manipulation of the programmable valves in individual patients causes discomfort, those patients will have their valves reset and will be excluded from Aim #1 of the study.

(5) Once a patient enrolls in the study, a unique identifier will be assigned and data will be stored by that identifier in a locked cabinet in the offices of the Section of Pediatric Neurosurgery. In the event that medical abnormalities are identified in the course of the study pertaining to the CSF pressures, the neuropsychological testing, or any other aspect of the subject's medical status, those results will be reviewed with the patient or his/her guardian. If appropriate, referral within the University system will be offered in order to facilitate appropriate treatment for the identified abnormality. The study staff will also offer to communicate fully about any recognized anomalies with the patient's primary care physician and assist him/her with referral outside the University system if desired.

(6) The risks to the subjects in undergoing ICP monitoring and neuropsychological tests are very minimal, and may not exist at all, other than the potential for fatigue and the time lost in undergoing testing. Potential benefits to individual subjects include the identification of neuropsychological deficits that might help in maximizing school interventions or in referring to other professional help. The importance of the knowledge gained in determining the best shunting pressure dynamic for cognitive outcome may positively impact the subjects and other shunted hydrocephalics over the course of their lives, as shunting devices malfunction and are replaced.

F. Vertebrate Animals

Not applicable.

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H. Consortium/Contractual Arrangements

Not applicable.

I. Consultants

Neil Pliskin, PhD. (5% effort), was the Director of Clinical Neuropsychology at the University of Chicago and a Co-Investigator on the initial application for this funding. He is currently Chief of Neuropsychology Services at the University of Illinois at Chicago but still involved in the development of this application and committed to the completion of this project. Dr. Pliskin will be responsible for providing support and oversight to Drs. Lacy and Hunter to insure uniformity in the collection of neurocognitive data in the study. His letter of support is attached.

APPENDICES

David Frim, PI

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